OVERACTIVE BLADDER (OAB)

Clinical Evidence

DISEASE PREVALENCE
Prevalence

CONSERVATIVE THERAPIES
Behavioral Therapy
Medication

ADVANCED THERAPIES
Sacral Neuromodulation
OnabotulinumtoxinA (Botox®)

Resources

Medtronic
OAB IS A HIGHLY PREVALENT AND UNDERTREATED DISEASE

- Adult population in Europe: >400 million\textsuperscript{1,2}
- Adults with OAB in Europe: >47m (11.8\%\textsuperscript{3,3b})
- OAB with Symptom Bother: >25.3m (54\%\textsuperscript{4})
- Seeking Care: >13.2m (52\%\textsuperscript{4})
- Non-adherent / Failure of Medication: >7.4m (56-89\%\textsuperscript{5,6,7,7b})

There is a need for more advanced therapies.
BEHAVIORAL THERAPIES

- Bladder training
- Pads
- Pelvic floor muscle training
- Fluid management

Behavioral therapies may be combined with anti-muscarinic therapies or a β-3 Agonist.
LONG-TERM ADHERENCE TO CONSERVATIVE TREATMENT IS POOR

23% Behavioral treatments$^{8,8b}$

≤44% Medications$^{5,6,7}$ at 12 month follow-up

- Efficacy of Medication
- Mechanism of Action
TREATMENT
PROGRESSION

Evaluation
Urge incontinence, urgency and frequency

Conservative treatments
Pelvic floor exercises, fluid/diet changes, biofeedback and physical therapy

Medications

Evaluate for specialized therapies
MEDICATION
SIMILAR EFFICACY, DIFFERENT SIDE EFFECTS

Major adverse events included dry mouth, constipation, and blurred vision.

Most frequent adverse events included hypertension, nasopharyngitis, urinary tract infection and headache.
Anticholinergics
Impacts M3 receptors to inhibit detrusor contraction.¹¹

β₃ Agonist
Impacts β₃ adrenergic receptors to relax detrusor muscle during filling phase.¹¹,¹²
SACRAL NEUROMODULATION (SNM)

Mechanism of Action

Patient Selection

Efficacy

Quality of life

Safety

Patient preferences

Percent of OAB responders (%)

SNM

SMT

Per protocol analysis
SMT: Standard Medical Treatment after 6 months of follow-up
LEADING THEORIES IN MECHANISM OF ACTION

Restoring function by targeting bladder-brain communication in idiopathic OAB patients.

Normal bladder function
Dysfunction of afferent signaling in OAB
How does SNM work
InterStim™ implant
**NORMAL BLADDER FUNCTION**

*Afferent sensory* pathways convey sensory information on bladder fullness.\(^{13,14,15}\)

*Efferent motor* pathways respond, resulting in voluntary urine control.\(^{16,17}\)

Dysfunction of the afferent neural pathways alters the balance of inhibitory and excitatory stimuli critical to voluntary bladder control.\(^{18}\)
OAB (Overactive Bladder) may be a result of increased abnormal afferent activity, resulting in increased efferent signaling.\textsuperscript{15,18}

Consequently, voluntary control of micturition is compromised.\textsuperscript{18}
HOW DOES
SNM WORK?

Sacral neuromodulation electrically stimulates somatic afferent nerves in a sacral spinal root and sends signals to the CNS.¹⁸

The action potentials induced by electrical stimulation are thought to alter abnormal sensory input from the bladder.¹⁴,¹⁹

Efferent pathways are uninhibited so as not to suppress voluntary voiding.²⁰

Unlike other therapies that target the bladder, bladder regulation occurs without directly influencing the bladder or sphincter muscles.²¹
Medtronic sacral neuromodulation sends electrical stimulation to the sacral nerve via the InterStim™ System, which includes an implanted neurostimulator and a lead.

The sacral nerve, in particular influences pelvic floor behaviour and is believed to modulate neural reflexes.\(^{22}\)
SNM appears to modulate cortical and subcortical structures, which are important for alertness and attention, the timing of micturition and sensation of bladder filling. Acute SNM modulates predominantly areas involved in sensorimotor learning. A joint mechanism of action of SNM for bladder and bowel dysfunctions reflects expert opinion.

MEDTRONIC SACRAL NEUROMODULATION MECHANISM OF ACTION
SELECTING APPROPRIATE PATIENTS

- Urge Urinary Incontinence (OAB wet)
- Urgency Frequency Syndrome (OAB dry)
- Non-obstructive Urinary Retention
- Chronic Fecal Incontinence
- Mixed urinary incontinence where Urge Incontinence is the primary complaint

For patients who have failed or were not able to benefit from more conservative treatments.
**Inclusion criteria**

- Diagnosis of OAB (≥ 8 voids per day and/or ≥ 2 involuntary leaking episodes in 72 hours)
- Failed or are not a candidate for more conservative treatment (e.g., pelvic floor training, biofeedback, and behavioral modification)
- Failed or could not tolerate at least one antimuscarinic medication and have at least one antimuscarinic medication not yet attempted

**Exclusion criteria**

- Skin, orthopedic, or neurologic anatomical limitations that could prevent successful placement of an electrode
- Neurological diseases such as multiple sclerosis, clinically significant peripheral neuropathy, or complete spinal cord injury
- Knowledge of planned MRIs, diathermy
- Primary stress incontinence or mixed incontinence where the stress component overrides the urge component
- Symptomatic urinary tract infection
- Pregnant or planning to become pregnant

*The list is not exhaustive*
PATIENT SELECTION
WHAT IS REFRACTORY OAB?

Although there is no agreed definition of refractory OAB and failure of pharmacotherapy, a treatment period of 8 – 12 weeks with medications has been recommended, before considering second-line therapies such as sacral neuromodulation or intradetrusor botulinum toxin injections\textsuperscript{26,27,27b,27c}.

In the INSITE trial 53% of patients had not more than two OAB medications prior to SNM implant\textsuperscript{25}.
**WOMEN WITH URINARY INCONTINENCE**
**EAU GUIDELINES 2018**

**Individualised behavioral and physical therapies including pelvic floor muscle training**
*Strong*

- **Stress incontinence**
- **Mixed incontinence**
- **Urgency incontinence**

**Advise on bowel function, drugs, co-morbidity, fluid intake**
*Strong*

- **Advise on weight loss**
*Strong*

- **Offer pads or other containment device if needed**
*Strong*

- **Offer timed or prompted voiding in elderly/care-dependant people**
*Strong*

**Urgency predominant**

- **Antimuscarinics**
  - *Strong*
  - or mirabegron
  - *Strong*

**Consider percutaneous posterior tibial nerve stimulation**
*Strong*
WOMEN WITH URINARY INCONTINENCE
EAU GUIDELINES 2018

Failed conservative or drug therapy

Offer urodynamics if finding may change choice of surgery

Weak

Failed Conservative / Medical Therapy: Advanced Therapies

Stress incontinence

Stress predominant

Treatment options include mid urethral slings (synthetic or autologous), autologous pubovaginal sling, colposuspension and urethral bulking agents

Strong

In case of failure, re-evaluate patient and consider second-line surgery

Strong

Mixed incontinence

Urgency predominant

Offer onabotulinum toxin A or sacral nerve stimulation

Strong

Urgency incontinence

Discuss bladder augmentation or urinary diversion

Weak
SUPERIOR EFFICACY VS. MEDICATIONS AT 6 MONTHS

Numbers reflected as treated analysis, defined as subjects with diary data at baseline and 6 months; subjects are grouped based on treatment received (p<0.01). Intent to treat results, which include all randomized subjects, are 61% for SNM and 42% for medications (p=0.02).

Therapeutic success was defined as a UUI or urgency-frequency response of ≥50% improvement in average leaks or voids per day or return to normal voiding.

Overall Symptom Improvement

<table>
<thead>
<tr>
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<th>Percent of OAB responders (%)</th>
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<tbody>
<tr>
<td>SNM</td>
<td>76%</td>
</tr>
<tr>
<td>SMT</td>
<td>49%</td>
</tr>
</tbody>
</table>

Complete Continence

For subgroup of patients with UI at baseline, complete continence was achieved in 39% of SNM and 21% of SMT patients (p=0.06)

SMT Standard Medical Treatment
INSITE
STUDY DESIGN

Phase 1: Randomized
SNM vs. SMT (6 months)
Patients randomized to Sacral Neuromodulation (SNM) or Standard Medical Therapy (SMT) in 1:1 ratio

Phase 2: Long Term
SNM Long Term (5 Years)
Evaluation of the safety and efficacy of SNM to 5 years for all implanted patients

6-MONTH FOLLOW-UP
LONG-TERM OAB THERAPEUTIC SUCCESS PROVEN EFFICACY

SNM Demonstrates Sustained Long-term Efficacy

<table>
<thead>
<tr>
<th>Month</th>
<th>Graduation</th>
<th>Completer Analysis Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 6</td>
<td>(n=240)</td>
<td>80%</td>
</tr>
<tr>
<td>Month 12</td>
<td>(n=220)</td>
<td>85%</td>
</tr>
<tr>
<td>Month 24</td>
<td>(n=203)</td>
<td>84%</td>
</tr>
<tr>
<td>Month 36</td>
<td>(n=193)</td>
<td>83%</td>
</tr>
<tr>
<td>Month 48</td>
<td>(n=183)</td>
<td>86%</td>
</tr>
<tr>
<td>Month 60</td>
<td>(n=150)</td>
<td>82%</td>
</tr>
</tbody>
</table>

Modified Completers analysis was 82% at 12 months, 76% at 36 months and 67% at 5 Years.
OAB response was defined as either ≥50% improvement in leaks/day for UI subjects or ≥50% improvement in voids/day or a return to normal voiding frequency (<8 voids/day) for UF subjects.
SIGNIFICANT IMPROVEMENTS IN TOTAL QUALITY OF LIFE

Greater quality of life improvements with SNM than MID (the minimally important difference indicates meaningful changes for the patient)

QOL was measured using the ICIQ-OABqol instrument

SNM=
SMT=
Other specialized therapies

MID (Minimally Important Difference = 10 points)

Mean improvement from baseline to 6 months

- Concern
- Coping
- Sleep
- Social
- HRQL Total
GREATER REDUCTION IN DAILY LIFE INTERFERENCE\textsuperscript{30}

Subjects reporting improved or greatly improved symptom interference

\begin{itemize}
\item SNM: 86%
\item SMT: 44%
\end{itemize}

\approx 2x

SNM subjects reported improved or greatly improved urinary symptom interference score compared to SMT at 6 months\textsuperscript{30}

Other specialized therapies
Siegel et al. concluded that after unsuccessful treatment with one or more anticholinergic medications, OAB subjects are more likely to benefit from SNM than an additional anticholinergic as a next step.
Device related AEs are defined as events with an etiology of programming/stimulation, implanted system, surgery/anesthesia, or incisional site/device tract.

1. No unanticipated adverse device effects reported.

2. The most common AEs were: undesirable change in stimulation; implant site pain and therapeutic product ineffective.

3. The rate of device related AEs and surgical intervention remained considerably lower than in previously published studies using older techniques and devices.
### Complications with reoperation

<table>
<thead>
<tr>
<th>Complication</th>
<th>Frequency in % (N=407)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound infection</td>
<td>2.2%</td>
</tr>
<tr>
<td>Back pain</td>
<td>1.0%</td>
</tr>
<tr>
<td>Pain in legs</td>
<td>1.2%</td>
</tr>
<tr>
<td>Pain at IPG site</td>
<td>8.8%</td>
</tr>
<tr>
<td>Lead migration</td>
<td>2.2%</td>
</tr>
<tr>
<td>Lead breakage</td>
<td>2.7%</td>
</tr>
<tr>
<td>Device malfunction</td>
<td>4.4%</td>
</tr>
</tbody>
</table>

Revision rates of 10% or lower have been reported in centers of excellence \(^{34,39,46}\).

Complication rates from a large case series with more than 400 patients implanted between 2004 and 2014. The follow-up ranged from 1.6 – 121.7 months (median 28.9 months). 19% of the patients were revised and 14% were explanted \(^{33}\).

Revision rates may vary greatly based on different implantation techniques, the surgeon's experience, the length of follow-up, the consideration of battery exchanges as revision surgeries and the number of salvage surgeries in the event of loss of effectiveness.
BOTOX (100 U) VS. MEDICATIONS
SIMILAR EFFICACY AND QOL IMPROVEMENTS

ABC Study Results at 6 months

118 participants randomly assigned to the anticholinergic medication group and 113 assigned to 100 U onabotulinumtoxinA group completed the study at 6 months.

Change from Baseline to 6 month (mean UI episodes/day)

-3.4
-3.3
p=0.81

<table>
<thead>
<tr>
<th></th>
<th>Anticholinergic</th>
<th>Botox</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urgency Incontinence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Resolution</td>
<td>13%</td>
<td>27%</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Quality of Life</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OABq-SF Severity Scale</td>
<td>-44.6</td>
<td>-44.1</td>
<td>0.87</td>
</tr>
<tr>
<td>OABq-SF QOL Scale</td>
<td>37.1</td>
<td>37.1</td>
<td>0.98</td>
</tr>
<tr>
<td>PFDI-SF</td>
<td>-43.7</td>
<td>-48.2</td>
<td>0.47</td>
</tr>
<tr>
<td>PFIQ-SF</td>
<td>-32.8</td>
<td>-33.9</td>
<td>0.88</td>
</tr>
</tbody>
</table>
Based on retrospective analysis of 27 neurogenic patients, Botox injections provide symptom relief but detrusor pressure remained significantly lower and did not return to baseline.

Authors suggest:

- **Detrusor contraction strength did not completely recover after Botox injections**
- **Detrusor contractility may decrease in patient repeatedly treated with Botox**
BOTOX: ALMOST TWO-THIRDS DISCONTINUE AT 3 YEARS

Of Botox patients who discontinued,

56% Stopped due to tolerability issues (e.g., UTI, CISC)

44% Due to lack of symptom relief

61% Discontinued therapy at 3 years (n=137)

Mohee Study Results37
BOTOX AND IDIOPATHIC OAB
HIGH DISCONTINUATION RATE

70% stopped at mean follow-up of 97 months (N=128 women)

79% stopped after first injection

19% stopped after second injection

EAU GUIDELINES
The discontinuation rate of Onabotulinum toxin A may be high.

Of those patients, who discontinued Botox
ROSETTA
TRIAL

1. The first randomized study between SNM with InterStim™ therapy and Botox (200 U).*

2. After two years, there was no difference between both therapies in terms of primary outcome (reduction in urge incontinence episodes per day).

3. SNM revision (3%) and removal rates (9%) were low at two years.

* Botox (200 U) is not licensed for idiopathic OAB.

** Dose ranging trials have shown that 200U Botox is more effective than 100U.40,40b.
### SNM VERSUS BOTOX®

**PATIENT PREFERENCES**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Ref</th>
<th>BTX : SNM preference ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balchandra</td>
<td>2014</td>
<td>41</td>
<td>1.0 : 0.35</td>
</tr>
<tr>
<td>Beusterien</td>
<td>2016</td>
<td>42</td>
<td>1.0 : 1.0</td>
</tr>
<tr>
<td>Hashim</td>
<td>2015</td>
<td>43</td>
<td>0.26 : 1.0</td>
</tr>
<tr>
<td>Fontaine*</td>
<td>2017</td>
<td>44</td>
<td>1.0 : 1.0</td>
</tr>
<tr>
<td>Nobrega</td>
<td>2018</td>
<td>45</td>
<td>0.5 : 1.0</td>
</tr>
</tbody>
</table>

There appears to be a significant disparity between clinicians and patient preferences for treatment of refractory OAB\(^45\).

* SNM (PNE)
REFERENCES

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34. Pettit P. Current opinion: complications and troubleshooting of sacral neuromodulation. Int Urogynecol J. 2010 Dec;21 Suppl 2:S491-6
Sacral neuromodulation therapy provided by the InterStim™ system is indicated for the management of the following chronic intractable (functional) disorders of the pelvis and lower urinary or intestinal tract: overactive bladder, fecal incontinence, and nonobstructive urinary retention.

See the appropriate InterStim™ device manual for detailed information regarding the instructions for use, the implant procedure, indications, contraindications, warnings, precautions, and potential adverse events. If using an MRI SureScan® device, see the MRI SureScan® technical manual before performing an MRI. For further information, contact your local Medtronic representative and/or consult the Medtronic website at www.medtronic.com.

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Consult instructions for use at this website. Manuals can be viewed using a current version of any major Internet browser. For best results, use Adobe Acrobat Reader® with the browser.