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[1,2]

Adults with OAB in Europe: >47m
(11.8%[3,3b])

OAB with Symptom Bother: >25.3m
(54%[4])

Seeking Care: >13.2m
(52%[4])

Non-adherent / Failure of Medication: >7.4m
(56-89%[5,6,7,7b])

There is a need for more advanced therapies

Up to

50m

suffer from OAB in Europe.

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

ICI guidelines

Evaluation

Urge incontinence, urgency and frequency

Conservative treatments

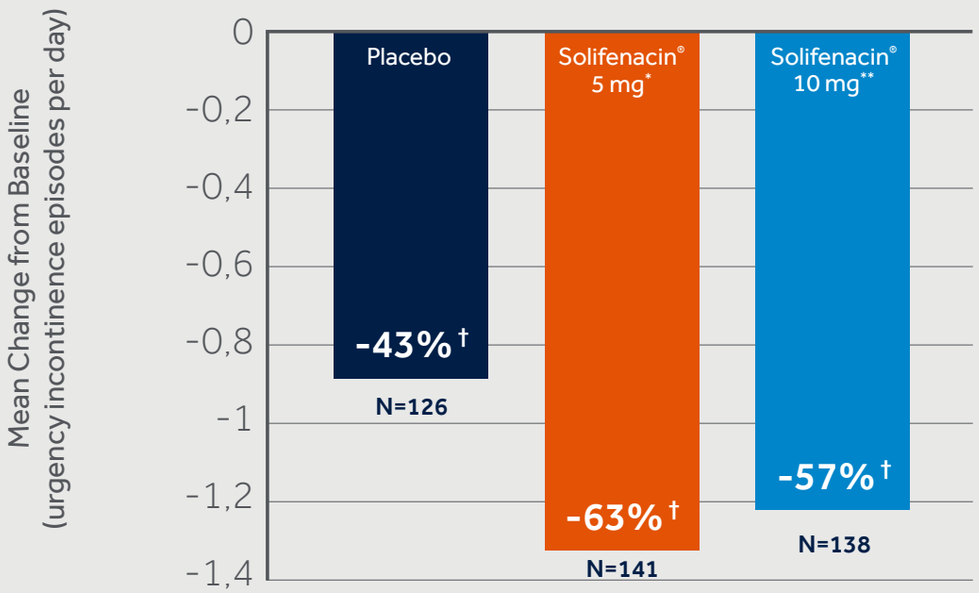
Pelvic floor exercises, fluid/diet changes, biofeedback and physical therapy

Medications

Evaluate for specialized therapies

MEDICATION
SIMILAR EFFICACY, DIFFERENT SIDE EFFECTS

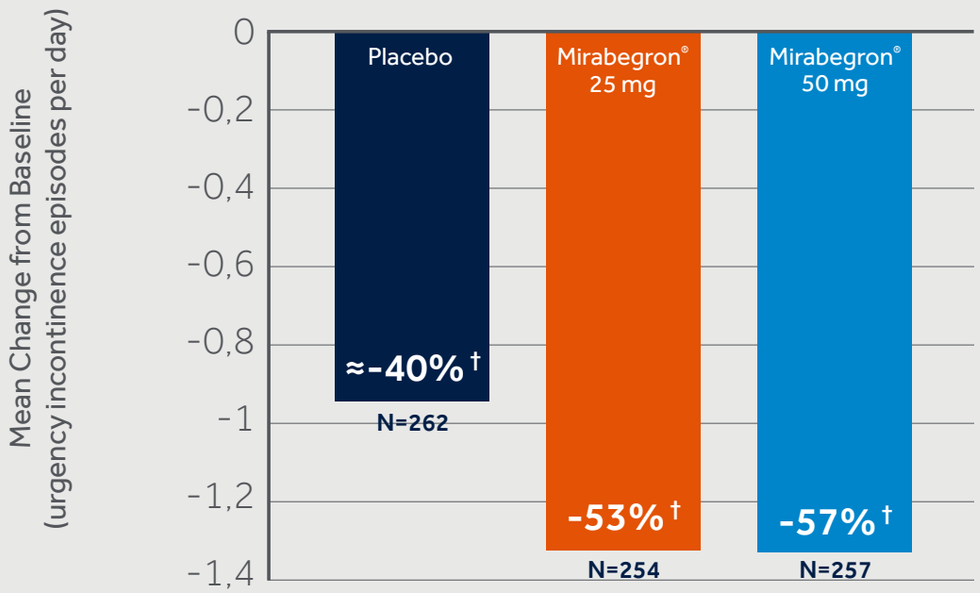
Solifenacin® vs. Placebo



* P = 0.014 (Placebo vs. Solifenacin 5 mg)
** P = 0.042 (Placebo vs. Solifenacin 10 mg)
† Reduction in urge incontinence episodes per day on a percentage basis

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

Mirabegron® vs. Placebo



† Reduction in urge incontinence episodes per day on a percentage basis

Most frequent adverse events included hypertension, nasopharyngitis, urinary tract infection and headache.

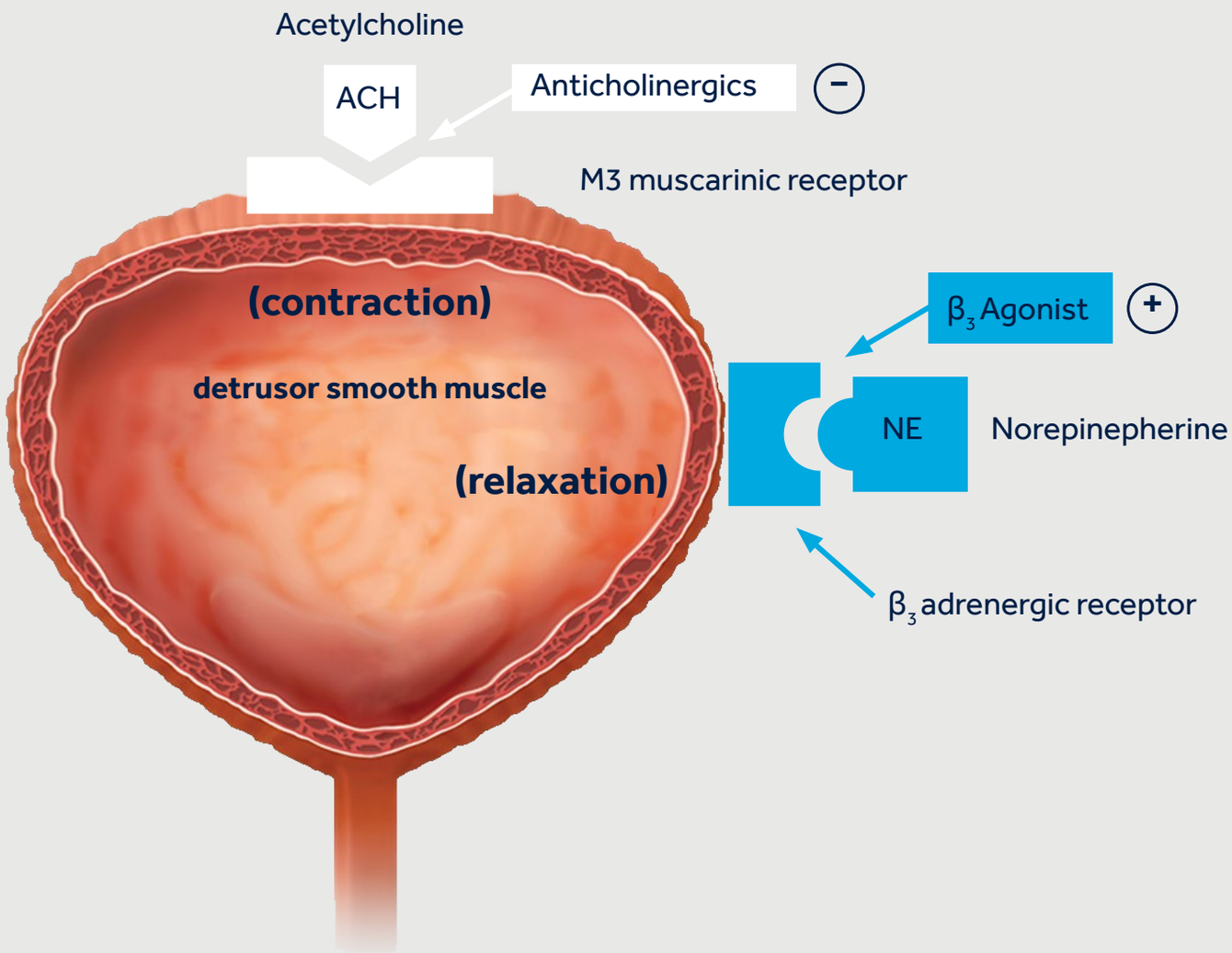
HOW MEDICATION WORKS

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

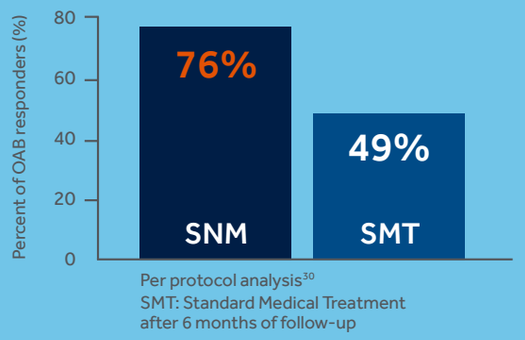
Patient Selection

Efficacy

Quality of life

Safety

Patient preferences



Per protocol analysis[30]
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.

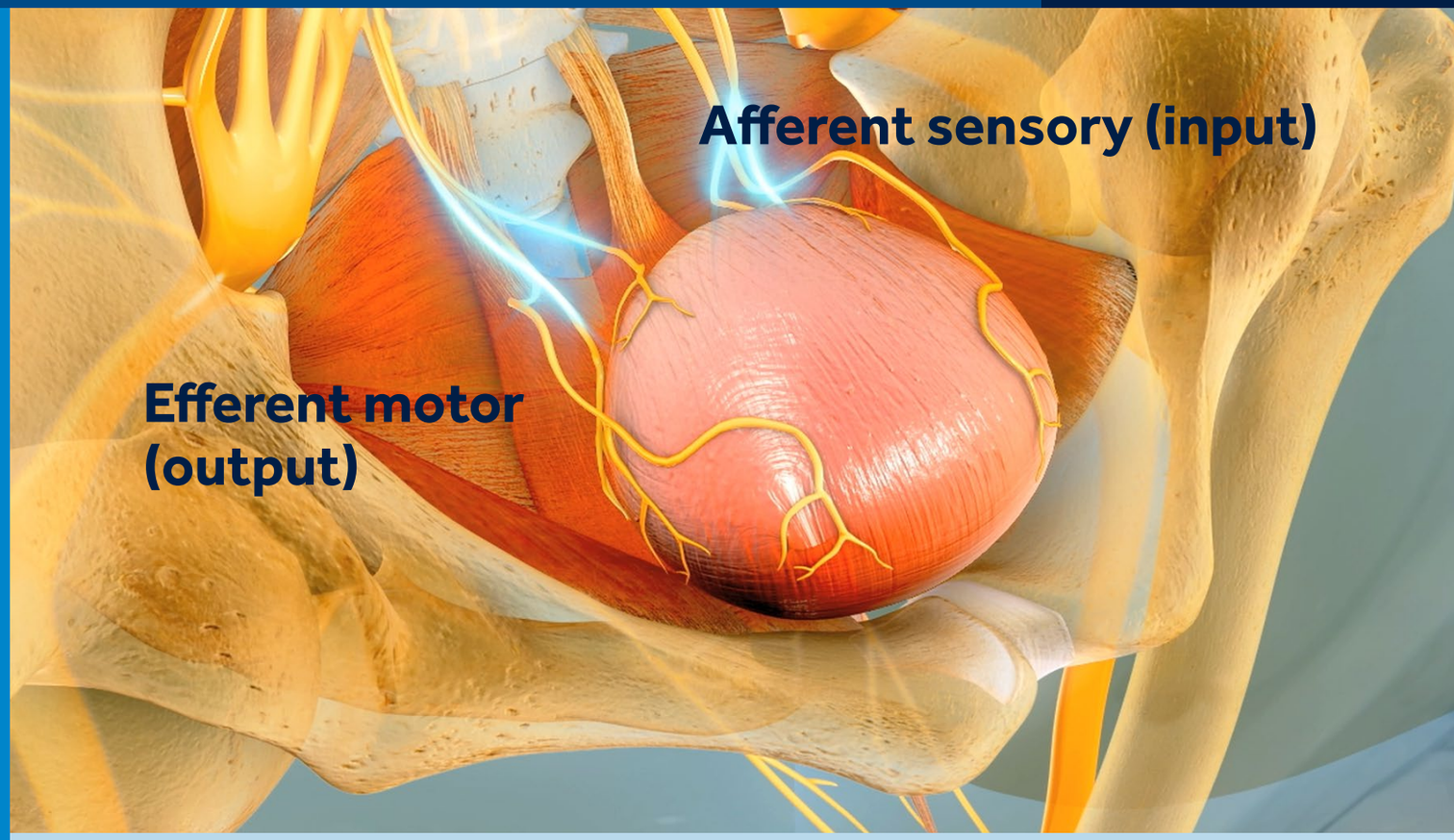
- Normal bladder function
- Dysfunction of afferent signaling in OAB
- How does SNM work
- InterStim™ implant

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]

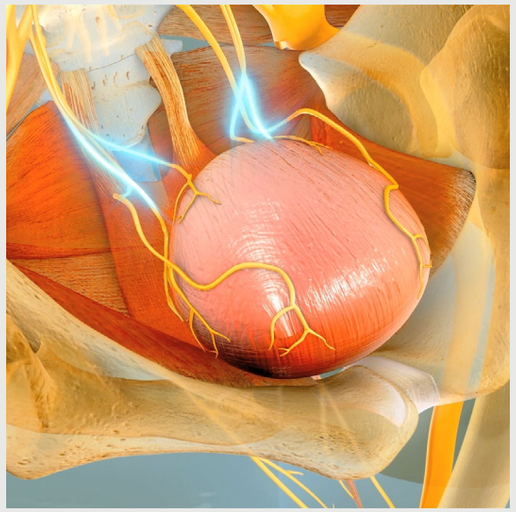


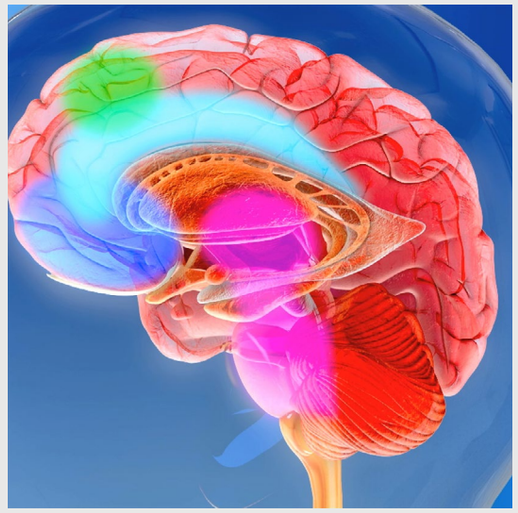
DYSFUNCTION OF AFFERENT SIGNALING IN OAB

OAB (Overactive Bladder) may be a result of increased abnormal afferent activity, resulting in increased efferent signaling.[15,18]

Consequently, voluntary control of micturition is compromised.[18]

Abnormal afferent activity





Increased efferent activity stimulates urgency

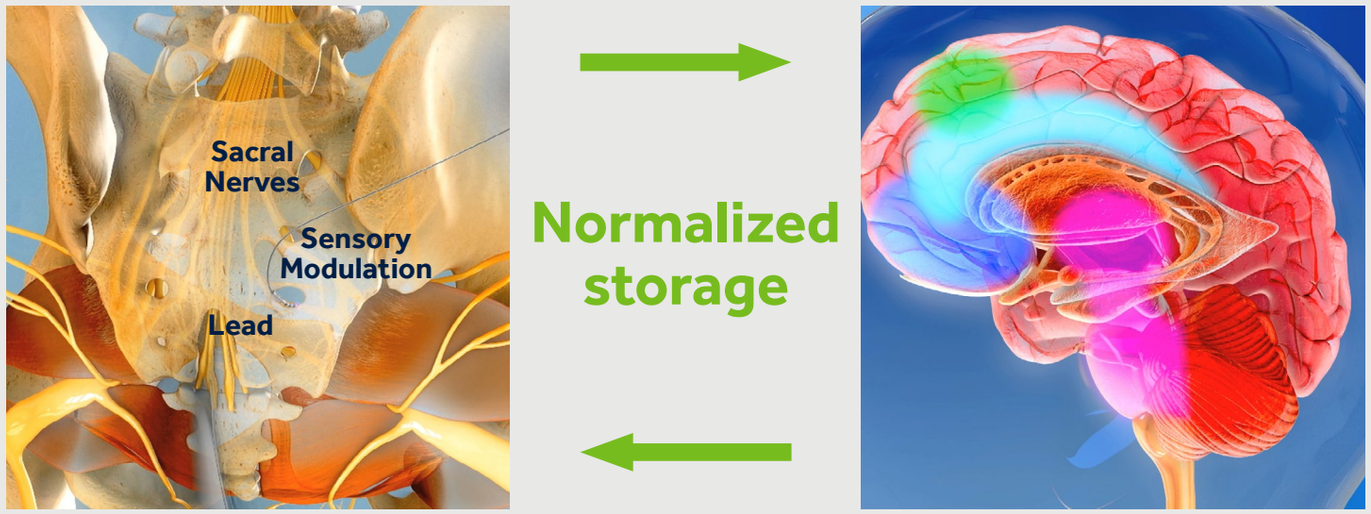
HOW DOES SNM WORK?

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 unihibited so as not to suppress voluntary voiding.[20]

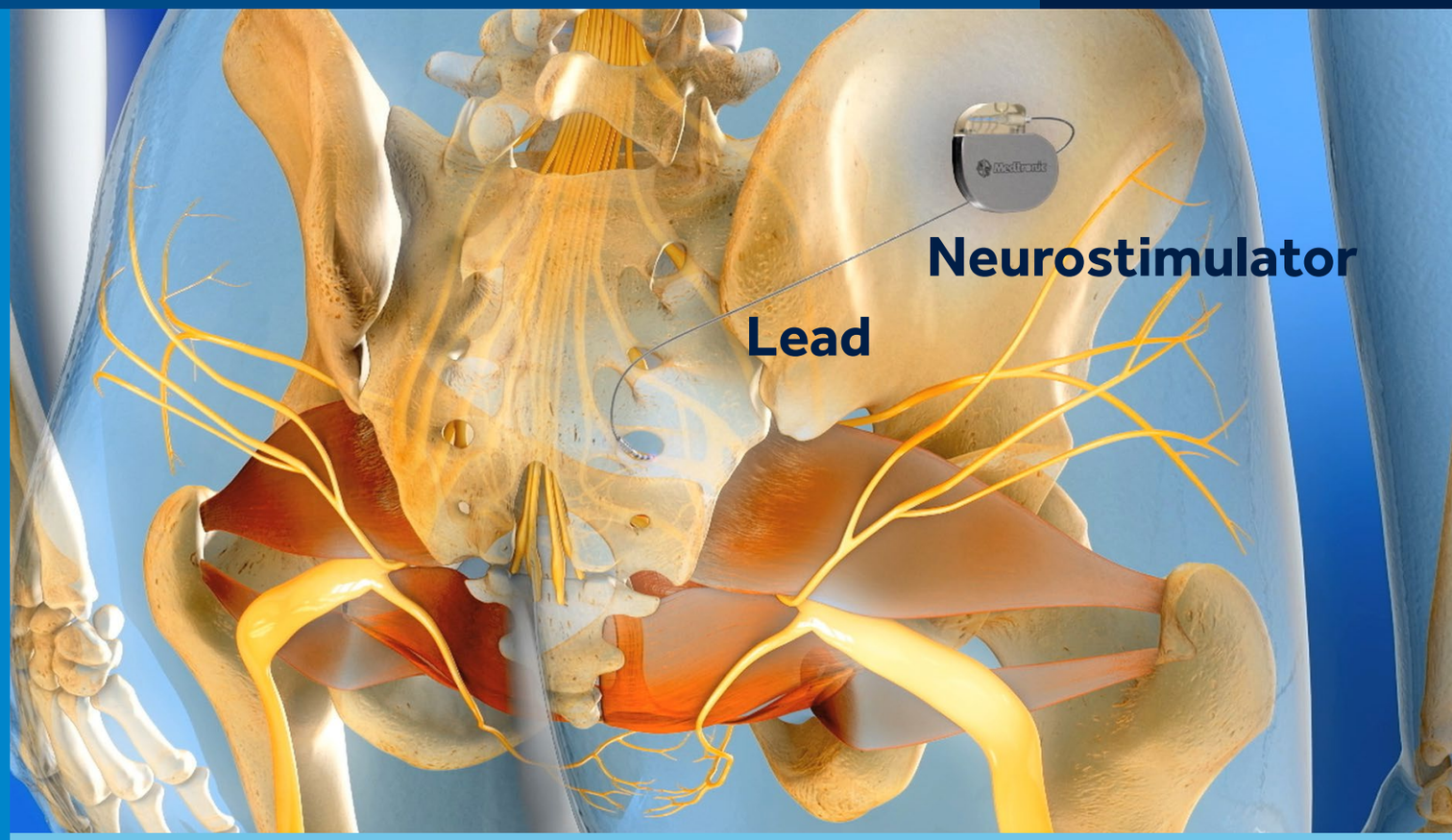
Unlike other therapies that target the bladder, bladder regulation occurs without directly influencing the bladder or sphincter muscles.[21]



INTERSTIM™ IMPLANT

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]



MEDTRONIC SACRAL NEUROMODULATION
MECHANISM OF ACTION

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[23].

A joint mechanism of action of SNM for bladder and bowel dysfunctions reflects expert opinion[24].

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

INSITE TRIAL
PATIENT SELECTION FOR OAB[25]

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

* The list is not exhaustive

Exclusion criteria

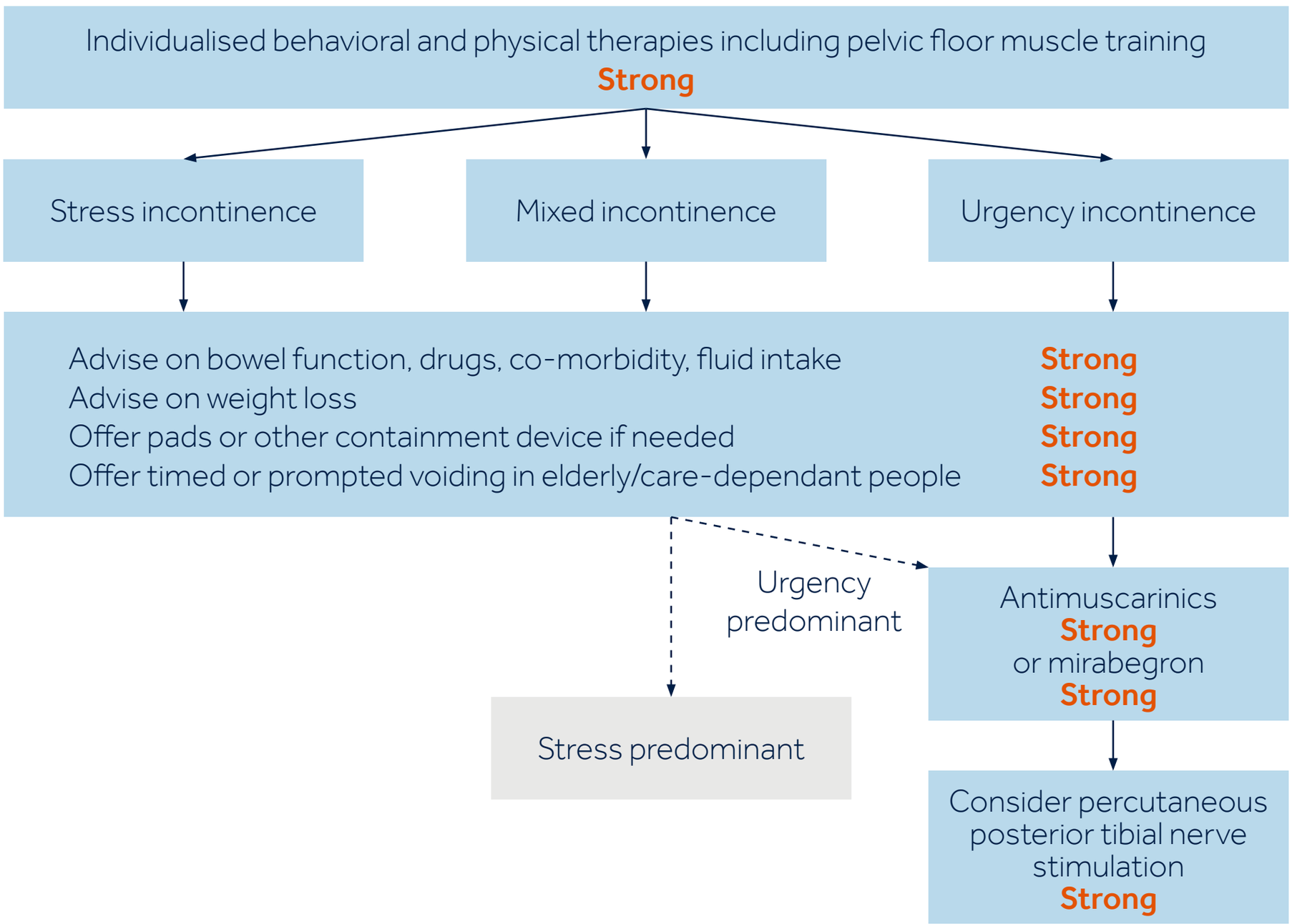
- Skin, orthopedic, or neurologic anatomical limitations that could prevent successful placement of an electrode
- Neurological diseases such as multiple sclerosis, clinically significant peripheral neuropathy, or complete spinal cord injury
- Knowledge of planned MRIs, diathermy
- Primary stress incontinence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

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[26,27,27b,27c].

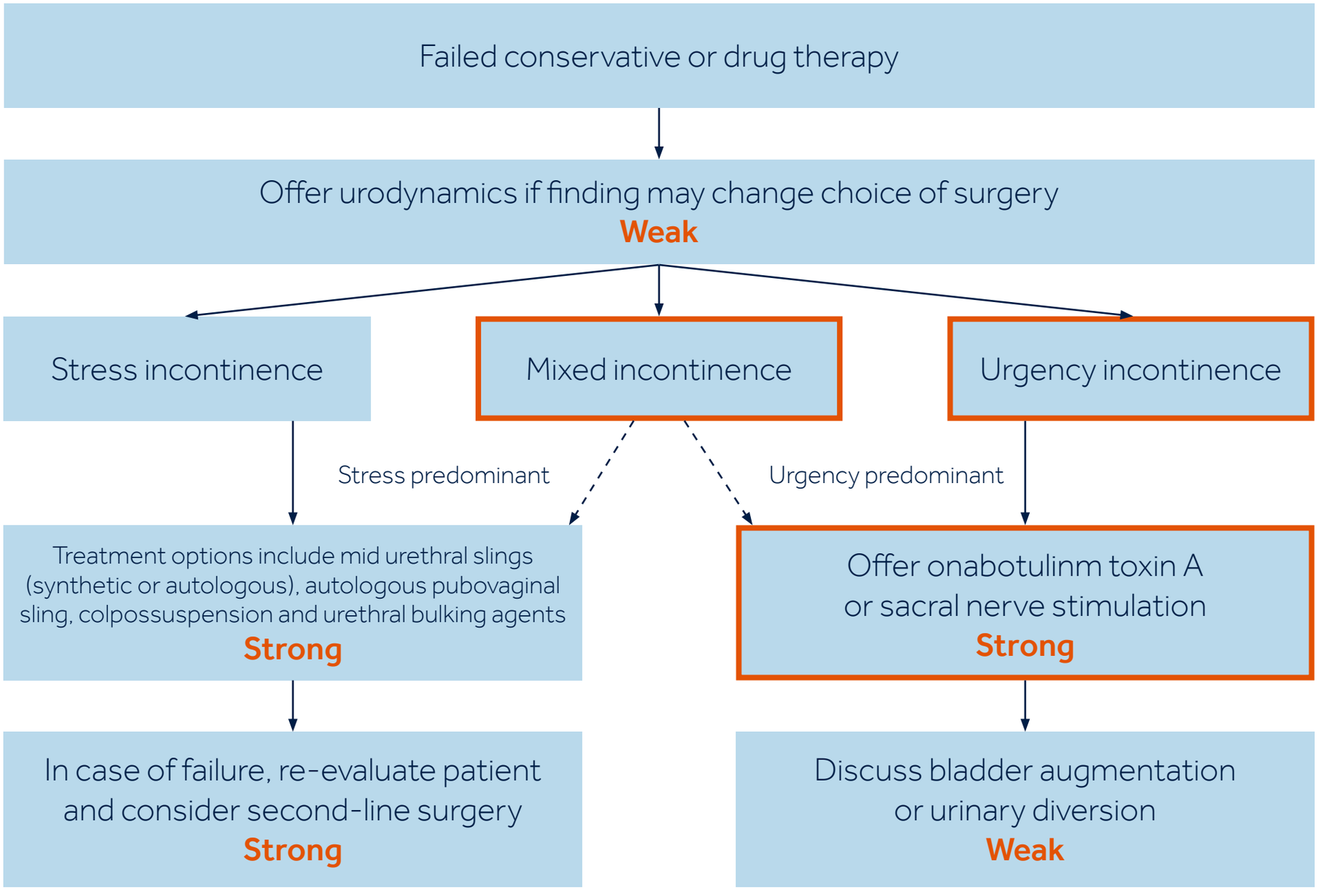
In the INSITE trial 53% of patients had not more than two OAB medications prior to SNM implant[25].

WOMEN WITH URINARY INCONTINENCE
EAU GUIDELINES 2018[29]



Conservative / Medical Therapies

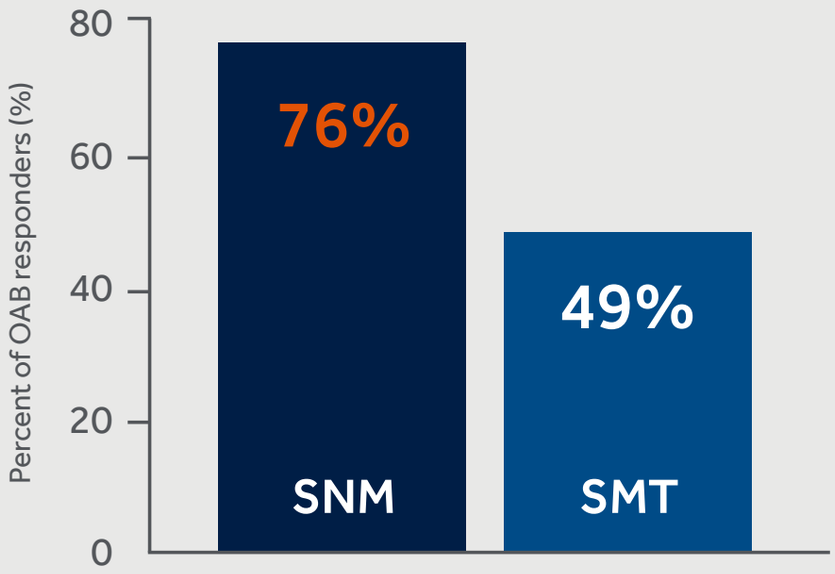
WOMEN WITH URINARY INCONTINENCE
EAU GUIDELINES 2018[29]



Failed Conservative / Medical Therapy:
Advanced Therapies

SUPERIOR EFFICACY VS. **MEDICATIONS AT 6 MONTHS**

Overall Symptom Improvement[30]



39%

Complete Continence

For subgroup of patients with UI at baseline, complete continence was achieved in 39% of SNM and 21% of SMT patients[30] (p=0.06)

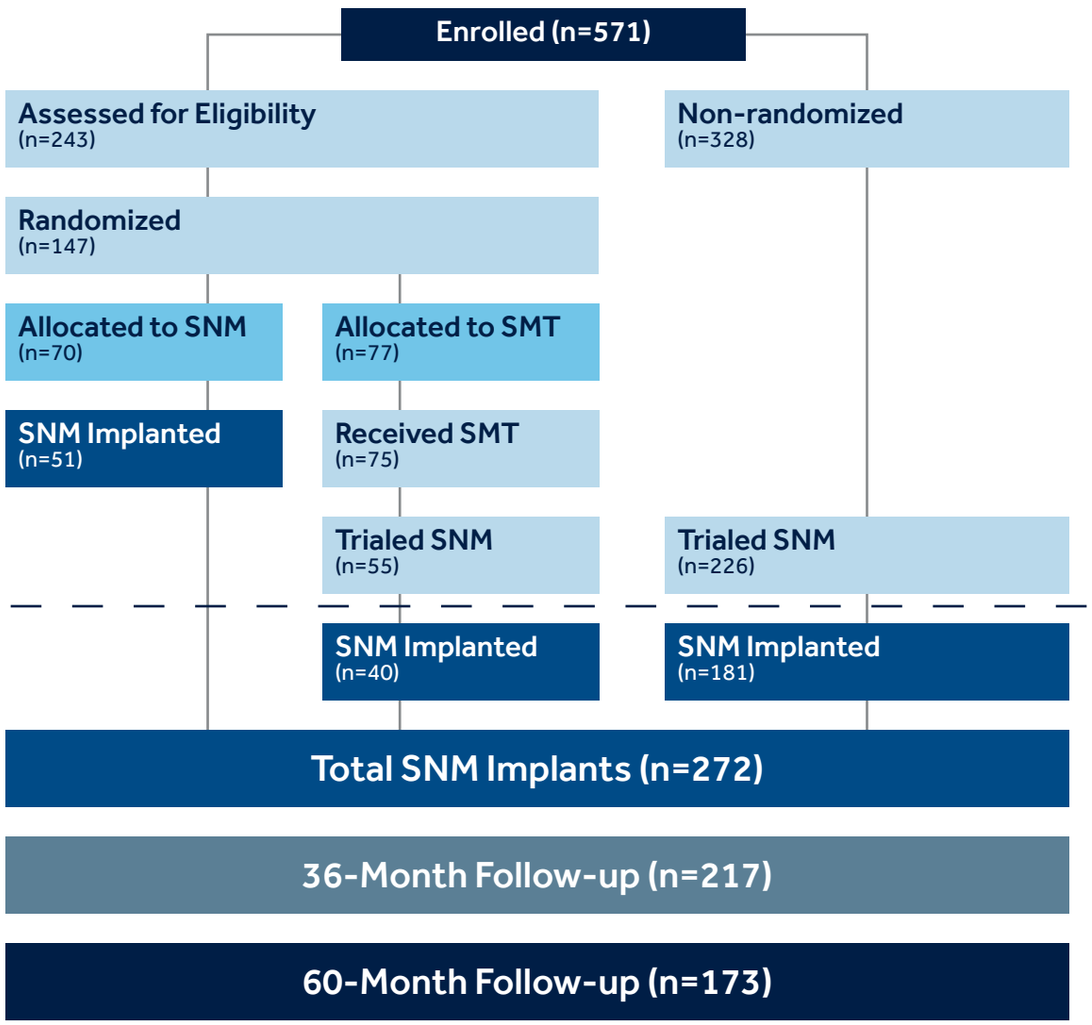
SMT Standard Medical Treatment

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.

Other specialized therapies

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

6-MONTH FOLLOW-UP

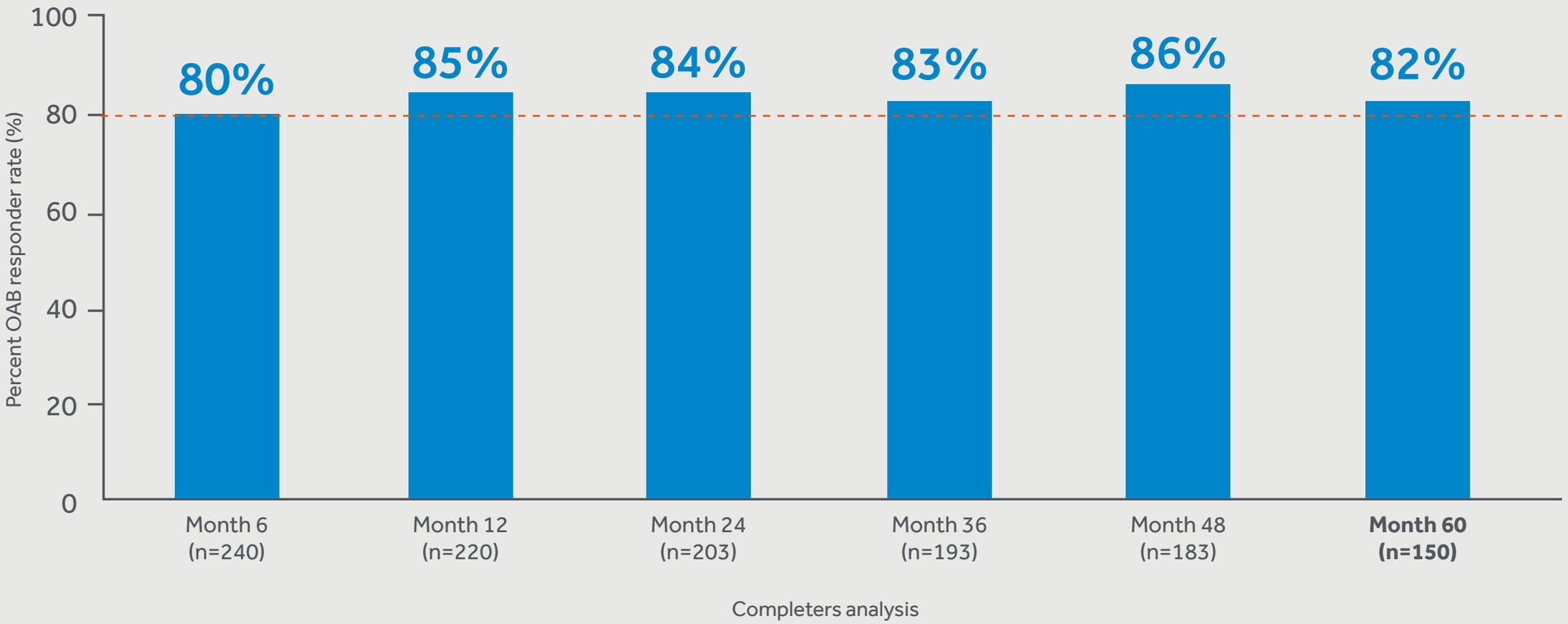
Phase 2: **Long Term**

SNM Long Term (5 Years)

Evaluation of the safety and efficacy of SNM to 5 years for all implanted patients

LONG-TERM OAB THERAPEUTIC SUCCESS[31]
PROVEN EFFICACY

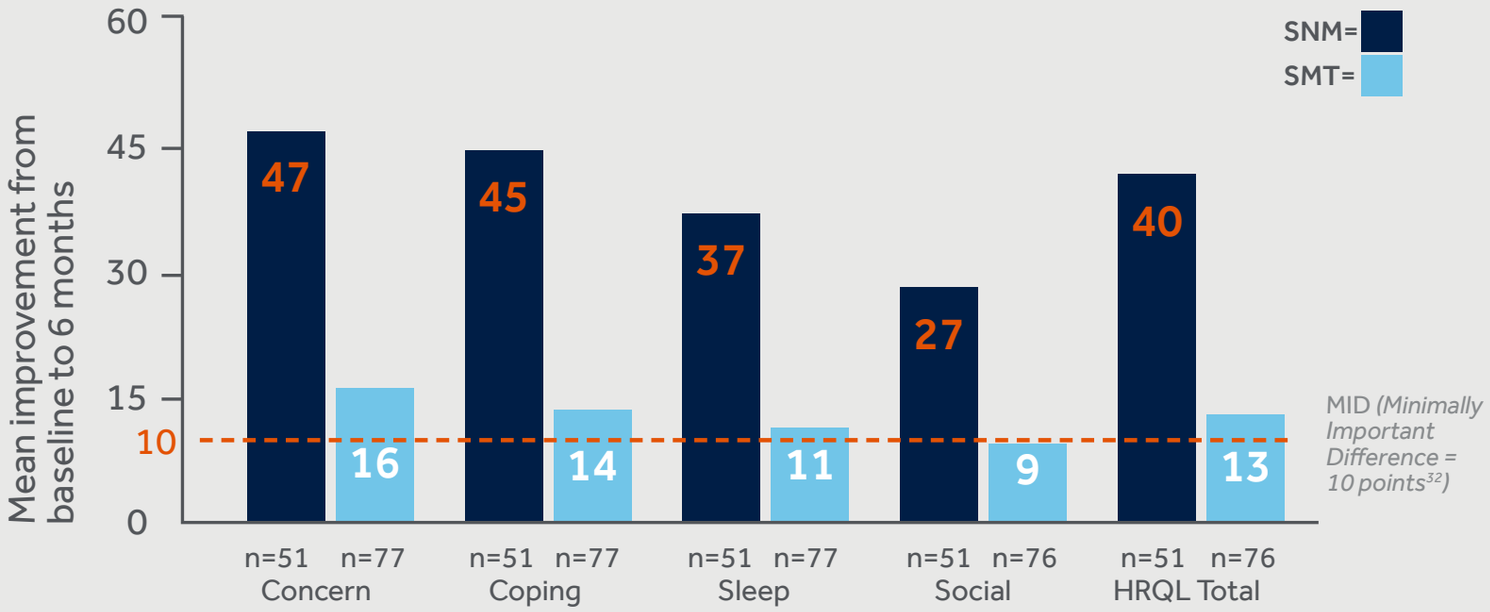
SNM Demonstrates Sustained Long-term Efficacy



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[30]



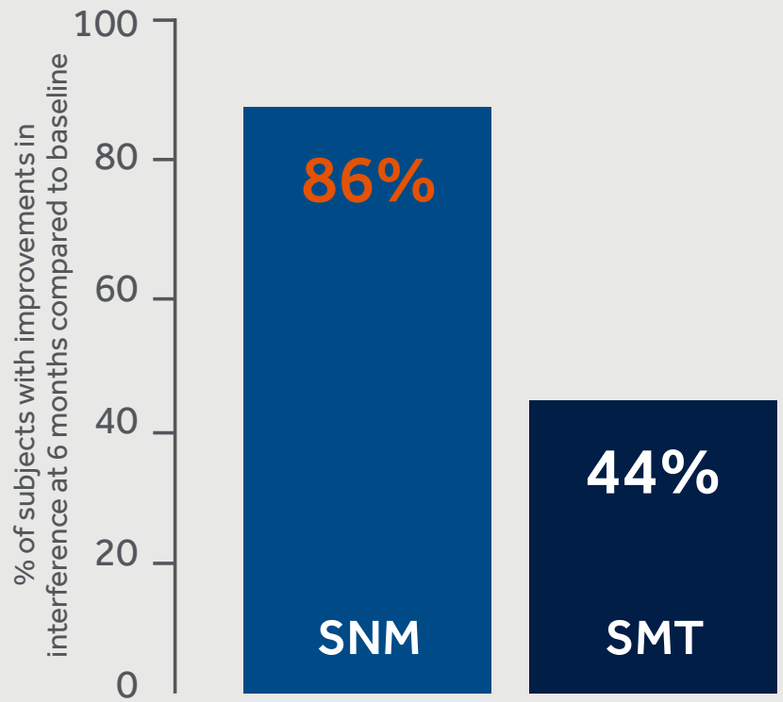
QOL was measured using the ICIQ-OABqol instrument

4x

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

Other specialized therapies

GREATER REDUCTION IN **DAILY LIFE INTERFERENCE**[30]



Subjects reporting improved or greatly improved symptom interference

≈2x

SNM subjects reported improved or greatly improved urinary sympton interference score compared to SMT at 6 months[30]

Other specialized therapies

CONCLUSIONS
SNM VERSUS SMT[30]

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.

SAFETY[31]

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.

Device related AEs are defined as events with an etiology of programming/stimulation, implanted system, surgery/ anesthesia, or incisional site/device tract.

SAFETY
AND REVISION RATES[33]

Complications with reoperation	Frequency in % (N=407)
Wound infection	2.2%
Back pain	1.0%
Pain in legs	1.2%
Pain at IPG site	8.8%
Lead migration	2.2%
Lead breakage	2.7%
Device malfunction	4.4%

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.

OTHER
SPECIALIZED THERAPIES

SNM (InterStim™)

BOTOX®

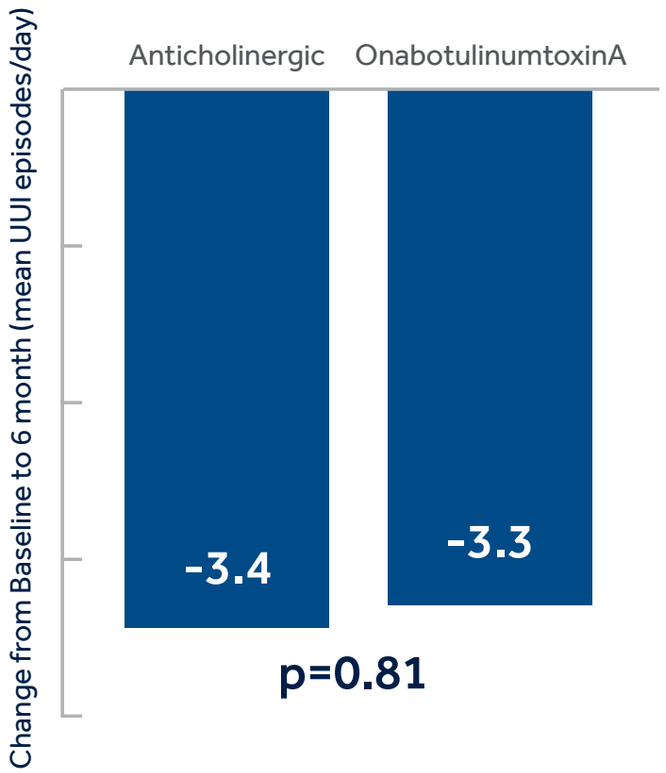
ABC Trial

Pannek

Mohee

Marcelissen

BOTOX (100 U) VS. MEDICATIONS
SIMILAR EFFICACY AND QOL IMPROVEMENTS[35]



	Anticholinergics	Botox	P Value
Urgency Incontinence			
Complete Resolution	**13%**	**27%**	**0.003**
Quality of Life			
OABq-SF Severity Scale	**-44.6**	**-44.1**	**0.87**
OABq-SF QOL Scale	**37.1**	**37.1**	**0.98**
PFDI-SF	**-43.7**	**-48.2**	**0.47**
PFIQ-SF	**-32.8**	**-33.9**	**0.88**

ABC Study Results at 6 months[35]

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

ABC

Pannek

Mohee

Marcelissen

BOTOX MAY LEAD TO IMPAIRED DETRUSOR **CONTRACTION STRENGTH**

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**

Pannek Study Results[36]

ABC

Pannek

Mohee

Marcelissen

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)

ABC

Pannek

Mohee

Marcelissen

Mohee Study Results[37]

BOTOX AND IDIOPATHIC OAB
HIGH DISCONTINUATION RATE[38]

70%

stopped at mean follow-up of 97 months (N=128 women)[38]

EAU

GUIDELINES

The discontinuation rate of Onabotulinum toxin A may be high[29].

Of those patients, who discontinued Botox

79%

stopped after first injecton[38]

19%

stopped after second injecton[38]

ROSETTA TRIAL[39]

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[29].

** Dose ranging trials have shown that 200U Botox is more effective than 100U[40,40b].

SNM VERSUS BOTOX®
PATIENT PREFERENCES

Author	Year	Ref	BTX : SNM preference ratio
Balchandra	2014	41	1.0 : 0.35
Beusterien	2016	42	1.0 : 1.0
Hashim	2015	43	0.26 : 1.0
Fontaine*	2017	44	1.0 : 1.0
Nobrega	2018	45	0.5 : 1.0

There appears to be a significant disparity between clinicians and patient preferences for treatment of refractory OAB[45].

* SNM (PNE)

REFERENCES

1. https://ec.europa.eu/eurostat/statistics-explained/index.php/Population_and_population_change_statistics
2. http://www.viewsoftheworld.net/?p=4201
3. Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S et al (2006) Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. Eur Urol 50(6):1306-1314

3b. Temml C, Heidler S, Ponholzer A, Madersbacher S. Prevalence of the overactive bladder syndrome by applying the International Continence Society definition. Eur Urol. 2005 Oct;48(4):622-7.

4. Irwin DE, Milsom I, Kopp Z, Abrams P; EPIC Study Group (2008) Symptom bother and health care-seeking behavior among individuals with overactive bladder. Eur Urol 53(5):1029-1037
5. Sussman D, Yehoshua A, Kowalski J, Lee W, Kish J, Chaudhari S, Murray B. Adherence and persistence of mirabegron and anticholinergic therapies in patients with overactive bladder: a real-world claims data analysis. Int J Clin Pract. 2017 Mar;71(3-4)
6. Chapple CR, Nazir J, Hakimi Z, Bowditch S, Fatoye F, Guelfucci F et al (2017) Persistence and Adherence with Mirabegron versus Antimuscarinic Agents in Patients with Overactive Bladder: A Retrospective Observational Study in UK Clinical Practice. Eur Urol 72(3):389-399
7. Wagg A, Franks B, Ramos B, Berner T. Persistence and adherence with the new beta-3 receptor agonist, mirabegron, versus antimuscarinics in overactive bladder: Early experience in Canada. Can Urol Assoc J. 2015 Sep-Oct;9(9-10):343-50

7b. Yu YF, Nichol MB, Yu AP, Ahn J. Persistence and adherence of medications for chronic overactive bladder/urinary incontinence in the California Medicaid program. Value Health. 2005;8(4):495-505.

8. Dumoulin C, Hay-Smith J, Frawley H, McClurg D, Alewijnse D, Bo K, Burgio K, Chen SY, Chiarelli P, Dean S, Hagen S, Herbert J, Mahfooza A, Mair F, Stark D, Van Kampen M; International Continence Society. 2014 consensus statement on improving pelvic floor muscle training adherence: International Continence Society 2011 State-of-the-Science Seminar. Neurourol Urodyn. 2015 Sep;34(7):600-5

8b. Sluijs EM, Kok GJ, van der Zee J. Correlates of exercise compliance in physical therapy. Phys Ther. 1993 Nov;73(11):771-82

9. Cardozo L, Lisec M, Millard R, van Vierssen Trip O, Kuzmin I, Drogendijk TE, Huang M, Ridder AM. Randomized, double-blind placebo controlled trial of the once daily antimuscarinic agent solifenacin succinate in patients with overactive bladder. J Urol. 2004 Nov;172(5 Pt 1):1919-24
10. Herschorn S, Barkin J, Castro-Diaz D, Frankel JM, Espuna-Pons M, Gousse AE, Stölzel M, Martin N, Gunther A, Van Kerrebroeck P. A phase III, randomized, double-blind, parallel-group, placebo-controlled, multicentre study to assess the efficacy and safety of the β_3 adrenoceptor agonist, mirabegron, in patients with symptoms of overactive bladder. Urology. 2013 Aug;82(2):313-20
11. Andersson KE. β3-receptor agonists for overactive bladder--new frontier or more of the same? Curr Urol Rep. 2013 Oct;14(5):435-41
12. Nitti VW, Chapple CR, Walters C, Blauwet MB, Herschorn S, Milsom I, Auerbach S, Radziszewski P. Safety and tolerability of the β3 -adrenoceptor agonist mirabegron, for the treatment of overactive bladder: results of a prospective pooled analysis of three 12-week randomised Phase III trials and of a 1-year randomised Phase III trial. Int J Clin Pract. 2014 Aug;68(8):972-85
13. Andersson KE. Mechanisms of Disease: central nervous system involvement in overactive bladder syndrome. Nat Clin Pract Urol. 2004 Dec;1(2):103-8
14. Chancellor MB, Chartier-Kastler EJ. Principles of Sacral Nerve Stimulation (SNS) for the Treatment of Bladder and Urethral Sphincter Dysfunctions. Neuromodulation. 2000 Jan;3(1):16-26

REFERENCES

15. Gillespie JI, van Koeveringe GA, de Wachter SG, de Vente J (2009) On the origins of the sensory output from the bladder: the concept of afferent noise. BJU Int 103(10):1324-1333
16. Fowler CJ, Griffiths D, de Groat WC. The neural control of micturition. Nat Rev Neurosci. 2008 Jun;9(6):453-66
17. de Groat WC. Integrative control of the lower urinary tract: preclinical perspective. Br J Pharmacol. 2006 Feb;147 Suppl 2:S25-40
18. Leng WW, Morrisroe SN. Sacral nerve stimulation for the overactive bladder. Urol Clin North Am. 2006 Nov;33(4):491-501
19. Elkelini MS, Abuzgaya A, Hassouna MM (2010) Mechanisms of action of sacral neuromodulation. Int Urogynecol J 21 Suppl 2:S439-446
20. Leng WW, Chancellor MB. How sacral nerve stimulation neuromodulation works. Urol Clin North Am. 2005 Feb;32(1):11-8
21. van der Pal F, Heesakkers JP, Bemelmans BL. Current opinion on the working mechanisms of neuromodulation in the treatment of lower urinary tract dysfunction. Curr Opin Urol. 2006 Jul;16(4):261-7
22. Buback D. The use of neuromodulation for treatment of urinary incontinence. AORN J. 2001 Jan;73(1):176-190
23. Blok BF, Groen J, Bosch JL, Veltman DJ, Lammertsma AA (2006) Different brain effects during chronic and acute sacral neuromodulation in urge incontinent patients with implanted neurostimulators. BJU Int 98(6):1238-1243
24. Jones J, Van de Putte D, De Ridder D, Knowles C, O'Connell R, Nelson D et al (2016) A Joint Mechanism of Action for Sacral Neuromodulation for Bladder and Bowel Dysfunction? Urology 97:13-19
25. Noblett K, Siegel S, Mangel J, Griebling TL, Sutherland SE, Bird ET, Comiter C, Culkin D, Bennett J, Zylstra S, Kan F, Berg KC. Results of a prospective, multicenter study evaluating quality of life, safety, and efficacy of sacral neuromodulation at twelve months in subjects with symptoms of overactive bladder. Neurourol Urodyn. 2016 Feb;35(2):246-51
26. Phé V, de Wachter S, Rouprêt M, Chartier-Kastler E. How to define a refractory idiopathic overactive bladder? Neurourol Urodyn. 2015 Jan;34(1):2-11
27. Wong J, Tincello DG. Management of refractory overactive bladder. The Obstetrician & Gynaecologist 2016;18:173–81. DOI: 10.1111/tog.12265

27b. Incontinence : 4th International Consultation on Incontinence, Paris, July 5-8, 2008. Ed: Paul Abrams, Linda Cardozo, Saad Khoury, Alan Wein

27c. Smith A, Bevan D, Douglas HR, James D. Management of urinary incontinence in women: summary of updated NICE guidance. BMJ. 2013 Sep 10;347:f5170.

28. Goldman HB, Lloyd JC, Noblett KL, Carey MP, Castaño Botero JC, Gajewski JB et al (2018) International Continence Society best practice statement for use of sacral neuromodulation. Neurourol Urodyn Apr 11. doi: 10.1002/nau.23515. [Epub ahead of print]
29. F.C. Burkhard (Chair), J.L.H.R. Bosch, F. Cruz, G.E. Lemack, A.K. Nambiar, N. Thiruchelvam, A. Tubaro. EAU Guidelines. Edn. presented at the EAU Annual Congress Copenhagen 2018. ISBN 978-94-92671-01-1. http://uroweb.org/guideline/urinary-incontinence/#4
30. Siegel S, Noblett K, Mangel J, Griebling TL, Sutherland SE, Bird ET, Comiter C, Culkin D, Bennett J, Zylstra S, Berg KC, Kan F, Irwin CP. Results of a prospective, randomized, multicenter study evaluating sacral neuromodulation with InterStim therapy compared to standard medical therapy at 6-months in subjects with mild symptoms of overactive bladder. Neurourol Urodyn. 2015 Mar;34(3):224-30
31. Siegel S, Noblett K, Mangel J, Bennett J, Griebling TL, Sutherland SE et al (2018) Five-Year Followup Results of a Prospective, Multicenter Study of Patients with Overactive Bladder Treated with Sacral Neuromodulation. J Urol 199(1):229-236

REFERENCES

32. Coyne KS, Matza LS, Thompson CL, Kopp ZS, Khullar V. Determining the importance of change in the overactive bladder questionnaire. J Urol. 2006 Aug;176(2):627-32
33. Peters KM, Killinger KA, Gilleran JP, Bartley J, Wolfert C, Boura JA (2017) Predictors of reoperation after sacral neuromodulation: A single institution evaluation of over 400 patients. Neurourol Urodyn 36(2):354-359
34. Pettit P. Current opinion: complications and troubleshooting of sacral neuromodulation. Int Urogynecol J. 2010 Dec;21 Suppl 2:S491-6
35. Visco AG, Brubaker L, Richter HE, Nygaard I, Paraiso MF, Menefee SA, Schaffer J, Lowder J, Khandwala S, Sirls L, Spino C, Nolen TL, Wallace D, Meikle SF; Pelvic Floor Disorders Network. Anticholinergic therapy vs. onabotulinumtoxina for urgency urinary incontinence. N Engl J Med. 2012 Nov 8;367(19):1803-13
36. Pannek J, Göcking K, Bersch U. Long-term effects of repeated intradetrusor botulinum neurotoxin A injections on detrusor function in patients with neurogenic bladder dysfunction. BJU Int. 2009 Nov;104(9):1246-50
37. Mohee A, Khan A, Harris N, Eardley I. Long-term outcome of the use of intravesical botulinum toxin for the treatment of overactive bladder (OAB). BJU Int. 2013 Jan;111(1):106-13
38. Marcelissen TA, Rahnama'i MS, Snijkers A, Schurch B, De Vries P. Long-term follow-up of intravesical botulinum toxin-A injections in women with idiopathic overactive bladder symptoms. World J Urol. 2017 Feb;35(2):307-311
39. Amundsen CL, Komesu YM, Chermansky C, Gregory WT, Myers DL, Honeycutt EF et al Two-Year Outcomes of Sacral Neuromodulation Versus OnabotulinumtoxinA for Refractory Urgency Urinary Incontinence: A Randomized Trial. Eur Urol 74(1):66-73
40. Dmochowski R, Chapple C, Nitti VW, Chancellor M, Everaert K, Thompson C, Daniell G, Zhou J, Haag-Molkenteller C. Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: a double-blind, placebo controlled, randomized, dose ranging trial. J Urol. 2010 Dec;184(6):2416-22

40b. Mangera A, Apostolidis A, Andersson KE, Dasgupta P, Giannantoni A, Roehrborn C, Novara G, Chapple C. An updated systematic review and statistical comparison of standardised mean outcomes for the use of botulinum toxin in the management of lower urinary tract disorders. Eur Urol. 2014 May;65(5):981-90

41. Balchandra P, Rogerson L. Women's perspective: intra-detrusor botox versus sacral neuromodulation for overactive bladder symptoms after unsuccessful anticholinergic treatment. Int Urogynecol J. 2014 Aug;25(8):1059-64
42. Beusterien K, Kennelly MJ, Bridges JF, Amos K, Williams MJ, Vasavada S. Use of best-worst scaling to assess patient perceptions of treatments for refractory overactive bladder. Neurourol Urodyn. 2016 Nov;35(8):1028-1033
43. Hashim H, Beusterien K, Bridges JF, Amos K, Cardozo L. Patient preferences for treating refractory overactive bladder in the UK. Int Urol Nephrol. 2015 Oct;47(10):1619-27
44. Fontaine CL, Rudd I, Pakzad M, Hamid R, Ockrim JL, Greenwell TJ (2017) Patient treatment preferences for symptomatic refractory urodynamic idiopathic detrusor overactivity. Urol Ann 9:249-252
45. Nobrega R, Greenwell TJ, Pickard R, Ockrim JL, Harding CK. Sacral nerve stimulation versus intravesical botulinum toxin injections for medically refractory overactive bladder: A contemporary review of UK treatment from both clinician and patients' perspectives. J Clin Urol 2018 11(5):339–344
46. Van Ophoven A. Re: Management of device-related complications after sacral neuromodulation for lower urinary tract disorders in women: a single center experience: Tilemachos Kavvadias, Markus Huebner, Sara Yvonne Brucker, Christl Reisenauer. Arch Gynecol Obstet. 2017 Jul;296(1):129-130

REGULATORY **STATEMENT**

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.

See the device manual for detailed information regarding the instructions for use, the implant procedure, indications, contraindications, warnings, precautions, and potential adverse events. For further information, contact your local Medtronic representative and/or consult the Medtronic website at www.medtronic.com

www.medtronic.com/manuals

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.

Medtronic

Medtronic International Trading
Sarl
Route du Molliau 31
Case postale
1131 Tolochenaz
Switzerland
Tel: +41 (0) 21 802 70 00
Fax: +41 (0) 21 802 79 00

medtronic.eu

Medtronic Limited
Building 9
Croxley Park
Hatters Lane
Watford, Hertfordshire
WD18 8WW
Tel: +44 (0) 1923 212213
Fax: +44 (0) 1923 241004

medtronic.co.uk