Neuromodulation to Treat Voiding Dysfunction
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Disclosures
- Consultant for Medtronic Inc.
- Consultant for Trillium Therapeutics
- Investigator for Boston Scientific
- Investigator for Allergan
- Investigator for Pfizer
- Investigator for Uroplasty, Inc.

Objective:
To discuss clinical issues associated with the treatment of overactive bladder (OAB), its prevalence, care seeking cycle, treatment challenges, etc. and how neuromodulation may provide an effective solution to patients, physicians and payors.

Epidemiology of Overactive Bladder (OAB)

Overactive Bladder: Prevalence & Impact

- Overactive bladder (OAB) affects over 33 million people in the United States, making it more prevalent than many more well known diseases1, 2
- Estimated total economic cost of OAB in 2000 was over $12 billion in the United States3

Management of OAB
**Treating OAB**

- Behavioral Techniques (i.e., Kegel exercises, diet modification, etc)
- Biofeedback
- Medical Management
- InterStim® Therapy
- Tibial Nerve Stimulation

**Medical Management**

- Easy to prescribe
- 7 established brand names on the market
- Over 13 new drugs in development
- Direct to consumer marketing
- High rate of discontinuation
- Patient tolerability often challenging

**Drug Therapy Persistence is Poor Among OAB Patients**

<table>
<thead>
<tr>
<th>Initial Rx</th>
<th>1st Refill</th>
<th>2nd Refill</th>
<th>3rd Refill</th>
<th>4th Refill</th>
<th>11th Refill</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>88%</td>
<td>64%</td>
<td>51%</td>
<td>34%</td>
<td>15%</td>
</tr>
</tbody>
</table>

- 56% of patients chose not to refill their prescription a second time
- Only 15% of patients continued with their therapy through the first year

**Drug Therapy: Leading Reasons for Discontinuation**

- In a Gallup Survey of 164 patients, the number one reason for patients discontinuing their drug therapy was the medication did not work for them

<table>
<thead>
<tr>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication didn't work</td>
</tr>
<tr>
<td>Side effects</td>
</tr>
<tr>
<td>Provider recommended stopping</td>
</tr>
<tr>
<td>Medication too expensive</td>
</tr>
</tbody>
</table>

- In a separate investigation of 50 women after at least 6 months adherence to pharmacological treatment, only 36% reported still taking their anticholinergic medication. 45% discontinued their therapy because of the perception that the medication did not relieve their symptoms

**Overactive Bladder: Treatment**

- With over 7 choices of medications to choose from, many patients will likely discontinue their therapy or choose alternate care providers due to poor persistence and adherence.
- Associated discontinuation rates with incontinence medications are exceptionally high due to adverse side effects

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>% of Mentions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry Mouth</td>
<td>43%</td>
</tr>
<tr>
<td>Constipation</td>
<td>39%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32%</td>
</tr>
<tr>
<td>UTIs</td>
<td>25%</td>
</tr>
<tr>
<td>Hesitancy</td>
<td>23%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>21%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18%</td>
</tr>
</tbody>
</table>

- Most frequently reported side effects of incontinence medications (n=606)

**InterStim® Therapy**


Sacral nerve stimulation is an effective treatment for voiding dysfunction patients who have not been helped or could not tolerate more conventional treatments, including pharmacotherapy.

Utilizes mild electrical pulses to the nerves associated with voiding function. Through neurostimulation, significantly improved or normal voiding is restored.

**Predictors of Success:**

**Sensory or Motor Response?**

- In an independent investigation of 35 patients receiving permanent INS placement, 95% of those eliciting a positive intraoperative motor response were found to have a successful test stimulation.
- If a positive sensory response only was elicited, patients had a 4.7% chance of having a positive test stimulation.

**Intraoperative Measurements**

<table>
<thead>
<tr>
<th>MOTOR Response</th>
<th>Sensory Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>95%</td>
<td>5%</td>
</tr>
<tr>
<td>90%</td>
<td>10%</td>
</tr>
<tr>
<td>85%</td>
<td>15%</td>
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<tr>
<td>80%</td>
<td>20%</td>
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<tr>
<td>75%</td>
<td>25%</td>
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<tr>
<td>70%</td>
<td>30%</td>
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<td>65%</td>
<td>35%</td>
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<td>60%</td>
<td>40%</td>
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<td>55%</td>
<td>45%</td>
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<td>35%</td>
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<td>20%</td>
<td>80%</td>
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<td>15%</td>
<td>85%</td>
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<tr>
<td>10%</td>
<td>90%</td>
</tr>
<tr>
<td>5%</td>
<td>95%</td>
</tr>
</tbody>
</table>

**Clinical Efficacy**

- 45% remained completely dry
- 34% experienced ≥ 50% reduction in leaking episodes

**Sustained Results Over Time**

- 54% remained dry at 12 months
- 56% remained dry at 24 months
- 57% remained dry at 36 months

**Urge Incontinence**

- 45% remained completely dry
- 34% experienced ≥ 50% reduction in leaking episodes

**Urgency Frequency**

- 31% returned to normal voids (4 to 7 voids/day)
- 13% experienced ≥ 50% reduction in voids

**Retention**

- 61% eliminated use of catheters
- 15% experienced ≥ 50% amount of urine emptied from catheter usage

1. MDT-103 Study, Medtronic data on file.
**Current Literature: Urge Incontinence**

Independent investigations confirm sustained results with InterStim® Therapy:

- In an independent investigation of 41 patients refractory to conservative therapy, 90% reported >50% improvement in presenting symptoms and quality of life.
- Mean follow up time exceeded 12 months.

**Sacral Neuromodulation Implant**

**Long-term Results of a Multicenter Study**

![Graph showing percent of patients achieving continence or >50% improvement in symptoms over time.]

**Current Literature: Systematic Review: Urge Incontinence**

Randomized Controlled Trials vs. Case Series Reports:

- In an independent investigation of 1,827 implants from 34 clinical trials, InterStim Therapy was shown to be an effective treatment option for the treatment of urinary urge incontinence.

**InterStim® Therapy: Clinical Safety**
**Implantation:**

Ranking of Adverse Events in first 12 Months Post-implant

- Pain at neurostimulator site 15.3%
- New pain 9.0%
- Suspected lead migration 8.4%
- Infection 6.1%
- Transient electric shock 5.5%
- Pain at lead site 5.4%
- Adverse change in bowel function 3.0%

Note: Additional events occurred - each less than 2.0%

Source: MDT-103 Study 1993-1998, data on file Medtronic

**Quality of Life**

- Patients implanted with InterStim System reported significantly improved ratings (p < 0.00625) in health-related quality of life (HRQOL) measures.¹
- The largest gain was noted in the subject’s perceived ability to increase their level of work performance or other daily activity.²
- An improvement of 10% to 40% in Beck Depression Inventory scores has been shown in urge incontinent patients.²
- Improved results in both (HRQOL & depression) have been seen at three months and sustained for a 12-month period of follow-up.³


**Selecting Patients for InterStim® Therapy**

- Initial Screening
- Voiding Diary
- Urodynamic Workup
  - Behavioral Techniques
  - Interventional Techniques
  - Medication
- Test Stimulation
- Implant InterStim System

**Benefits of InterStim® Therapy**

- Test stimulation allows informed choice for patient and doctor
- Effective treatment in properly screened patients
- Safe
- Reversible
- Does not preclude use of alternative treatments

**Test Stimulation Procedure**

- A test is done prior to implant to determine how a patient will respond to the implanted device
- Performed in the office or surgery center
- A lead is surgically implanted near the S3 sacral nerve
- Lead is connected to an external device worn on the patient’s belt for a period of 3-7 days
- Patient will record his/her voiding behavior in a diary
Two Minimally Invasive Ways to Test

**Peripheral Nerve Evaluation (PNE):**
- 19g Seldinger needle placement
- Minimally Invasive
- Reversible
- Single wire electrode
- In-office procedure
- 3-7 day evaluation period
- If successful, move to system implant
- Not successful, move to Stage One

**Stage One:**
- 5 F Chronic lead placement
- Minimally Invasive
- Reversible
- Outpatient procedure
- 4 electrodes
- 3-7 day evaluation period
- If successful, move to Stage Two (system implant)

Test Stimulation Procedure

- Locate & identify sacral nerves
- Verify neural integrity
- Allow the patient to feel the stimulation
- Assess viability of sacral nerve stimulation on voiding behavior (goal is efficacy > 50% improvement in symptoms)

Test Stimulation

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Staged Approach

- Advances in technology have made a staged InterStim test a minimally-invasive procedure

Procedure

- Pass foramen needle at 60-degree angle through superior, medial aspect of foramen
- Apply current and assess sensory and motor response
- Ideal response is comfortable pulsating sensation in rectal, genital area, sacral flattening, and small amount of greater toe movement

Procedure (cont.)

- Advance quadripolar tined lead so that proximal electrode is at lower bone plate
- Test each electrode for motor and sensory response
- Adjust as necessary to achieve optimal response
- Carefully remove lead introducer deploying the tines
Completed First-stage Sacral Implant

Intra-stage Testing
- Patients are sent home with a screener box for 14 to 21 days
- Instructed to adjust voltage to comfortable stimulation
- Voiding diaries are maintained
- Adjustments can be made over the phone or in the clinic regarding the electrode stimulated rate and pulse width
- Implantable pulse generator placed for those demonstrating at least a 50% improvement in symptoms

Stage II
- Mark site on buttock for incision for IPG
- The medial portion of this incision is where the connector of the temporary extension lead is buried
- Carefully open incision, externalize proximal permanent lead and its connection to percutaneous lead
- Remove percutaneous lead by loosening set screw
- Sharply create subcutaneous pocket large enough to accommodate IPG

Implantation of IPG

Selecting InterStim® Therapy Later in the Treatment Algorithm May Not Necessarily Benefit Patients

InterStim® Therapy: Patient Selection

In an independent investigation evaluating women with refractory, nonobstructive urinary urge incontinence after stress incontinence surgery, factors predictive of a positive response to SNS therapy included:
- Patients younger than 55 (p=0.01)
- Test stimulation performed within 4 years of the surgical procedure (p=0.01)
- Evidence of pelvic floor muscle activity (p=0.01)

Identifying the Refractory Patient: How Long Should a Patient Wait?

- Starkman et al. reported a mean duration of symptoms of 4.6 years before implantation.
- Non-responders were found to have had a longer duration of symptoms (6.5 vs. 3.8 years).

Other Potential Benefits of SNS
- Fecal Incontinence
- Chronic Constipation
- Pelvic Pain
- Vulvodynia
- Interstitial cystitis
- MS, Parkinson’s, Partial SCI

Tibial Nerve Stimulation
- Based on the teaching of acupuncture
- Tibial nerve sends afferents through the sacral nerve plexus
- Non-controlled data demonstrates improvement in voiding dysfunction

PTNS for Refractory OAB
- 53 patients; 47 completed
- 12-week study; prospective, multi-center
- 71% “treatment successes”
- Results:
  - 25% daytime (25%) and nighttime (21%) voiding frequency
  - 35% urge incontinence improvement in QoL
  - No serious device-related adverse events
  - Three non-serious events resolved spontaneously: right foot pain, needle-site pain, stomach ache

PTNS for OAB
- 11 patients: mean age 51
- Mean PTNS therapy 13 months
- PTNS therapy discontinued, then restored
- Subjective and objective deterioration occurs when PTNS therapy discontinued
- Maintenance therapy is necessary for sustained symptom reduction
Urodynamic Effects of PTNS

- Prospective, multi-center study
- 90 patients with OAB
- 12 PTNS sessions

Results
- ↑ bladder capacity
- ↑ volume at which first unstable detrusor contraction occurred

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12 PTNS sessions
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Tibial Nerve Stimulation vs Detrol

- Prospective, multi-center study
- Randomized to 12 weekly sessions of tibial nerve stimulation vs Detrol LA
- At 12 weeks Tibial nerve stimulation is objectively equal to Detrol LA and subjectively better for OAB symptoms
- Long-term extension arm results pending

Peters et al., J. Urol. 2009

Current Status of TNS

- FDA approved: Urgent® PC – Uroplasty, Inc.
- No reimbursement code
- Sham controlled trial recently completed

Future of Neuromodulation

- Pudendal nerve stimulation
- Dorsal Genital Nerve stimulation
- Cutaneous approaches to neuromodulation
- Pharmacologic neuromodulation
  - Botox
  - Capsaicin
  - RTX

Pudendal Neuromodulation: A Viable Option to Sacral Nerve Stimulation

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William Beaumont Hospital, Royal Oak, Michigan
Introduction

- Stimulation of the 3rd sacral nerve has been shown to be effective in treating voiding dysfunction
- The pudendal nerve is a distal branch of S2, S3, and S4
- The potential benefit of pudendal nerve stimulation is increased afferent stimulation through the sacral nerve roots

Background

Animal Studies

  - 5 spinal cord injured cats
  - Stimulation of pudendal nerve more selective for inhibition of bladder contraction than SNS

- Yamanishi, T. Induction of Urethral Closure and Inhibition of Bladder Contraction by Continuous Magnetic Stimulation, Neurourol urodyn, 1999
  - 12 dogs with magnetic coil in ischio-rectal fossa at pudendal nerve
  - Intraurethral pressure increased and bladder contraction was inhibited

Neurogenic Bladder

- Sacral nerve stimulation not as effective for neurogenic bladders
- 15 refractory patients had pudendal lead placed with neurophysiologic testing (8 non-traumatic, 7 traumatic, all with urge incontinence, 7 with constipation, 1 fecal incontinence, all with urge incontinence, 7 with constipation, 1 fecal incontinence, 3 ED)
- 12 of 15 were implanted: 8 continent, 2 > 80%, 2 > 50%, 4/7 constipated subjects normalized evacuation and 1/1 fecal incontinence resolved
- Programming parameters variable (5 Hz-15 Hz), on-demand vs continuous
- 6 of 12 had 6 month CMG: MCC increased from 153 cc to 331 cc

Sacral vs. Pudendal Nerve Stimulation Using the Tined Quadripolar Lead

- Stimulate with Foramen Needle
  - Foramen needle
  - Stimulation up to 10 mA

Background Monitor C-MAP

- Monitor C-MAP
**Background**

**Final Placement Of Electrodes**

- Began offering pudendal nerve stimulation for sacral failures and other difficult patients
- If a patient fails a staged sacral stimulation trial, will offer a pudendal lead at the second stage surgery

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**Materials and Methods**

- Retrospective chart review from November 2003 to December 2008
- Questionnaire sent to homes to assess symptom improvement with GRA and treatment satisfaction

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**Results**

- 84 patients had a pudendal lead placed
  - 78.6% female, 21.4% male
  - Mean age: 51.8 years
- Primary diagnosis
  - Interstitial cystitis/PBS: 42 patients
  - Urgency/Frequency or urge incontinence: 26 patients
  - Urinary Retention: 13 patients
  - Pelvic pain: 2 patients
  - Tethered sacral cord: 1 patient
- Pudendal neuropathy 3 patients
- Median follow-up 24.1 months

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**Results**

- 60/84 (71.4%) had a greater than 50% improvement in symptoms
- 55/84 had IPG placed at pudendal nerve lead (5 chose sacral as part of our crossover trial)
- Of the 84 patients, 44 had failed previous sacral nerve stimulation
- Of the previous sacral failures, 42/44 (95.5%) responded to pudendal stimulation and had an IPG placed

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Results

Average volume per void

<table>
<thead>
<tr>
<th>Time point</th>
<th>Baseline</th>
<th>1 week</th>
<th>2 months</th>
<th>6 months</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean volume (cc)</td>
<td>0</td>
<td>100</td>
<td>80</td>
<td>60</td>
<td>40</td>
</tr>
</tbody>
</table>

Results

Incontinence episodes per day

<table>
<thead>
<tr>
<th>Time point</th>
<th>Baseline</th>
<th>1 week</th>
<th>2 months</th>
<th>6 months</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Results

Pelvic pain scores

<table>
<thead>
<tr>
<th>Time point</th>
<th>Baseline</th>
<th>1 week</th>
<th>2 months</th>
<th>6 months</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Complications

- 1 superficial wound infection not requiring explant
- 5 staged revisions (3 for lead migrations and 2 for pain)
  - Back pain, leg pain, sciatic pain and shocks
- Reoperations
  - 2 battery replacements for EOS
  - Second pudendal lead placed for bilateral stimulation in 2 patients
- 5 devices were explanted

Results

Mailed GRA Survey: Median follow-up 24.1 months

- Survey mailed to 55 on CPN
- 72.7% (40/55) returned the survey
- 35/40 (87.5%) indicated that they still had the device
- 82.8% had it on 100% of the time

Survey Results

7-point likert scale: markedly worse to markedly better
- Moderate or marked improvement (slight, moderate, marked):
  - In overall symptoms: 43% (60%)
  - Pelvic Pain: 30% (58%)
  - Leaking: 27% (58%)
  - Urgency: 34% (60%)
  - Frequency: 35% (57%)
  - Bowel Function: 9% (21%)
  - Sexual Function: 6% (9%)
- 74% would have the procedure again
- 84% would recommend the treatment to a friend
Figure 1. Patients reporting improvements* in symptoms after CPNS.

**Conclusions**

- Pudendal InterStim® is a viable alternative to SNS
- 93% of patients who failed sacral nerve stimulation responded to pudendal stimulation
- The patients presented represent some of the most complex patients in my practice
- At almost 4-years follow-up, moderate or marked improvement in symptoms are still seen in many patients
- Complications have been relatively low

Funding: Ministrelli Program for Urology Research and Education (MPURE)

**Summary**

- Voiding dysfunction is very common
- Pharmacologic therapy for OAB is not well tolerated and efficacy is limited
- Neuromodulation is an effective and safe method to treat voiding dysfunction
- Should offer neuromodulation early
- Elderly have less success with neuromodulation

**Beaumont®**

William Beaumont Hospital