Practical Aspects of Urologic Neuromodulation

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Sacral Nerve Neuromodulation (SNM) : Past, present, and future

• The concept of in vivo nerve stimulation in the 19th century

• Treatment of neuromuscular disorders, pain, urologic conditions in the late 20th century

• Implantable devices
  – Eretile dysfunction (ED)
  – Urinary retention
  – Interstitial cystitis
  – Urinary incontinence
  – Recently, fecal incontinence
    \( \rightarrow \) Urge incontinence, pelvic pain, retention

• Further large scale studies and advances are needed

1981  Tanagho and Schmidt UCSF
1994  European CE Mark
1997  FDA approves for Urge Incontinence
1999  FDA approves for UF and NOUR
2002  FDA approves for OAB
2002  Wide use of fluoro, staged implant/tined lead
2006  Small stimulator
2009  Anticipate FDA approval for bowel indication
Now  Over 50,000 patients worldwide
Potential Applications of Electrical Stimulation in the Treatment of Voiding Dysfunction

<table>
<thead>
<tr>
<th>Facilitate filling-storage</th>
<th>Facilitate emptying</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibit detrusor contractility</td>
<td>Stimulate detrusor contraction (spinal cord-injured patient)</td>
</tr>
<tr>
<td>Increase bladder capacity</td>
<td></td>
</tr>
<tr>
<td>Decrease urgency and frequency</td>
<td></td>
</tr>
<tr>
<td>Decrease nociception</td>
<td></td>
</tr>
<tr>
<td>Increase outlet resistance</td>
<td></td>
</tr>
</tbody>
</table>

- **V**, **A**, **SP**, **PT**
- **CP**, **SR**, **IV**
- **SAR**
- **SR**, **IV**

**Neuromodulation**

**Direct stimulation** (efferent nerves or roots)

A, anal; CP, common peroneal; IV, intravesical; PT, posterior tibial; SAR, sacral anterior (ventral) roots; SP, suprapubic; SR, sacral roots; V, vaginal.
## Sacral Nerve Responses

<table>
<thead>
<tr>
<th>Sacral Nerve</th>
<th>Motor and Sensory Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor</strong></td>
<td><strong>Sensory</strong></td>
</tr>
<tr>
<td>S2</td>
<td>Plantar flexion of the entire foot with lateral rotation and anal clamp movement</td>
</tr>
<tr>
<td>S3</td>
<td>Dorsiflexion of the great toe and a bellows reflex (anal wink)</td>
</tr>
<tr>
<td>S4</td>
<td>Bellows reflex only</td>
</tr>
</tbody>
</table>
The guarding reflex promotes continence and allows the outlet to contract the urinary sphincter during periods of stress (e.g., cough). The brain can turn this reflex off during voiding. Ä

the bladder afferent reflex promotes continence during periods of bladder filling and is quiet during micturition

In neurologic disease, the supraspinal circuitry is disconnected and therefore cannot turn off the spinal guarding reflex, and thus retention occurs.

Sacral neuromodulation (SNS) can restore the normal voluntary pattern of micturition by inhibition of the spinal guarding reflex.

SNS, sacral nerve stimulation

Treatment for Overactive Bladder Symptoms

- Behavioral therapies
- Drugs
- Minor procedures
  - Urethral dilation
  - Bladder distention
- Surgery

64% of incontinent patients are dissatisfied with results of treatment (NAFC, 1999)
## Treatment Algorithm for OAB

<table>
<thead>
<tr>
<th>Primary measures</th>
<th>Others (efficacy debatable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Behavioral modification</td>
<td></td>
</tr>
<tr>
<td>✓ Drug therapy</td>
<td></td>
</tr>
<tr>
<td>✓ Denervation (decentralization)</td>
<td></td>
</tr>
<tr>
<td>✓ Electromagnetic therapy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary measures</th>
<th>Under study</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ <strong>Neuromodulation</strong></td>
<td></td>
</tr>
<tr>
<td>✓ Augmentation cystoplasty</td>
<td></td>
</tr>
<tr>
<td>✓ Urinary diversion</td>
<td></td>
</tr>
<tr>
<td>✓ Intravesical drug therapy for deafferentation</td>
<td></td>
</tr>
<tr>
<td>✓ Detrusor injection of botulinum toxin</td>
<td></td>
</tr>
</tbody>
</table>
Mechanism of Neuromodulation

- Still unclear
- Stimulation of A-delta myelinated fibers especially S3
  - Enhance sphincter and pelvic tone
  - Inhibitory effect on the detrusor reflex

S2-4 somatic afferents stimulation
- Inhibition of sacral micturition reflex
- Sympathetic hypogastric activity
- Reflex inhibitory effects by electrostimulation of external urethral sphincter rather than by direct stimulation of afferent fibers
Sacral Nerve Modulation

Chronic modulation of S3, S4 sacral nerve root

Modulates reflexes between the:
- Bladder
- Urethral sphincter
- Pelvic floor muscles
What are SNM Indication?

- Refractory OAB
  - Failed drugs and behavioral therapy
- Urinary Retention
  - Idiopathic non-obstructive
- Non-neurogenic etiology
- Bowel dysfunction
  - European indications

Treats both OAB and retention
- Blocks ascending sensory pathway inputs
- Turns on voiding reflexes by suppressing the guarding reflex pathways

Criteria for Selection of Patients

- Many LUTS and dysfunctions are secondary to a neuromuscular etiology.

- History and physical examination
  - Reveal the nature (Acute versus chronic)
  - Classify the causes (Neurogenic, anatomic, postsurgical, functional, inflammatory, or idiopathic)
Criteria for Selection of Patients

- SNM is frequently attempted in patients,
  - Approved in US for urinary urgency, frequency, urge incontinence, non-obstructive urinary retention.
  - With failure on conservative treatment
    (Such as bladder retraining, pelvic floor biofeedback, and medications)
  - Before more invasive surgical procedures
    (Such as enterocystoplasty and urinary diversion)
Special Populations

• Neurogenic bladder
  – Multiple sclerosis
  – Spinal cord injury
• Interstitial cystitis (Painful bladder syndrome)
• Chronic pelvic pain
• Pediatric Voiding dysfunction
• Fecal incontinence and bowel disorders
  – Fecal incontinence
  – Constipation
Special Populations

• Neurogenic bladder
  – Multiple sclerosis
    • Chronic demyelinating disease in CNS and PNS
    • Cause a variety of voiding dysfunction
      – Neurogenic detrusor overactivity
      – Detrusor-sphincter dyssynergy
      – Areflexia
      – And combinations of these
  – Spinal cord injury
    • Incontinent from neurogenic detrusor overactivity and/or concommitant sphincteric dyssynergy
Special Populations

• Intrerstitial cystitis (Painful bladder syndrome)
  – IC is not a true FDA-approved indication for SNM
  – However, the symptom complex of urinary urgency and frequency is well within the standard criteria.

• Chronic pelvic pain
  – Sacral root stimulation may decrease pelvic floor spasticity.
Special Populations

• Pediatric Voiding dysfunction (not approved by the FDA)
  – Hinman bladder syndrome
    • Overactive bladder
    • Urinary retention
    • Non-neurogenic neurogenic bladder

• Fecal incontinence and bowel disorders
  – Fecal incontinence
  – Constipation
Patient Selection: Who Benefits Most?

Patients who are most likely to discontinue drug therapy may have the best chance for remaining completely dry.

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

Lavers et al. reported a mean duration of symptoms of 116 months (range 9-600) before implantation. All 104 patients investigated had sustained significant (p <0.05) decreases in:

- Voids/24 hours
- Voids/night
- Leaks/24 hours
- Pads/24 hours

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

SNS Responders

- Starkman et al.\(^1\) 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)

Additional Application of SNM

• Expanding clinical indications
  – Neurogenic detrusor overactivity
  – Interstitial cystitis
  – Pelvic pain
  – Pediatric voiding dysfunction
  – Bowel disorders

• Transcutaneous or implantable neuromodulation devices are available.
Clinical Considerations for Excluding Patients from SNM

• Anatomic abnormalities in the spine or sacrum
• Mental incapacitation of patients who
  – Cannot manage their device
  – Cannot judge the clinical outcome
• Physical limitations of patient from achieving normal pelvic organ function, such as functional urinary incontinence
• Noncompliance of the patient
Relative Contraindications for Patients

• MRI
  – Removal of the neuroelectrode lead only
  – Preservation of the pulse generator in preparation for elective MRI
  – After the MRI procedure, a new neuroelectrode may be placed and connected to the previously implanted and preserved pulse generator.

• Pregnancy
  – Potential for teratogenicity or abortion (but not known)
  – No adverse effects of electrical stimulation on pregnant rats and their offspring at termination of pregnancy

Wang and Hassouna. J Urol 199
Sacral Neuromodulation Therapy

- SNS (Sacral n. stimulation) by the InterStim– (Medtronic, Minneapolis, Minn.)
- Implantable, programmable neuromodulation system
- Two Stage Therapy
  - Stage I: A clinical trial of a temporary or permanent lead for external stimulation
  - Stage II: Implantation of a subcutaneous implantable pulse generator (IPG).
Sacral Neuromodulation Therapy

- **PNE (Percutaneous nerve evaluation)**
  - Test stimulation procedure (3 to 7 days, temporary)

- **Staged Lead Implant**
  - Placement of potentially permanent lead for up to 4 weeks

- **Chronic Implant**: implantation neurostimulator and lead when not done as a staged procedure
New Medtronic Tined Lead Percutaneous Implant

Minimally invasive implant procedure

- Local anesthesia
- Faster recovery time
- Less muscle trauma
- Minimized surgical incision
- Reduce surgical time
- Sutureless anchoring
The tined lead is introduced typically into the S3 nerve foramen. The tines allow the lead to be fixed into the fascial layers above the sacrum. This lead has a quadripolar configuration (four contact points).

(Courtesy of Medtronic Inc.)
Technique of SNM

- PNE (percutaneous nerve evaluation)
  - *Initial* introduction of sacral neuromodulation therapy
  - By the placement of a *unilateral* percutaneous lead in the S3 for *amen* (local anesthesia)
  - Lead was connected to an external pulse generator for several days
  - False negative results d/t improper lead placement and migration

- Preoperative iv antibiotics, aseptic technique
- Prone position
- Buttocks retraction: anus is visible during stimulation
Technique of SNM

• If improvement is minimal or absent
  → Revision or bilateral percutaneous lead placement

• If more than 50% improvement in symptoms
  → A permanent IPG (implantable pulse generator) is implanted

• In patients with urgency-frequency syndrome and urge incontinence
  → 2- to 4-week trial is generally adequate

• For retention, a longer trial of 4 weeks or more may be necessary before a desired clinical response is obtained
**Technique of SNM**

**The percutaneous test stimulation**
- A small lead wire is placed into S3
- Connected to an external stimulator for 1 wk
  - Stimulation to the nerve roots

**Measurement of the S3 nerve foramen**
- Typically 9 cm to the coccyx and 11 cm to the anal verge
- One measures 1 to 2 cm lateral to this mark to find the rough site of the S3 nerve foramen.
- Cross hair technique to find the midline fluoroscopically and the lower aspect of the sacroiliac joints laterally to find the S3 nerve foramen as well.
Technique of SNM
Technique of SNM
Technique of SNM

Typical lead configurations
1) Muscle: ipsilateral toe contractions
2) Sensory: vaginal, penile, or scrotal pulsating feeling

Campbell-Walsh Urology, 9th ed. 2007
A 3 to 4cm counterincision in the upper gluteal crease is made for a deep subcutaneous pocket to allow implantation of the IPG.
InterStim/InterStim II INS Comparison

<table>
<thead>
<tr>
<th>InterStim INS</th>
<th>InterStim II INS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater longevity</td>
<td>Smaller size</td>
</tr>
<tr>
<td>Size: 27 cc, 42 g</td>
<td>Size: 14 cc, 22 g</td>
</tr>
<tr>
<td>Extension: Required</td>
<td>Extension: N/A; integrated strain relief</td>
</tr>
<tr>
<td>Setscrews: 8</td>
<td>Setscrews: 1</td>
</tr>
<tr>
<td>Coating: Parylene</td>
<td>Coating: No</td>
</tr>
</tbody>
</table>
Outcome

• Outcomes of SNS from two studies
  – Schmidt and co-workers (1999)
    • 76 patients with refractory urge incontinence from 16 centers
    • Demonstrated more than 50% reduction in incontinence episodes
  – Hassouna and colleagues (2000)
    • Outcomes of SNS on refractory urgency-frequency conditions in 51 patients randomized from 12 centers
    • Showed improvement in the number of daily voids, voided volume, degree of urgency, and SF-36 quality of life measures

• Limited but conformational results of the earlier randomized trials and approval by the Food and Drug Administration (FDA) for SNS
  
Pettit et al, 2002
**Sacral neuromodulation**

<table>
<thead>
<tr>
<th>Study</th>
<th>Total</th>
<th>Patients with UI</th>
<th>Patients with U/F</th>
<th>Patients with IUR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cured</td>
<td>&gt;50%</td>
<td>Improved</td>
</tr>
<tr>
<td>US National Patient Register</td>
<td>81</td>
<td>27/43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amundsen 2002</td>
<td>12</td>
<td>12/12</td>
<td>2/12</td>
<td></td>
</tr>
<tr>
<td>Hedlund 2002</td>
<td>14</td>
<td>13/14</td>
<td>8/14</td>
<td></td>
</tr>
<tr>
<td>Bosch 2000</td>
<td>45</td>
<td>27/45</td>
<td>18/45</td>
<td></td>
</tr>
<tr>
<td>Shaker 1998</td>
<td>18</td>
<td>12/18</td>
<td>8/18</td>
<td></td>
</tr>
<tr>
<td>Siegel 2000</td>
<td>112</td>
<td>21/41</td>
<td>19/41</td>
<td></td>
</tr>
<tr>
<td>Schmidt 1999</td>
<td>34</td>
<td>16/34</td>
<td>10/34</td>
<td>26/34</td>
</tr>
<tr>
<td>Grunewald 1999</td>
<td>39</td>
<td>13/18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jonas 2001</td>
<td>29</td>
<td></td>
<td>20/29</td>
<td></td>
</tr>
<tr>
<td>Hassouna</td>
<td>25</td>
<td>14/25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aboseif 2002</td>
<td>32</td>
<td></td>
<td>18/20</td>
<td>2/20</td>
</tr>
</tbody>
</table>

**Abbreviations:** IUR, idiopathic urinary retention; U/F, urgency frequency; UI, urge incontinence.
Bilateral Stimulation and Neuromodulation

- In failed unilateral lead placements
- For potential salvage or added benefit as the bladder receives bilateral innervation

Van Kerrebroeck et al, 2005

  - Both unilateral and bilateral test stimulation was continued for 72 hours
  - No significant difference between the groups in UUI, frequency, or severity of leakage in OAB group
  - Better results in emptying (volume per void) with bilateral test in the retention group
Selective Nerve Stimulation

1) Pudendal Nerve
   - Direct **efferent** pathways toward the urethral sphincter
     : Activate **storage** of bladder
   - **Afferents** pathways
     : An important targets for neuromodulating the **inhibitory** reflex on the **micturition** reflex

   - Selective pudendal nerve stimulation was introduced by Vodusek and coworkers (1986)
     : To reduce side effects of off-target stimulation are being developed.
Pudendal nerve afferent firing can modulate and accordingly inhibit the bladder micturition reflex.

If the suprasacral pathways are altered, the guarding and urethral reflexes still exist and cannot be turned off. This may cause retention, as in the spinal cord injured patient who in turn has detrusor-sphincter dyssynergia resulting in urinary retention. Thus, inhibition of the guarding reflexes may allow urinary retention states to be improved.

SNS, sacral nerve stimulation

Selective Nerve Stimulation

2) Dorsal Genital Nerve

- Terminal and most superficial branches of the pudendal nerve
- Dorsal nerve of the penis in males
  - Clitoral nerve in females
- Contributes to the pudendal-pelvic nerve reflex that has been proposed as a mechanism of bladder inhibition
  - Direct electrical stimulation in experimental and clinical studies appears promising in producing an inhibition of the micturition reflex
3) Posterior Tibial Nerve

- Mixed sensory and motor nerve containing fibers originating from spinal roots L4 through S3
- Modulate the somatic and autonomic nerves to the pelvic floor muscles, bladder, and urinary sphincter
- Clinical trials have been performed in detrusor overactive conditions with and without pelvic pain and urinary retention
## Complications

<table>
<thead>
<tr>
<th>No. of Patients/No. of test stimulation procedures</th>
<th>Adverse effect (% of the total procedures)</th>
<th>Types of complications And managements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siegel et al. (2002)</td>
<td>581/914</td>
<td>Lead migration (11.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Technical problems (2.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pain at 12 months (15.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>→ Surgical revision of 33.3% (73/219)</td>
</tr>
<tr>
<td>Everaert and associates (2004)</td>
<td>53</td>
<td>Dysuria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perineal pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>→ Physiotherapy, no explantation</td>
</tr>
<tr>
<td>Hijiz and Vasadava (2005), review</td>
<td>180 (Stage I)</td>
<td>Poor response (92%, 46 of 50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infection (8%, 4 of 50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surgical revision (12.2%, 22/180)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>→ Marginal response (13 of 22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>→ Frayed subcutaneous extension wire (6 of 22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>→ Lead infection (13 of 22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>→ Improper localization of stimulus (1 of 22)</td>
</tr>
<tr>
<td></td>
<td>130 (stage II)</td>
<td>Surgical revision (20%, 26/130)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>→ d/t infection, poor response</td>
</tr>
</tbody>
</table>
# Adverse Events (Test Stimulation)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected lead migration</td>
<td>11.8%</td>
</tr>
<tr>
<td>Technical problem</td>
<td>2.6%</td>
</tr>
<tr>
<td>New pain</td>
<td>2.1%</td>
</tr>
<tr>
<td>Suspected device problem</td>
<td>1.1%</td>
</tr>
<tr>
<td>Other* (less than 1%)</td>
<td></td>
</tr>
<tr>
<td>Includes persistent skin irritation</td>
<td>(0.7%)</td>
</tr>
<tr>
<td>Adverse change in bowel function</td>
<td>(0.4%)</td>
</tr>
<tr>
<td>Infection at test stimulation lead site</td>
<td>(0.3%)</td>
</tr>
<tr>
<td>Adverse change in voiding function</td>
<td>(0.3%)</td>
</tr>
<tr>
<td>Transient electric shock</td>
<td>(0.1%)</td>
</tr>
</tbody>
</table>
## Implantation Adverse Events

12 Months Post-Implant

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain at neurostimulator site</td>
<td>15.3%</td>
</tr>
<tr>
<td>New pain</td>
<td>9.0%</td>
</tr>
<tr>
<td>Suspected lead migration</td>
<td>8.4%</td>
</tr>
<tr>
<td>Infection</td>
<td>6.1%</td>
</tr>
<tr>
<td>Transient electric shock</td>
<td>5.5%</td>
</tr>
<tr>
<td>Pain at lead site</td>
<td>5.4%</td>
</tr>
<tr>
<td>Additional events occurred</td>
<td>each less than 3%</td>
</tr>
</tbody>
</table>
Summary

• Indication of sacral neuromodulation
  – Refractory urgency-frequency
  – Urge incontinence
  – Non-obstructive urinary retention.

  : Safe, effective

• Successful stage I to stage II conversion rates
  – Based on 50% symptom improvement in more than 60% of patients for urge-frequency and urge incontinence.

• More selective nerve stimulation
  – For patients with neurogenic bladders.
Thanks For Your Attention!