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## Neuromodulation in 2017: PTNS, InterStim & the Future

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## Disclosures

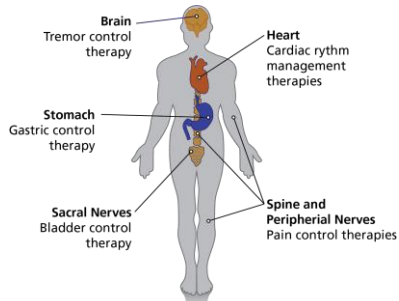
- Grant/Research Study and Consultant  
–Allergan, Astellas, Boston Scientific, Coloplast, Ipsen
- Grant/Research Study  
–Amphora, Contura, Cook Myosite, Taris
- Consultant  
–Cogentix



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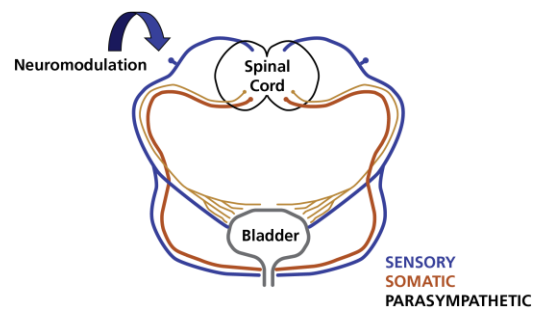
## Neuromodulation

- Stimulation of nerves (peripheral or central) intended to modulate reflex activity



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## Neuromodulation

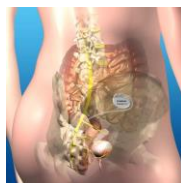


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## SACRAL NEUROMODULATION

### How it works:

- Focuses mild electrical pulses on the nerves that control the pelvic floor and lower urinary tract<sup>1,2\*</sup>
- Offers control of symptoms through direct modulation of the nerve activity
- Different from oral medications, which target the muscular component of bladder control<sup>1,2\*</sup>



1. Griebeling TL. Neuromodulation: mechanisms of action. In: Kessler K, Dmochowski R, eds. *The Overactive Bladder: Evolution and Management*. London, England: Informa UK Ltd; 2007:293-302.

2. Long WW, et al. How sacral nerve stimulation works. *Urol Clin N Am*. 2005;32:11-18.

\* While the precise mechanism of action of Sacral Neuromodulation has not been fully established, efficacy has been proven in clinical studies.



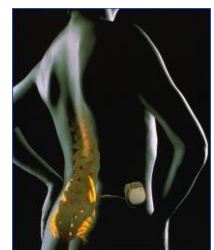
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## Sacral Nerve Stimulation

Indicated for the treatment of:

- Urinary urge incontinence (9/97)
- Urgency, Frequency
- Urinary Retention (4/99)
- Fecal Incontinence (3/15)

FDA approved for > 18 years for urinary indications



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## Overview of SNS Therapy

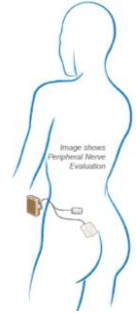


1. Tined lead is placed parallel to the sacral (S2, S3, or S4) nerve
2. Implantable neurostimulator generates mild electrical pulses that are delivered through the lead electrodes
3. Clinical and patient programmers are used to set the parameters of the electrical pulses



## Temporary Lead Test (Basic Evaluation): In-Office Test

- A temporary lead is placed during simple in-office procedure and connected to an external stimulator
- The patient and MD assess therapy efforts for 3-7 days
- If successful, patient may proceed directly to long-term lead and device implant through an outpatient procedure
- If test is inconclusive or unsuccessful, the chronic lead test (advanced procedure) is recommended



## Interstim Peripheral Nerve Evaluation (PNE)

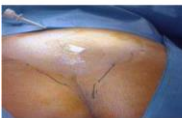


## Look for Motor and Sensory Responses

Nerve Innervation	Response		Sensation
	Pelvic Floor	Foot/calf/leg	
S2 Primary somatic contributor of pudendal nerve for external sphincter, leg, foot	"clump" of anal sphincter	Leg/hip rotation, plantar flexion of entire foot, contraction of calf	Contraction of base of penis, vagina
S3 Virtually all pelvic autonomic functions and striated muscle (levator ani)	"bellows"*** of perineum	Plantar flexion of great toe, occasionally other toes	Pulling in rectum, extending forward to scrotum or labia
S4 Pelvic autonomic and somatic. No leg or foot	"bellows"***	No lower extremity motor stimulation	Pulling in rectum only

\* Clump: contraction of anal sphincter and, in males, retraction of base of penis. Move buttocks aside and look for anterior/posterior shortening of the perineal structures.  
 \*\*\* Bellows: lifting and dropping of pelvic floor. Look for deepening and flattening of buttock groove.

## Peripheral Nerve Evaluation (PNE) Basic Evaluation



## Benefits of Temporary Lead (Basic Evaluation)

- Verifies neural integrity
- Allows the patient to feel stimulation
- Provides an opportunity to assess the viability of SNS therapy
- Helps the physician and patient make an informed choice about the long-term therapeutic value of the SNS therapy



## Interpretation of Success

### > 50 % improvement

#### Urge Incontinence

- Number of leaking episodes
- Severity of leaking episodes
- Number of pads replaced per day

#### Urgency-Frequency

- Number of voids/day
- Volume voided /void
- Degree of urgency prior to void



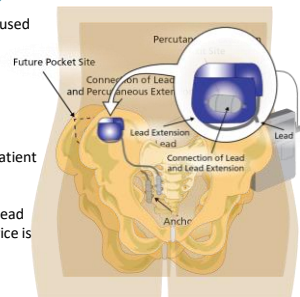
## Problems with PNE (Basic Evaluation)

- Lead migration
- Equivocal patient response
- Some patients not tolerate temporary lead test - anxiety
- Reliability of temporary lead in same location as implant
- Difficult placement without fluoroscopy



## Chronic Lead Test (Advanced Evaluation) Staged Test

- The staged implant procedure is used when the percutaneous test stimulation is inconclusive
- Utilizes a tined lead to reduce migration
- Placed in the OR during an out-patient procedure
- With successful test results, the lead remains in place and the IPG device is implanted

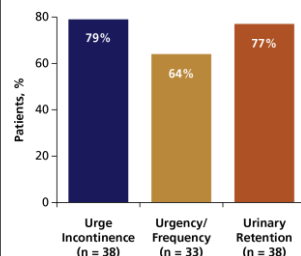


IPG: implantable pulse generator.  
Danesghari F. *Int Braz J Urol.* 2006;32:262-272.

## Benefits of Advanced Evaluation

- Secure fixation - eliminate lead migration
- Quadrapolar lead vs unipolar lead (more programmable options)
- Longer test period duration available
- Beneficial in equivocal temporary lead cases
- Avoids temporary lead and chronic lead differences in response

## 12-Month Clinical Success



InterStim Therapy Clinical Summary Insert, 2006.

- **79% of urge incontinence patients achieved clinical success**
  - 45% remained completely dry
  - Additional 34% experienced ≥50% reduction in leaking
- **64% of urge-frequency patients achieved clinical success**
  - 31% returned to normal voids (4-7 voids/day)
  - Additional 33% experienced ≥50% reduction in number of voids
- **77% of urinary retention patients achieved clinical success**
  - 61% eliminated use of catheters
  - Additional 16% experienced ≥50% reduction in catheterized urine volume

## 5-Year Results of SNS Therapy for Urinary Voiding Dysfunction: Prospective Worldwide Study

- 68% urge incontinent (UI) patients achieved ≥50% reduction in leaks/day
- 56% of urgency-frequency (UF) patients achieved ≥ 50% increase in volume voided/void and improved degree of urgency
- 71% of urinary retention patients achieved ≥ 50% reduction in volume/catheterization

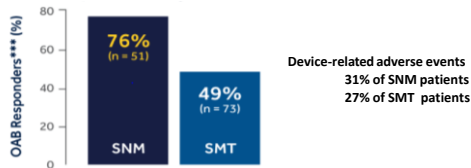
Clinical Success Rates for 5 Years After Implantation by Indication and Visit

Outcome	1-Year	2-Year	3-Year	4-Year	5-Year
<b>UI, % (no/total no)</b>					
Leaks/day	51 (49/96)	60 (58/96)	59 (57/96)	58 (56/96)	58 (56/96)
Heavy leaks/day	50 (40/80)	61 (48/79)	67 (52/78)	68 (53/78)	68 (53/78)
Pads/day	51 (45/88)	60 (53/89)	54 (48/89)	58 (50/87)	61 (53/87)
<b>UF, % (no/total no)</b>					
Voids/day	40 (10/25)	48 (12/25)	52 (13/25)	48 (12/25)	40 (10/25)
Volume/void	60 (15/25)	68 (17/25)	64 (16/25)	56 (14/25)	56 (14/25)
Degree of urgency	68 (17/25)	72 (18/25)	68 (17/25)	60 (15/25)	56 (14/25)
<b>Retention, % (no/total no)</b>					
Catheters/day	68 (21/31)	65 (20/31)	68 (21/31)	68 (21/31)	58 (18/31)
Volume/catheter	68 (21/31)	77 (24/31)	77 (24/31)	71 (22/31)	71 (21/31)

Van Kerrebroeck PE et al. *J. Urol.* 2007;178(5):2029-2034.

## INSITE TRIAL – SNM vs SMT

InSite study results compare SNM delivered by the InterStim™ system to standard medical therapy (SMT) in patients with mild symptoms of OAB:



\* Anticholinergic/antimuscarinic

\*\* Numbers reflect all treated patients, defined as subjects with diary data at baseline and 6 months (n=502) based on test results, which include all randomized subjects, are 61% for SNM and 42% for SMT (p=0.02).

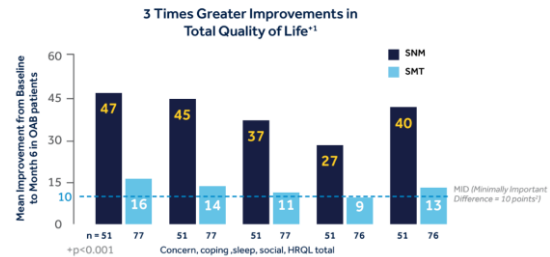
\*\*\* OAB response was defined as either 25% improvement in micturition frequency for 10 subjects or 25% improvement in voiding or a return to normal voiding frequency (≤6 voids/day) for 10 subjects.

1. Siegel, B., Hobbes, K., Mangel, J., et al. 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. 2015. *Neurology*. 34: 228-235. doi: 10.1002/wnu.22544



## INSITE TRIAL – SNM vs SMT

### QUALITY OF LIFE

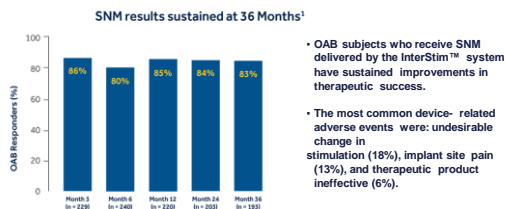


Siegel, B., Hobbes, K., Mangel, J., et al. Results of a prospective, randomized, multicenter study evaluating sacral neuromodulation with InterStim™ therapy compared to standard medical therapy at 6 months in subjects with mild symptoms of overactive bladder. 2015. *Neurology*. 34: 228-235. doi: 10.1002/wnu.22544



## INSITE TRIAL – SNM vs SMT

### 36 MONTHS OAB RESPONSE



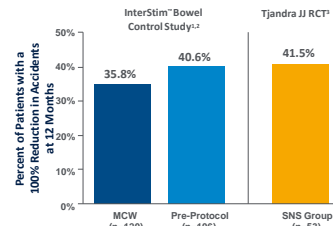
OAB therapeutic success rate over time. Analyses included subjects with diary data at baseline and follow-up visits (3, 6, 12, 24, and 36 months). OAB response was defined as either 25% improvement in micturition frequency for 10 subjects or 25% improvement in voiding or a return to normal voiding frequency (≤6 voids/day) for 10 subjects.

1. Siegel, B., et al. Three Year Follow-Up Results of a Prospective, Multicenter Study in Overactive Bladder Subjects Treated with Sacral Neuromodulation. *Urology*. 2016;94:57-63.



## 12 MONTHS - RESOLUTION OF FECAL

### Complete Resolution of FI with Sacral Neuromodulation<sup>1,2</sup>



1. Wexner SD, Collier JA, Desrosiers G, et al. Sacral nerve stimulation for fecal incontinence: results of a 120-patient prospective multicenter study. *Ann Surg*. 2010;251(3):441-449.

2. Medtronic Clinical Summary. Medtronic InterStim™ Therapy. 2014.

3. Tjandra JJ, Chan MY, Tish CH, et al. Sacral nerve stimulation is more effective than optimal medical therapy for severe fecal incontinence: a randomized, controlled study. *Dis Colon Rectum*. 2000;43(5):646-652.

nsim

## UNDERSTAND THE RISKS

The most common adverse events experienced during clinical studies include:

### Bladder Control<sup>1</sup>

- Pain at implant site
- New pain
- Lead migration
- Infection
- Technical or device problems
- Adverse change in bowel or voiding function
- Undesirable stimulation or sensations

### Bowel Control<sup>1,2</sup>

- Pain at implant site
- Paresthesia
- Infection
- Adverse change in bowel or voiding function
- Undesirable stimulation or sensations

Any of these may require additional surgery or cause return of symptoms

1. Medtronic Clinical Summary. Medtronic InterStim™ Therapy. 2014.

2. Wexner SD, Collier JA, Desrosiers G, et al. Sacral nerve stimulation for fecal incontinence: results of a 120-patient prospective

nsim

## Predictors of Success for SNS

- Decreased pad weight during test stimulation
- Younger age
- Less than 3 chronic conditions (eg, diabetes, hypertension, depression, arthritis)
- No neurologic condition (eg, MS, Parkinson's disease, CVA)

CVA: cerebrovascular accident; MS: multiple sclerosis.

Amundsen CL et al. *Urology*. 2005;66:746-750. Foster RT Sr et al. *Neurosci Urology*. 2007;26:213-217.



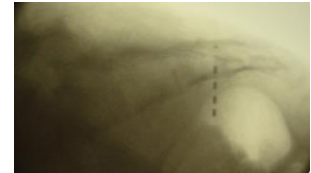
## Critical Techniques for Optimizing SNM Success

5/22/2017



After an initially unsuccessful attempt to treat an appropriately selected OAB patient with an InterStim implant, your next step is likely:

- A. Remove the devices
- B. Revise the sacral lead
- C. Switch to Botulinum toxin
- D. Other



## Lead Placement

Important for:

- Efficacy
- Programming options
- May influence longevity of device

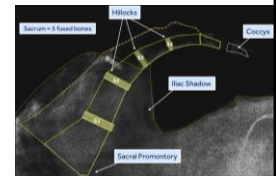


## Identify Bony Landmarks

AP View



Lateral View



S3 nerve expected to:

- Exit the foramen on the anterior surface of the sacrum just above the hillock
- Follow a medial to lateral path

## Mark Medical Edges of Sacral Foramina in AP View



Start with patient in prone position  
Use AP fluoro to define medial edges of foramina  
Mark the S3 medial edge



## Determining S3 in Lateral View

Flouro perpendicular

S2 at sacro-iliac joint

S3 first below sacro-iliac joint



Images provided by Steven Siegel, MD

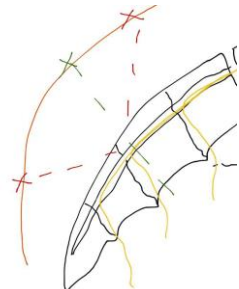
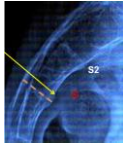
## Identifying Skin Entry Point – Lateral View

In lateral fluoro view, use snap to mark skin

Imaginary line from mark comes out above hillock, parallels bone seam



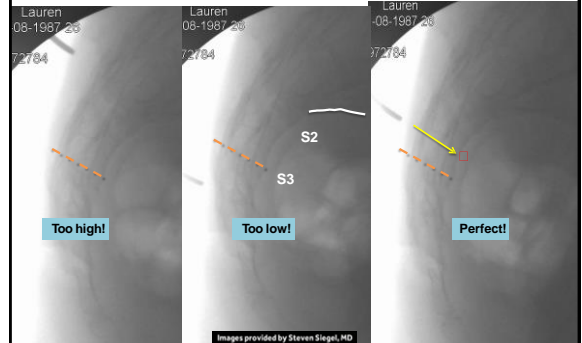
Images provided by Steven Siegel, MD



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## Determining Skin Entry Point

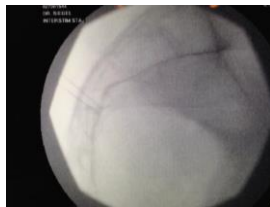
Use of lateral fluoro with snap on skin moved up and down along medial edge of foramen



Images provided by Steven Siegel, MD

## Find Lowest “Opening Threshold”

- Parallel fusion plane
- High and Medial as possible
- Test only at anterior margin
- No trolling!
- Aim for response  $\leq 1.0$  V

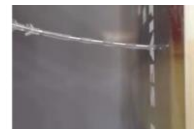


Images provided by Steven Siegel, MD



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## Curved Vs. Stiff Stylet



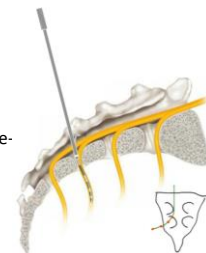
Jacobs, et al. NeuroUrol. Urod. 9999:1-4, 2013



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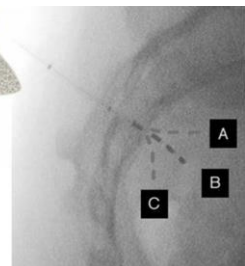
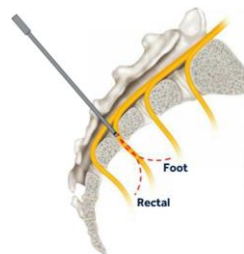
## Steps to Ideal Lead Placement

- Maintain launch point  $\frac{1}{2}$  way in
- Aim curved stylet down and out
- Be smooth, single motion
- Pull back to launch point, turn and re-
- Straddle bone edge with 2 & 3
- Alter launch point if needed
- Start again or go to other side if unsuccessful



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## Follow Expected Path of the Nerve



Images provided by Steven Siegel, MD



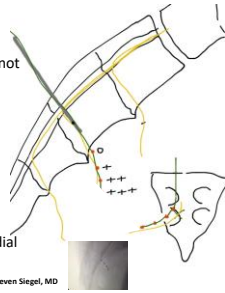
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## Pay Attention to Contact Spacing

Looks Like This if Ideally Placed

- Use 3889 lead and curved stylet to achieve consistent results
- All four equally spaced means lead is not deployed ideally
- Distal spaces should appear narrow on lateral view
- Proximal appear lateral on AP
- Lead should flange out laterally
- Pattern of stronger distal responses means lead inserted too far from medial edge



Images provided by Steven Siegel, MD



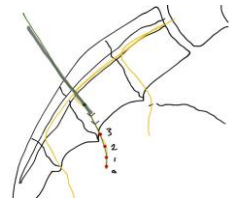
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## Final Lead Deployment

- All four yielding equal responses
- Tines not deployed with 2 and 3 straddling bone
- Advance lead so that point 3 is at anterior surface



Images provided by Steven Siegel, MD

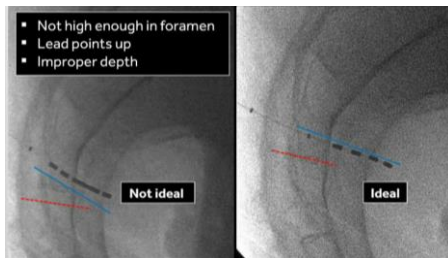


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## What's Wrong With This Lead Placement?

Revision for Poor Efficacy

- Not high enough in foramen
- Lead points up
- Improper depth



Images provided by Steven Siegel, MD

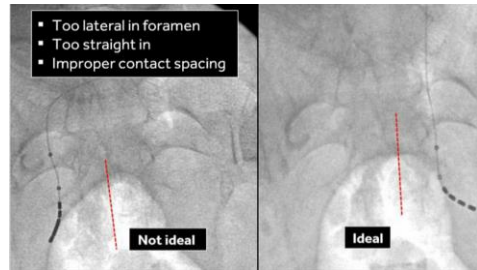


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## What's Wrong With This Lead Placement?

Revision for Poor Efficacy

- Too lateral in foramen
- Too straight in
- Improper contact spacing



Images provided by Steven Siegel, MD



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## Best Practice Recommendations Implant Techniques

- Place lead parallel to nerve path
  - Define upper medial edge of sacrum using AP and lateral fluoro
  - Work to obtain low "opening threshold" with foramen needle at anterior sacral edge
  - Use 3889 lead and curved tip stylet
  - Pay attention to spacing between contact points to insure lateral orientation of lead
- Aim for obtaining appropriate responses from all four electrodes at low thresholds: (<2volts) every time
- Invest time to get the lead positioned. This may result in more programming options, better potential for success, and a longer lasting implant.



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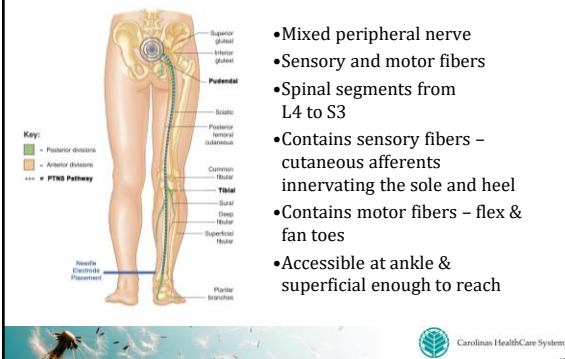
## Posterior Tibial Nerve Stimulation

5/22/2017



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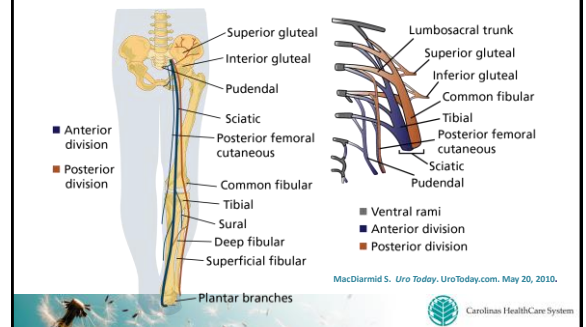
## Tibial Nerve Pathway



- Mixed peripheral nerve
- Sensory and motor fibers
- Spinal segments from L4 to S3
- Contains sensory fibers – cutaneous afferents innervating the sole and heel
- Contains motor fibers – flex & fan toes
- Accessible at ankle & superficial enough to reach

## Posterior Tibial Nerve Stimulation

- Impulses travel from the ankle along the tibial nerve to the sacral nerves
  - Tibial nerve has axons from L1-S4



MacDiarmid S. Uro Today, UroToday.com, May 20, 2010.

## Percutaneous Tibial Nerve Stimulation



- Stimulation delivered via a 34-gauge needle electrode inserted medial/above medial malleolus
- Surface electrode on arch of foot
- Connected to a battery-powered stimulator
- Current slowly increased to maximal comfortable level
- 30-minute treatment

## PTNS Contraindications

### Contraindications

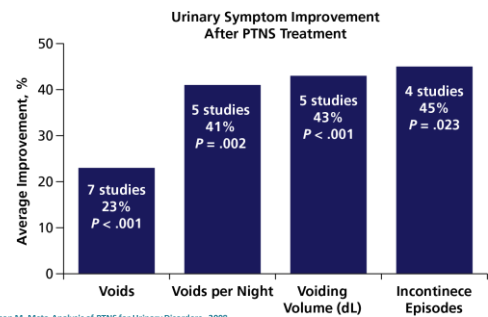
- Patients with pacemakers or implantable defibrillators
- Patients prone to excessive bleeding
- Patients with nerve damage that could impact either percutaneous nerve function or pelvic floor function
- Patients who are pregnant or planning to get pregnant while using the product

## PTNS Clinical Effectiveness

- 50+ US and other peer-reviewed publications demonstrate safety and clinical efficacy
  - Effective in up to 80% of patients
  - Reduces urgency, urge incontinence, and frequency
  - Minimal and mild adverse events
  - Improves QOL
  - 3 RCTs compare PTNS to drugs and placebo
  - 12-, 24-, and 36-month durability data
  - Observational, “real-world” studies support positive conclusions of RCTs

Staskin D et al. Curr Urol Rep. 2012;13:327-334.

## Meta-Analysis of 7 PTNS Studies



Martinson M. Meta-Analysis of PTNS for Urinary Disorders. 2008.



## PTNS Adverse Events

- Most common side effects are temporary
- Minor events reported
  - Mild pain or skin inflammation at or near the stimulation site
  - Painful sensation during stimulation that did not interfere with treatment
  - Minor bleeding at insertion site



## Newest PTNS System FDA Approved

- Stimulator with permanently attached single insulated lead wire
- Single-use accessories which are sold separately, acupuncture needle, needle holder electrode pad.
- Includes a micro USB-to-USB cable and a USB3 wall charger.
- One purchases therapy credits from a commercial website.  
credits are downloaded to the device through the micro-USB connection to a computer with a USB port and internet access.



## Comparison of PTNS Available Therapies

### Clinical Acceptance and Validation

	Urgent® PC	NURO®
Published Clinical Studies	Yes (50+)	No
Randomized sham-controlled clinical studies with specific device	Yes	No
Established superiority to sham therapy with specific device	Yes	No
Long term efficacy data with specific device	Yes	No

### Device Differences

	Urgent® PC	NURO®
Maximum treatment current	9 milliamps	19 milliamps (per 510k)
Pad location	Bottom of foot	Ankle
Battery voltage	9 volts	3.7 volts



## Advantages of Urgent PC

- Non-surgical
- No side effects of meds
- No vaginal or rectal probe
- No adverse events
- OK for children
- Effective treatment



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## Future Neuromodulation Systems

5/22/2017



## Future Sacral Neuromodulation Systems

### r-SNM System

- Miniaturized, rechargeable SNM technology platform  
Charge once every 2 weeks < 60 minutes
- Titanium-ceramic implantable pulse generator  
Battery last 15 years
- Transforaminal lead placement targeting S3 nerve – 4 electrode tined lead
- Standard lead and IPG implantation procedures
- CE mark in June 2016 and Health Canada marketing approval in Dec. 2016  
ARTISAN – 120 UUI patients, IDE pivotal in US



## RELAX-OAB Study

ClinicalTrials.gov - NCT02620410

Prospective, single - arm study

51 OAB patients - 7 European sites

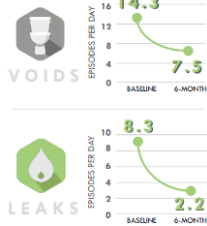
Single - stage implant – post - implant simulated test period in place of external test

72 - hour voiding diaries, ICIQ - OAB, subject satisfaction

75% female 25% male  
Aged 21 - 77 years old (median: 52)

- 73% OAB - wet
- 27% OAB - dry

1 month visit : 71% responders



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## Implantable Tibial Neuromodulation

- Surgically implanted device stimulates tibial nerve proximal to medial malleolus
- Miniature, battery-less, MRI compatible
- Patient controls via external unit
- Physician can program to remotely set stimulation settings



Bluewind Medical system safety and performance in treatment of patients diagnosed with overactive bladder (OAB): amendment to allow extended follow up of patients. J Heesakkers et al.

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## Implantable Tibial Neuromodulation Preliminary Data

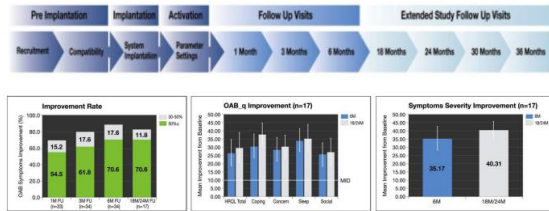


Figure 3: OAB symptoms improvement. Comparison of voiding diary data from baseline and follow-up visits 1, 3, 6 and 18/24/30/36 months (50-100% and 200% improvement in OAB symptoms).

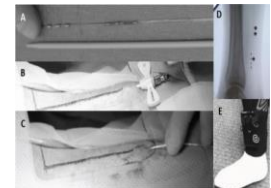
Figure 4: OAB quality of life and symptoms severity improvement. All measures (HPQL, total, coping, concern, sleep, social and symptoms severity, demonstrated a statistically significant improvement at each follow-up visit as compared to baseline (Paired t test, P<0.05). All HPQL subscale displayed an average score greater than the minimally important difference of 10 points. MDD: the smallest score change that is perceived beneficial to patients and is often used to determine whether changes in scores are considered clinically significant).

Bluewind Medical system safety and performance in treatment of patients diagnosed with overactive bladder (OAB): amendment to allow extended follow up of patients. J Heesakkers et al.

Carolinus HealthCare System

## Implantable Tibial Neuromodulation

- Episodic stimulation of tibial nerve in outpatient setting
- Chronically implanted device
- New, minimally invasive device with external charger without need for office visits
  - Increase convenience
  - Increase compliance



A) Chronic implant next to 9F dilator  
B) Dilator inserted in LA at the tibial bone  
C) Inserted chronic implant  
D) X-Ray to verify the correct positioning. \* Microchip, \*\* Electrodes  
E) External device after the stimulation positioned at the ankle

Kessler TM1, Knappeler SL, De Wachter S2, Kossman M1, Sievert K3, Balgust University Hospital, 2, UZA, 3, University of Lubeck, KS 2015 Abstract  
Funding: Implantable devices provided by StimGuard

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## Implantable Tibial Neuromodulation Preliminary Data

- 2013: Initial three month study in four OAB patients
  - Reduction in urgency index
- 2014 study: two male nLUTD patients
  - improved significantly within 48 hours
  - Completely dry (No UI or nocturia) two months post-op
- April 2016: 16 patients received implant
  - Increase in mean volume voided
  - End nocturia
  - Significant decrease in UI
  - Delayed improvement in QoL indicators

Sievert K1, Milovic L2, Fadich E3, Roggenkamp A2, Kessler TM4, De Wachter S5, University Hospital of Vienna, 2, SALK, 3, PMU, 4, University Hospital Zurich, 5, University Hospital Augsburg/NOVEL CHRONIC TIBIAL NEUROMODULATION/TIBIAL TREATMENT OPTION FOR OAB SIGNIFICANTLY IMPROVES URGENCY (UI)/URGE INCONTINENCE (UI) AND NORMALIZES SLEEP PATTERNS

Carolinus HealthCare System

## Implantable Tibial Neuromodulation

- Fully implantable small neurostimulation device
  - eCoin
  - Electrodes integrated into the housing utilizing a watch battery
- Stimulates the tibial nerve



1st Generation



Watchdog software



Circuit Board Assembly



Electromechanical Packaging



Completed Device

**eCoin is not approved for sale in any country. eCoin is approved in certain countries for investigational use only.**

<http://valenciatechnologies.com>

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Neuromodulation in 2017:  
PTNS, InterStim & the Future

