Percutaneous tibial nerve stimulation

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OAB – Urgency - The Driver for Multiple Symptoms

Urgency

- Increased Frequency and Reduced Intervoid Interval
- Nocturia
- Reduced Volume Voided per Micturition

Incontinence

- Quality of Life
- Perception of Bladder Condition “Bother”

### Bladder Filling Sensations
Different for Detrusor Overactivity and Urodynamic Stress Incontinence

<table>
<thead>
<tr>
<th>Urodynamic diagnosis</th>
<th>Abdominal sensation</th>
<th>Perineal sensation</th>
<th>Abdominal &amp; Perineal sensation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detrusor overactivity</td>
<td>3</td>
<td>13</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>Urodynamic stress incontinence</td>
<td></td>
<td>12</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>Mixed urodynamic diagnosis</td>
<td>1</td>
<td>6</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Normal urodynamics</td>
<td>4</td>
<td>7</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Reduced bladder sensation</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>
Innervation of the Human Bladder

- Cortex: permission & attention
- Midbrain: safety
- Brainstem: relay center ‘on /off’
- Th_{10-2}: sympathetic nerve: storage
- S_{2-3}: parasympathetic system: voiding
- S_{2-3}: pudendal nerve: control
Innervation of the Bladder

![Diagram of bladder innervation]

- **Sympathetic** nerve fibers originate from thoracic spinal cord (T12-L2).
- **Parasympathetic** nerve fibers originate from sacral spinal cord (S2-S4).
- **Pudendal nerve** contains both sympathetic and parasympathetic fibers.
- **Visceral afferent pathway** connects the bladder to the spinal cord via the sacral nerves.
- **Bladder neck**, **external sphincter**, and **trigone** are innervated by both sympathetic and parasympathetic fibers.
The Emerging Picture is Complex

- Pain
  - Pain C fibres
  - HT fibres
  - LT fibres
  - Silent fibres

- Static - mechanical
  - Stretch receptors
  - Aδ/C

- Chemical
  - Urothelial modulation

- Mechanical
  - Myofibroblasts

- Motor/sensory
  - Motor/sensory

Detrusor contraction

Gillespie JI, van Koeveringe GA, de Wachter SG, de Vente J. BJU Int. 2009; 103: 1324-1333
Working mechanism of PTNS

Diagram:

- **Part a:**
  - Pontine storage centre
  - Bladder
  - Pelvic nerve
  - External urethral sphincter
  - Pudendal nerve
  - (+) sign indicating contraction of bladder outlet and inhibition of detrusor

- **Part b:**
  - Pontine micturition centre
  - Hypogastric nerve
  - Pelvic nerve
  - (+) sign indicating contraction of bladder
  - (-) sign indicating relaxation of bladder
  - PAG (Periaqueductal grey)
Hypothesis working mechanism PTNS

OAB symptoms are the result of disbalance between inhibitory and excitatory control systems

1. Sensory input through pudendal nerve inhibits detrusor activity and enhances external sphincter tone. This facilitates storage of urine.

2. Bladder normally responds to neural stimulation with rapid contraction and slow, longer lasting relaxation. With recurrent repetitive stimuli, the bladder response is down regulated.

Hypothesis working mechanism PTNS

1.

2.

3. Stimulation of afferent sacral nerves in lower extremities increases the inhibitory stimuli to the efferent pelvic nerve and reduces detrusor contractility.

4. Affects the neuro-axis and restores balance between inhibitory and excitatory regulation at various locations.

Concept of PTNS

• It is feasible to effectively influence behaviour of the lower urinary tract via the Posterior Tibial Nerve

• Discontinuous stimulation can work for some time after the stimulation has stopped

Sites of Neuromodulation for LUTS

- Anal/Vaginal
  [Fall et al 1978]

- Dorsal Clitoral/Penile Nerve
  [Nakamura & Sakurai 1984, Fjorback et al 2007]

- Sacral Nerve Implants
  [Schmidt 1988]
Why the Tibial Nerve?

- 1983 – McGuire - treated urge, frequency, and incontinence with tibial nerve electrical stimulation
- 1999 – Stoller – modified technique using near nerve needle stimulation
- Tibial nerve stimulation is more acceptable than genital/anal stimulation
Tibial Nerve Pathway

- Innervates muscles including big toe flexor
- A toe extension may not be present in all cases
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
Urgent® PC Neuromodulation System
PTNS: Procedure

- “frog” position (optional)
- puncture 5 cm upwards of the medial malleolus
- attach reference electrode
- connect to stimulator
- adjust stimulator current
PTNS: Procedure

- Sensory response
  - radiating sensation in the sole of the foot

- Motor response
  - toe flexion and/or fanning
PTNS: Protocol

• 12 (bi)weekly sessions of 30 min.

• Adjust stimulation intensity during session

• Out-patient setting

• Performed by doctor or nurse practitioner

• Success expected after 6-8 sessions

• Successful cases: continue as the patient requires (tapering protocol) → once every 2 - 4 weeks
Indications

- OAB syndrome (OAB wet and OAB dry)
- Pelvic Pain
- Voiding Dysfunction
- Fecal incontinence
Urgent PC Contraindications

• Patients who are pregnant or planning to become pregnant while using this product
• Patients with pacemakers or implantable defibrillators
• Patients prone to excessive bleeding
• Patients with nerve damage that could impact either percutaneous tibial nerve or pelvic floor function
Clinical data on PTNS

- Meta-Analyses
- OrBIT - RCT compared to drug
- SUmiT - RCT compared to placebo
- Long-Term Data
  - OrBIT 12 month – Results sustained for 12 months
  - STEP – up to 3 years
  - “Real Life” Clinical Studies
Clinical Success Measurements

- Reduce leak episodes by > 50%
- Reduce frequency to ≤ 8 voids/24 hr (normal)
- Patient requests continuation of therapy
60 – 80% Response

Urgent® PC Objective Success
Results from RCTs & Meta-Analyses

<table>
<thead>
<tr>
<th></th>
<th>RCT</th>
<th>Meta-Analyses</th>
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</thead>
<tbody>
<tr>
<td>Peters n=50</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>Finazzi-Agro n=18</td>
<td>71%</td>
<td>71%</td>
</tr>
<tr>
<td>MacDiarmid n=244</td>
<td>71%</td>
<td>60.6%</td>
</tr>
<tr>
<td>Burton n=940</td>
<td></td>
<td></td>
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</tbody>
</table>
OrBIT – PTNS versus tolterodine

- Multicenter, RCT
- 12 week phase
- 12 month responder follow-up
- 1:1 randomization (n=100)
- Physician and patient impression of improvement
- Voiding diaries, QoL measures

OrBIT Results at 12 Weeks

OrBIT Results at 12 Weeks

OrBIT – Adverse events

- Constipation reported less often in PTNS arm compared to drug arm (p=0.04)
- Dry mouth reported less often in PTNS arm compared to drug arm (p < 0.001)
- PTNS group reported pain, discomfort or redness at ankle (assessed for PTNS group only)

OrBIT 12 Week Conclusion

Urgent® PC and slow release tolterodine provide similar (significant) objective and subjective improvement.

SUmiT Trial – UPC vs. Sham

- Double blind, RCT, placebo-controlled
- 220 patients, 23 sites
- Validated, previously published sham
- Patients were not on OAB drugs during the study
- Voiding diaries and QoL measures
- Intent-to-treat analysis

SUmit Results

• Statistically significantly better outcome compared to sham for:
  • Urinary urgency (p=0.003)
  • Urinary frequency (p<0.001)
  • Urinary urge incontinence (p=0.02)
• No serious adverse events or device malfunctions

SUmiT Trial conclusion

- Urgent PC is superior to sham,
- Effect is not due to placebo effect

STEP Study: 36 Months follow-up

- **Sustained Therapeutic Effect of Percutaneous Tibial Nerve Stimulation**
- Subjects were participants in the SUmiT trial
- Multi-center, randomized, double-blind
- 29 subjects through 36 months
- Voiding Diary and OAB-q questionnaires
- Evaluation of long-term therapy efficacy

STEP Study - Results

• 29 subjects completed tapering protocol and followed up through 36 months
• Subjects received 1 PTNS treatments per month
• Sustained significant efficacy and safety of PTNS for OAB demonstrated
• No treatment related adverse events

STEP Study – 36 Months

STEP Study – 36 Months

STEP Study – 36 Months

Mean number of treatments per month

STEP Study – 36 Months

OAB-q HRQoL and Symptom Severity Scores by Follow-up Visit ITT-LVCF n=50 (p<0.0001)

When do patients respond?

- Retrospective, single-site
- 141 female refractory OAB patients

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Weeks to improvement (median)</th>
<th>Weeks to improvement (range)</th>
<th>Percent patients w/ late response (&gt; 8 txs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nighttime Voiding</td>
<td>5</td>
<td>2-12</td>
<td>9.9%</td>
</tr>
<tr>
<td>Frequency</td>
<td>7</td>
<td>2-12</td>
<td>8.1%</td>
</tr>
<tr>
<td>Urgency</td>
<td>6</td>
<td>2-12</td>
<td>18%</td>
</tr>
<tr>
<td>Urge Incontinence</td>
<td>6</td>
<td>2-12</td>
<td>18.6%</td>
</tr>
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</table>

Cost-effectiveness: PTNS versus SNS

• Comparison of cost-effectiveness between PTNS and sacral nerve stimulation during 2 years
• The costs were $4,867 and $24,342 for PTNS and SNS, with 71% and 90% subjective cure rates
• An incremental cost-effectiveness ratio of $99,872 when staying on therapy was assessed.
• “PTNS and SNS are both safe, effective neuromodulation therapies for OAB. In this economic model PTNS had substantially lower cost.”

AMC data

Phase 1
  • Drug therapy combined with behavioral therapy
  • Drug therapy

Phase 2
  • PTNS
  • Botox

Phase 3
  • Botox

Phase 4
  • Bladder augmentation
Patient characteristics

• 2012 – 2013
• N = 85 in 2 locations (Amsterdam and Utrecht)
• Previous use of antimuscarinics: 80%
• Previous pelvic physiotherapy: 50%
• Concomitant stress incontinence: 40%
Outcome of PTNS

Number of treatments:
Response after first 12 weeks:
• No response = 15/80 = 19%
• Positive response: 39/80 = 49%
• Complete response: 26/80 = 33%
Response at end of therapy:
• No response = 25/80 = 31%
• Positive response: 16/80 = 20%
• Complete response: 39/80 = 49%
Meta-Analysis – Burton

- Includes 16 studies, 940 total patients
- Subjective success rate of 61.4% (95% CI 53-72%)
- Objective success rate of 60.6% (95% CI 84-75%)
- Statistically superior to Sham [RR 7.02 CI 1.69 – 29.17]
- No significant differences in the change in bladder diary parameters compared to antimuscarinics; PTNS associated with a better side-effect profile

## Meta-Analysis - MacDiarmid

Includes 7 studies, 244 patients
71% of patients improved

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Mean Improvement</th>
<th>Patients</th>
<th>Studies</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Daytime Voids</td>
<td>23%</td>
<td>244</td>
<td>7</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Nighttime Voids</td>
<td>41%</td>
<td>151</td>
<td>5</td>
<td>P&lt;0.002</td>
</tr>
<tr>
<td>Voiding Volume</td>
<td>43%</td>
<td>182</td>
<td>5</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Incontinence Episodes</td>
<td>45%</td>
<td>167</td>
<td>4</td>
<td>p=0.023</td>
</tr>
<tr>
<td>I-QoL</td>
<td>17%</td>
<td>122</td>
<td>3</td>
<td>P=0.033</td>
</tr>
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</table>

Take home message

• PTNS based on sound principle

• Approach of the posterior tibial nerve feasible for clinical application

• Outpatient procedure easy to do

• Level 1A proven efficacy in OAB!