

# Percutaneous Tibial Nerve Stimulation via Urgent<sup>®</sup> PC Neuromodulation System – An Emerging Technology for Managing Overactive Bladder

a report by

**CystoMedix, Inc.**

## Background and Significance

OAB ranks among the most prevalent and challenging problems in urology.<sup>1,2</sup> An estimated 34 million Americans and 46 million Europeans suffer from OAB, although fewer than 40% seek medical help.<sup>3-6</sup> A survey of individuals with OAB estimated that the total US economic costs of OAB are over US\$12 billion.<sup>7</sup>

In addition to clinical consequences and economic costs, OAB is associated with devastating losses in the quality of patient's lives.<sup>8-10</sup> Patients with OAB often reduce their social activities, become isolated and are predisposed to depression.<sup>11</sup> An array of pharmacologic, electromechanical, behavioural and surgical interventions are currently used to treat OAB.<sup>12,13</sup> However, for a significant proportion of patients, response to treatment is poor and/or may be compromised by troublesome or severe side effects. Because of the refractory nature of OAB, physicians previously had limited interest in treating such patients.<sup>14</sup>

## OAB Syndrome

OAB is distinguished from other forms of urinary incontinence, including stress incontinence and dysfunctions associated with neurogenic disorders and surgical injury.<sup>15,16</sup> The International Continence Society defines OAB as urinary urgency with or without urge incontinence, usually with urinary frequency (voiding eight or more times in a 24-hour period) and nocturia (awakening two or more times a night to void).<sup>17</sup> The key symptom in OAB is urgency – defined as a sudden compelling desire to void, which is difficult to defer.<sup>18</sup>

No precise cause for OAB has been identified, with physiologic abnormalities ruled out by diagnostic evaluation. Although aetiology remains elusive, a variety of risk factors are associated with the development of OAB including older age, side-effects of medications, systemic chronic conditions, pregnancy/childbirth, neurological abnormalities, endocrine irregularities, functional and behavioural factors and lower urinary tract conditions.<sup>19,20</sup>

## Mechanisms of Urinary Continence/Incontinence

Normal urinary control is entirely dependent upon competent neural pathways and co-ordination among the central nervous system, the peripheral nervous system, nerve pathways, bladder and sphincter.<sup>21,22</sup> Continence requires a relaxed bladder and closed urethra during the filling phase; at micturition, an intravesical pressure above the opening pressure of the simultaneously relaxing urethra has to be generated.<sup>23</sup> In clinically normal subjects, as the bladder fills the sensation of urge is mediated by slowly responding mechanoreceptors in the bladder wall. Afferent impulses are conveyed to the central nervous system at a certain level of fullness, while information is relayed through the spinal cord to the pons and cerebral cortex. The cortex provides for social continence, delaying voiding until socially acceptable.<sup>24</sup>

The same mechanoreceptors provide the triggering signal for both initiation of urination and the driving force required to sustain bladder contraction and emptying.<sup>25</sup> Parasympathetic stimulation allows relaxation of the proximal urethra and contraction of detrusor smooth muscle by release of acetylcholine on the muscarinic post-ganglionic receptors.<sup>26</sup>

Sympathetic stimulation leads to bladder storage and epinephrine and norepinephrine are the primary neurotransmitters for the post-ganglionic sympathetic nervous system.<sup>27</sup> Stimulation of beta-adrenergic receptors in the bladder promotes storage by inhibiting detrusor contractions and allowing relaxation of the bladder, while stimulation of alpha-adrenergic receptors contracts the bladder neck.<sup>27</sup> Thus, normal voiding is dependent on intact central and peripheral nervous system structures and pathways, as well as normal bladder and sphincter function.

If the responses of the afferent nerves associated with the voiding reflex circuitry are abnormal, bladder hyperactivity and urinary incontinence, resulting from loss of voluntary control, can result.<sup>28</sup> Disorders of the central or peripheral



nervous systems, altered levels of neurotransmitter and problems with the bladder smooth muscle can all lead to OAB.<sup>29</sup>

## OAB Treatment Options

### Pharmacotherapy

Pharmacotherapy, the mainstay of OAB treatment, is based on drugs that block bladder muscarinic receptors. Unfortunately, no treatment is bladder specific and therefore most drug therapies have unwanted systemic anticholinergic side effects.<sup>30</sup> Antimuscarinic agents are most frequently prescribed.<sup>31,32</sup> Some patients experience satisfactory results, but many do not. Because the side effects may be severe, overall adherence to treatment is poor with reported drug therapy discontinuance within 18 months.<sup>33,34</sup> Improved formulations show increased success, but even with the introduction of more 'bladder-selective' antagonists, treatment compliance remains a serious problem.<sup>35</sup>

### Exercises and Behavioural Modifications

Other frequently prescribed therapies include exercises for pelvic floor muscle retraining, lifestyle behavioural modifications and biofeedback techniques. Such therapies are frustrating and are effective for only a small proportion of highly motivated individuals.

### Surgery

Surgical treatment for OAB often involves bladder denervation to reduce the bladder overactivity; however, post-surgery requires patients to self-catheterise long term.<sup>36</sup> This surgery should be a last resort and is typically considered only in paraplegia patients.

### Neuromodulation

As previously described, normal urinary control is dependent upon competent neural pathways and co-ordination among the central and peripheral nervous systems, the nerve pathways, bladder and sphincter. Unwanted, unco-ordinated or disrupted signals along these pathways can lead to OAB. Therapy using neuromodulation incorporates electrical stimulation to target specific neural tissue and 'jam' the pathways transmitting unwanted signals.

To modulate bladder dysfunction, the stimulator signals must be delivered to the neural tissue affecting bladder activity. The pudendal nerve provides the major innervation of the bladder and pelvic floor, originating in the sacral plexus S2-4. Sacral parasympathetic pre-ganglionic fibres in the pelvic nerve provide the major excitatory input to the

bladder. Fibres originating in the thoracolumbar sympathetic pathways provide the inhibitory input.<sup>37</sup>

With the discovery that direct stimulation of the S1-S3 sacral segments results in micturition, the potential for sacral nerve stimulation (SNS) became apparent.<sup>38</sup> Animal and human studies further demonstrated how electrical stimulation of the pelvic and sacral nerves influenced voiding<sup>39-42</sup> and studies on stimulation of the bladder, pelvic floor, pelvic nerve, spinal cord, sacral root and detrusor apparatus<sup>43-49</sup> led to development of neuromodulation therapies for urologic disorders.

Research, development and significant clinical testing<sup>50-52</sup> resulted in the introduction of a surgically implanted device to stimulate the sacral nerve – the Interstim® Therapy for Urinary Control (Medtronic, Inc.) because the potential for SNS was evident.

Despite the high incidence of OAB and the clinical success of the Interstim device,<sup>53-56</sup> these instruments are not used widely among urologists due to poor patient acceptance and difficulties associated with effective long-term operation.<sup>57,58</sup>

Stoller's animal studies in monkeys,<sup>59</sup> based on research by McGuire (use of direct electrical stimulation of the tibial nerve as an alternate route to achieve SNS and to inhibit detrusor activity<sup>60</sup>) paved the way towards the clinical application of peripheral tibial nerve stimulation (PTNS).

Using a device of his design to administer PTNS, Stoller conducted a clinical study of patients diagnosed with urge incontinency, urgency/ frequency syndrome and/or pelvic pain.<sup>61</sup> Prior to enrollment, study subjects had sought care from an average of six physicians and reported daily average urinary frequency at 19 voidings (versus normal frequency of eight or fewer). Results were impressive, with 89% of the subjects responding to PTNS therapy,<sup>62</sup> including reductions in urgency, frequency, pain and urge incontinence. No serious adverse events or side effects were observed during or after treatments.

Stoller's device (formerly called Stoller Afferent Nerve Stimulator – SANS) has been revised, commercially developed and introduced by CystoMedix, Inc. as the Urgent® PC Neuromodulator (UPC) for treatment of OAB. The UPC was introduced in Europe mid-2003 and formally introduced in the US in early 2004.

### Equipment and Use

The UPC device used to deliver PTNS is a combination of electrode and generator components, including a small 34-gauge needle electrode, surface electrode, lead wires and hand-

held electrical generator. The low-voltage stimulator (9 volts) has an adjustable pulse intensity of 0–10mA, a fixed pulse width of 200 microseconds and a frequency of 20Hz. The device produces an adjustable electrical impulse that travels to the sacral nerve plexus via the tibial nerve.

### Treatment Protocol

The needle electrode is inserted percutaneously approximately two inches (5cm) cephalad to the medial malleolus. After the lead wire and surface electrode are attached, the device is turned on and amplitude is slowly increased until the patient's large toe begins to curl, the digits fan out or the entire foot extends, indicating proximity to the nerve bundle. Amplitude is then reduced slightly and treatment is continued for 30 minutes. Stoller's protocol specifies 12 once-weekly 30 minute treatments.

### Maintenance Therapy

Although benefit is sustained for long periods in most OAB patients, PTNS effects diminish over time. Sooner or later, all patients require periodic maintenance treatments. Therapy schedules are tailored to individual patient needs.<sup>63</sup>

### Clinical Efficacy of PTNS

An abundance of published peer-reviewed clinical trials demonstrate the safety and efficacy of the UPC devices for PTNS therapy.<sup>64–70</sup> (While many publications as well as current users reference the PTNS product and technology as 'SANS', the SANS and UPC products and technologies are relatively synonymous. PTNS technology is currently available with UPC devices.) There is significant intra-study agreement among these publications. Aggregately, in trials involving more than 275 adult OAB patients (treated with 30 minute stimulations for 10–12 once-weekly sessions), the overwhelming majority experienced statistically and clinically significant improvement of symptoms, defined uniformly as frequency of daytime and night-time bathroom visits, sensations of urgency and episodes of urine leakage or frank incontinence. A significant minority regained

bladder function equivalent to that of normal individuals. None reported significant adverse events or side effects. Uniformly, investigators concluded that PTNS with the UPC device offers a safe, minimally invasive and effective treatment for managing refractory overactive bladder and/or pelvic floor dysfunction.

Additional studies reported on the use of the PTNS therapy for other applications (note that UPC is indicated for pelvic floor dysfunction, for the treatment of patients with urinary urgency/frequency and urge incontinence). Two studies reported good results following treatment of children with a variety of aetiologies for bladder/sphincter dysfunction.<sup>71,72</sup> A single study found significant benefit using PTNS therapy to treat faecal incontinence.<sup>73</sup> A study using PTNS to treat pelvic pain found only modest success but enough evidence of benefit to conclude that PTNS should be considered for patients failing other forms of therapy.<sup>74</sup>

### Conclusion

OAB afflicts a significant portion of the population with significant costs to healthcare systems. Standard therapies fail to help millions of OAB sufferers. Pharmacologic and behavioural interventions are frequently unsuccessful, inappropriate or discontinued.

Surgery should always be a last resort. Although high rates of success with SNS techniques have been reported in numerous studies, disadvantages (surgical risks, the high cost, technical problems, side effects and poor patient compliance) may outweigh potential benefits.

The UPC provides an effective alternative therapy for OAB. In clinical trials, the device is shown to be effective, simple to administer and virtually risk-free. The UPC device is minimally invasive, comparatively inexpensive, has the potential to alleviate an enormous therapeutic need and for some patients it may eliminate the need for costly lifetime drug therapy. The UPC device should be considered as a first-line therapy for the burdensome, intractable problem of OAB. ■

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