Transcutaneous Electrical Nerve Stimulation of Lower Leg Afferents for the Potential Treatment of Overactive Bladder

by

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A thesis submitted in conformity with the requirements for the degree of Master of Health Science in Clinical Engineering

Institute of Biomaterials and Biomedical Engineering
University of Toronto

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Characterizing the Selective Activation of Lower Leg Afferents for Potential Treatment of Overactive Bladder by Transcutaneous Electrical Nerve Stimulation

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Abstract

Transcutaneous electrical nerve stimulation (TENS) has been used as a neuromodulation therapy for overactive bladder (OAB). There has been limited efficacy shown with non-invasive neuromodulation therapies compared to percutaneous tibial nerve stimulation. TENS therapy has been explored as using the tibial nerve, but preclinical data suggests that during tibial nerve stimulation there is coactivation of the saphenous nerve and that the plantar nerves may be better nerve targets. The goal of this research is to characterize the selective activation of lower leg afferents when stimulated with TENS and to determine the therapeutic efficacy of stimulating the saphenous nerve with TENS for OAB therapy. The clinical studies in this research suggest that the saphenous may be a good nerve target for therapy and its efficacy is explored. Based on these findings, TENS may provide patients with a convenient at-home treatment for OAB allowing them to manage their symptoms.
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List of Abbreviations

CNS: Central Nervous System

HRQL: Health Related Quality of Life

LPN: Lateral Plantar Nerve

MPN: Medial Plantar Nerve

OAB: Overactive Bladder

OABq: Overactive Bladder Quality of Life Questionnaire

PMC: Pontine Micturition Centre

PTNS: Percutaneous Tibial Nerve Stimulation

QoL: Quality of Life

REB: Research Ethics Board

SAFN: Saphenous Nerve

SNS: Sacral Nerve Stimulation

TENS: Transcutaneous Electrical Nerve Stimulation

T\text{\textsubscript{limit}}: Limit/Tolerance Threshold

TN: Tibial Nerve

T\text{\textsubscript{nerve}}: Nerve recruitment Threshold

T\text{\textsubscript{skin}}: Cutaneous Threshold

TTNS: Transcutaneous Tibial Nerve Stimulation

VAS: Visual to Analog Scale
TNS: Tibial Nerve Stimulation
Chapter 1

1 Introduction

1.1 Organization of Thesis

This thesis is divided into 7 chapters: (1) Introduction, (2) Background, (3) Research Aims, (4) Materials and Methods, (5) Results, (6) Discussion and (7) Conclusion and Future Work.

Chapter 1 (Introduction) describes the motivating problem of overactive bladder, the treatment options and the anatomy that will be tested in throughout this thesis. Chapter 2 (Background) provides a thorough literature review pertaining to transcutaneous electrical nerve stimulation (TENS), a comparison between the percutaneous and transcutaneous stimulation for overactive bladder (OAB) and the relevant pre-clinical trials that explains the decision of the nerve targets. Using the information outlined in Chapters 1 and 2, the research aims and objectives are described for this thesis in Chapter 3 (Research Aims). Chapter 4 (Materials and Methods) describes the methods and materials to achieve the objectives set in Chapter 3. From this point the thesis is divided into two clinical studies conducted for this thesis. Chapter 5 (Results) summarizes the results obtained in this research. Chapter 6 (Discussion) discusses the results from these two studies and puts them in perspective with the existing literature, describes where this therapy lies with the current studies on nerve stimulation as a therapy for OAB. Lastly, Chapter 7 (Conclusion and Future Work) provides a summary of the research conducted in this thesis and outlines what future work needs to be done in this topic.

At the end of this thesis there are 13 Appendices (A-M) that have a copy of all study materials used and provided to patients in both clinical studies.

1.2 Motivating Problem: Overactive Bladder (OAB)

Overactive bladder (OAB) is characterized by “symptoms of urgency, with or without urge incontinence, usually combined with symptoms of frequency and nocturia” [1]. It is also defined quantitatively by the need to urinate eight or more times in a 24-hour period including experiencing the need to urinate two or more times at night (nocturia). OAB adversely affects an individual’s
ability to perform everyday tasks, social interactions, and sleeping habits, and can be depicted by significant decreases in quality of life measures [2], [3]. Approximately 1 in 5, or 6 million Canadians over the age of 35 are affected by OAB [4], with an economic impact of approximately $380 million in Canada per year [5]. Generally, OAB is only reported to a physician when the symptoms begin to affect the individual’s quality of life because many individuals feel that this is a natural effect of aging [3].

1.3 Overview of Treatment Options for Overactive Bladder

There are a wide variety of treatment options for individuals who suffer from OAB including: behavioural therapies, drug interventions, botulinum toxin A (Botox) injections into the bladder and neuromodulation. Behavioural therapies are considered the first line of defense for OAB and pharmaceutical therapy is considered as a second line of therapy [6]. The third line of therapies include: Sacral Nerve Stimulation (SNS), Botox injections into the bladder, bladder augmentation surgery and long-term indwelling catheters to aid with voiding [6].

Behavioural treatments are lifestyle changes that the patient may choose to perform, such as, pelvic floor muscle exercises, bladder training, regulating fluid consumption or using absorbing pads. These are changes that the individual would need to work into their current daily routines and they are not always a solution for those that have more severe symptoms [1], [6].

The pharmaceutical remedies include many different types of anticholinergic medications such as oxybutynin or tolterodine [6]–[8]. These remedies are effective however, include side effects like dry mouth, blurred vision, impaired cognition and constipation [6]. In many cases the individual chooses to not continue with this form of treatment due to the side effects of the medication [8]. Botox injections are used to relax the bladder muscles but come with many risks such as worsening the bladder’s emptying ability [6], [7].

Surgical interventions are introduced when the symptoms of urge incontinence are severe. The first form of surgical intervention is to use a section of smooth muscle from the small intestine or from the bowel to increase the size of the bladder. Although the bladder capacity increases with this procedure, the density of mechanoreceptors (bladder fullness receptors) decreases causing the frequency of urgency to void the bladder to diminish [9]. The second form of surgical intervention is a full removal of the bladder, but this is only performed as a last resort [6]. A replacement is
either surgically constructed or an opening is created so that a bag can be attached to collect urine [6].

Nerve stimulation is the next form of therapy, which is considered as a third line of treatment after behavioural therapy and pharmaceutical interventions. Electrical neuromodulation is used as a treatment and utilizes electrical pulses to control the central nervous system circuits that, in turn, modulate urinary function. There are two methods of nerve stimulation used: first is Sacral Nerve Stimulation (SNS) and, second, is Percutaneous Tibial Nerve Stimulation (PTNS). SNS involves implanting an electrical stimulator into the lower back. The stimulator transmits electrical pulses via a multi-contact electrode that targets the third sacral root of the spinal cord (S3) [1], [6].

As an alternative to drugs and SNS [10], PTNS therapy is administered with a 34 G needle which is inserted, by a clinician, three finger-widths above and one finger-width behind the medial malleolus. Once proper placement of the needle electrode has been confirmed, as indicated by toe twitching or fanning, a continuous train of electrical pulses is applied for 30 minutes. This is repeated weekly for a total of 12 weeks, at which point significant improvements in bladder symptoms are achieved by patients [11]–[15].

1.4 Bladder Anatomy and the Nervous System

The following section will describe the anatomy of the bladder, tibial nerve (TN), plantar nerves, saphenous nerve (SAFN), and the mechanism behind tibial nerve stimulation (TNS).

The main function of the bladder is to store and eliminate waste in the body. Bladder control is a voluntary and involuntary action. There are periodic involuntary contractions as the bladder fills and begins to store urine causing the person to feel the urge to void. Bladder control is a voluntary action when the person is able to control and suppress the urge and can void when they want to. People who suffer from OAB experience frequency, urge and incontinence syndromes [1], [3]. The voluntary bladder control is inhibited causing the involuntary contractions to be so strong that it forces the individual to feel the urge to urinate when they don’t want or need to.
Figure 1.1: Cutaneous distribution of the lower leg[16]

Figure 1.2: Saphenous and Tibial nerve anatomy[16]
1.4.1 Tibial / Plantar nerve

The tibial nerve (TN) is a branch of the larger sciatic nerve which originates from the L4 – S3 dermatomes [16]. The sciatic nerve descends into the posterior part of the leg (thigh/gluteal region). Proximal to the knee, it splits into 2 nerves: (1) common fibular nerve and (2) the tibial nerve. The tibial nerve descends and innervates the posterior part of the leg and skin on the lateral-posterior side of the lower leg, the lateral side of the ankle and sole of foot. Between the medial malleolus and the heel, the tibial bifurcates into the medial and lateral plantar nerves. The medial plantar nerve (MPN) innervates the medial half of the sole including the first three toes while the lateral plantar nerve (LPN) innervates the lateral half of the foot including the last two toes. In PTNS therapy, the TN is activated near the medial malleolus where the nerve is closest to the skin surface.

1.4.2 Saphenous Nerve

The saphenous nerve (SAFN) is a branch of the femoral nerve which originates from the L2 – L4 dermatomes [16]. The femoral nerve descends from the spine through the pelvis and on the anterior side of the femur. The femoral nerve splits into anterior and posterior branches within the pelvis which innervate the thigh and anterior-medial aspects of the leg and foot. Although the femoral nerve splits into many motor nerves that supply many leg muscles the SAFN branch that is a long cutaneous, sensory nerve which travels along the medial side of the leg skin surface until the medial side of the foot. The SAFN accompanies the femoral artery before entering the knee, from

Figure 1.3: Cutaneous distribution of sole of the foot and plantar nerve anatomy[16]
where it travels along the medial side of the knee. The cutaneous fibers of the SAFN travel through the lower leg alongside the greater saphenous vein, supplying the skin on the medial side of the knee, leg and foot.

1.4.3 Tibial nerve and the Bladder

The physiological connection between the TN and bladder inhibition is not currently well-defined. Researchers have been investigating the mechanism behind why TNS has been effective in treating OAB patients. Studies have suggested that TNS evokes a supraspinal reflex but, it is still unclear what part of the brain is affected. The TN mechanism was first introduced by McPherson in 1966 suggesting that inhibition is lost when the spinal cord was transected in cats [17], leading us to believe that TNS is a supraspinal reflex. In 1993, Walter et. al. performed a study in cats that were transected at the thoracic level [18]. They found that TNS, conducted bilaterally, showed no inhibition was present in contrast to pudendal nerve stimulation, in which inhibition did occur [18]. Researchers then continued to test to uncover what aspects of the brain are then responsible for the TN mechanism for bladder inhibition [19], [20]. Ferroni et. al. tested the effects of TNS on decerebrate cats (by removing the cortex of the animal) and found that the forebrain is not essential to TNS [19]. There is speculation that the ascending pathway to the brain affects bladder capacity whereas, the descending pathway affects the voiding efficiency of the bladder. Lyon et al. found that TNS affects the bladder capacity and not the bladder efficiency [20]. Therefore, it blocks the signals going through the ascending pathway but when the voiding signal is sent via stimulation of the pontine micturition centre (PMC) in the brain, TNS is unable to block this pathway [20].
Chapter 2

2 Research Aims

2.1 Research Questions

The research conducted in this thesis contribute towards answering the following two questions:

1. Can transcutaneous electrical nerve stimulation be used to selectively activate nerves in the lower leg, which have been identified as potential therapeutic targets for treating OAB?
2. Can the TENS of the saphenous nerve be used as an effective OAB therapy?

2.2 Rationale and Hypothesis – Aim 1

Studies have shown that TENS may be used to restore normal bladder function by electrically stimulating the third sacral root (S3) [21]–[24], the pudendal nerve (PN) [20], [25] and the tibial nerve (TN)[26]–[28]. Recent pre-clinical work from our lab has identified additional neural targets, such as the individual branches of the TN, the medial and lateral plantar nerves (LPN, MPN) and the SAFN that can inhibit bladder function in anesthetized rats [28], [29]. Given the superficial nature of peripheral nerves, particularly those located in the lower leg, we hypothesized that a TENS device can selectively recruit these neural targets for treatment of OAB. However, there are no published studies that quantitatively characterize the non-invasive electrical activation of these nerves in humans.

2.2.1 Research Objectives

1. To characterize the electrical recruitment of cutaneous afferents; Tibial Nerve, Medial Plantar Nerve, Lateral Plantar Nerve and Saphenous Nerve during TENS of the lower leg in humans.
2. To determine the range of different amplitudes at which patients can electrically activate each neural target with TENS.
2.3 Rationale and Hypothesis – Aim 2

Pre-clinical work from our lab has shown that isolated stimulation of the SAFN trunk can induce significant inhibition of on-going bladder function [29] producing similar inhibition results as TN stimulation [28]. Therefore, we hypothesize that stimulation of the SAFN afferents can also provide therapeutic outcomes in patients.

2.3.1 Research Objectives

1. To determine the clinical effects of TENS of the SAFN in OAB patients.

2. To determine whether an at-home TENS protocol of the saphenous nerve provides effective treatment outcomes.
Chapter 3

3 Background

The primary goal of this study was to determine the feasibility of selectively activating each of the 4 nerve targets (saphenous nerve, tibial nerve, medial plantar nerve, and lateral plantar nerve) by using a non-invasive method of electrical stimulation (i.e., transcutaneous electrical nerve stimulation, TENS). The idea of PTNS was inspired by traditional Chinese acupuncture use and techniques to treat bladder syndromes. It was McGuire who applied transcutaneous stimulation to the TN and the peroneal nerves in the ankle to the SP6 location on the ankle [26]. His experiment showed improvement in 36% of the patients which was considered ground breaking since no one else had attempted such a treatment.

There have been many clinical and animal studies identifying percutaneous PTNS as an effective form of therapy and is enhanced when used in conjunction to anticholinergic drugs [30]. It is the use of transcutaneous tibial nerve stimulation (TTNS) that has been widely disputed as some researchers have found it to be useful while others have shown that the percutaneous method is more effective [31], [32].

3.1 TENS device

TENS has been primarily used and studied for it’s potential as a pain management therapy [33]. It is a device that delivers electrical currents to the nerves via surface electrodes placed on the skin surface. A standard TENS device is a small, battery-powered stimulating device that generates pulses of electrical current. These pulses are delivered to the body through the connected lead wires that have surface electrodes on the other end. The electrodes can be self-adhesive or rubber electrodes with conductive gel. Generally the pulse width is set between 50 – 250 µs, the frequency set between 1 – 150 Hz and the amplitude set between 0 – 100 mA [33].

3.2 PTNS

Peripheral nerve stimulation is an emerging therapeutic approach for treating OAB. Percutaneous tibial nerve stimulation (PTNS) is a minimally-invasive alternative to sacral neuromodulation that utilizes peripheral nerve stimulation to treat symptoms of OAB. A needle electrode is inserted 3
finger-widths above the medial malleolus and is confirmed by movement in the toes [10]. Stimulation is applied for 30 minutes a week and is repeated weekly for a total of 12 weeks, at which point significant improvements in bladder symptoms are achieved in approximately 37-82% of patients [11], [15]. Long term PTNS therapy can be limited by the repeated clinical visits required to continue ‘maintenance’ stimulation sessions every 3 weeks thereafter. In literature PTNS has shown consistent success rates but it is not 100% effective leading some researchers to think it should be changed to from a third line therapy to a first line therapy [34], [35]. One of the most cited PTNS studies has been the research conducted by Peters, MacDiarmid et. al. [12], [13], [36]. In 2009 Peters et. al. conducted a study where they compared the effects of PTNS and extended release tolterodine (ERT) for treating OAB [13]. One hundred participants were enrolled in the study but only 41 patients completed PTNS therapy while 43 patients took ERT for 12 weeks. In the 12 weeks, patients partook in weekly 30-minute stimulation sessions at 20 Hz and the amplitude was set below the pain threshold. The first electrode was placed 5 cm above the medial malleolus and posterior to the tibia while the return electrode was placed on the sole of the foot. Patients were required to submit 2-day voiding diaries and overactive bladder questionnaires before and after the 12 weeks of therapy. 79.5 % of the patients responded to PTNS therapy whereas 54.8% of patients responded to ERT.

MacDiarmid et. al. reported the long-term effects of this therapy in the next year. Of the 35 patients who responded to the therapy, 33 patients chose to continue with PTNS therapy from the study in 2009 [36]. At the end of the 9-month follow-up 25 patients remained and 96% of these patients maintained (or improved) their bladder responses. Once again 2-day bladder diaries and quality of life questionnaires were used to determine the improvement. In 2013, Peters reported on patients who underwent PTNS therapy for 3 years after the SUmiT trial [12], [14]. Patients were prescribed a 14 week tapering (maintenance therapy) protocol which consisted of 2 PTNS treatments every 14 days, 2 treatments at 21 day intervals and 1 treatment after 28 days [12]. After 14 weeks patients had an average of 1.1 PTNS treatments every month. They began with 50 patients enrolled in the study while 29 successfully completed the study. Overactive bladder questionnaires were completed every 3 months and bladder diaries were completed every 6 months over the 3-year period. They found that with this protocol at least 75% of patients had statistically significant responses to stimulation. They showed that PTNS is a feasible long-term therapy.
Scaldazza et. al. compared the effects of PTNS vs. electrical stimulation and pelvic floor muscle training (ES PFMT) [34]. Sixty patients enrolled in this study and were divided equally between the study groups. The ES PFMT group received treatment for 30 minutes, 3 times a week and the PTNS group received treatment for 30 minutes, biweekly for 6 weeks. 3-day bladder diaries and quality of life questionnaires were collected before and after the therapy was administered. They found both treatment methods to be effective but PTNS was slightly better.

3.3 TTNS

Transcutaneous tibial nerve stimulation (TTNS) has been studied as a potential non-invasive means of treating OAB but has shown inconsistent success rates raising questions about the effectiveness of TTNS [26], [37], [38]. McGuire first stimulated the tibial nerve transcutaneously with electrodes placed posterior to the medial malleolus and with the second electrode placed contralaterally to the first [26]. This approach resulted in detrusor inhibition but the location of TNS has been improved upon since. In 2003 a study was conducted indicating that there is a 50% success rate in the use of stimulating the tibial nerve using transcutaneous electrodes [32]. Amarenco et. al. conducted one stimulation session at 10 Hz, a pulse width of 200 µs and set the amplitude just below the motor threshold. One electrode was placed behind the medial malleolus and the second electrode was placed 10 cm above the first. The study had 44 neurogenic patients of which 22 exhibited a minimum of 50% decrease in involuntary bladder contractions. Although these results were promising, further investigation is necessary in providing a case where transcutaneous stimulation could be more effective.

De Sèze et. al. conducted a 3 month TTNS study where patients received 20 minutes of stimulation daily at 10 Hz, a pulse width of 200µs and set the amplitude just below the pain threshold [39]. The electrodes were placed above and below the medial malleolus and slightly posterior to the tibia. Data was collected via 3-day bladder diaries and overactive bladder questionnaires collected at day 0, 30 and 90. Of the 70 patients enrolled in the study only 66 completed it and of the 66 patients who underwent therapy there was an improvement rate of 83.3%. This study was conducted on patients with multiple sclerosis therefore, the effect on idiopathic overactive bladder is still unclear. Ammi et. al. performed an at home stimulation protocol which achieved a success rate of 53% [37]. Stimulation was set to 10 Hz and applied daily for 20 minutes for 1 month. One electrode was placed above the medial malleolus and the second electrode was placed 5 cm above
the first. Therapeutic effects were measured using Quality of Life (QoL) questionnaires and bladder diaries that provide information about the number of incontinence episodes experienced by the patient.

Somatic afferents in the foot (plantar nerves) were used to stimulate the tibial nerve (TN) in 2014 by Tai et. al. [38]. This was a follow-up study to the experiments that were conducted in 2011, where they stimulated lower leg afferents of the TN in cats using transcutaneous electrodes. This was the first time multiple sites in the foot were used as stimulation sites. They found that exciting the TN resulted in inhibition of the bladder due to the transcutaneous tibial nerve stimulation (TTNS) which increased bladder capacity [27]. Earlier that year they had performed a percutaneous experiment which involved using nerve cuffs on the cats where a 2 hour carry over effect was noticed [40]. The study they conducted in 2014 with eight subjects indicated that there was an increase in bladder capacity of more than 50% after 90 minutes of transcutaneous stimulation [38]. Two electrodes were placed across the sole of the foot to activate the entire tibial branch. The neural pathway that they stimulated in order to activate the TN was by stimulating the medial and lateral planter nerves at the same time since these are peripheral branches of the TN. More recently Ferroni et. al. used this electrode configuration to see if they can reduce nocturia (enuresis) in children by having participants perform a 1-hour daily stimulation protocol for 2 weeks. Stimulation occurred at 5 Hz, a pulse width of 200 µs with the amplitude set just below the pain threshold (between 0-100 mA). Patients were asked to record a night time bladder diary for 6 weeks, 2 weeks before the stimulation, 2 weeks during the therapy and 2 weeks after. They found that the 72.7% of patients responded to the treatment.

In 2015, a preliminary report of a “single-blinded sham controlled randomized” study by Patidar et. al. in which 40 participants received weekly 30 min TENS therapy sessions over a 12-week period. The stimulation frequency was set at 20 Hz, with a pulse width of 200 µs and the amplitude was between 0-10 mA. One electrode was placed a few centimeters cephalad to the medial malleolus while the second electrode was placed 10 cm above the first. There was no significant improvement from the sham stimulation group but the test group that received stimulation had a significant improvement. Of the patients that received TENS therapy, 71% reported no incontinence and 23% reported partial incontinence [41]. The limitation of this study is that the follow-up assessment of this therapy has not been reported [41]. Boudaoud et. al. used TTNS to manage symptoms of OAB in children as well and found a 45% response rate with their protocol
Participants underwent TTNS therapy, 30 minutes biweekly for 12 weeks at an amplitude of 10 mA, frequency of 10 Hz and pulse width of 200 µs. Patients were asked to fill bladder diaries for 7 days before and after the stimulation protocol. They placed an electrode above and below the medial malleolus for the duration of this study.

Manriquez et. al. compared the effects of TTNS to an extended release oxybutynin (ERO) in overactive bladder patients. There were 64 patients that completed the study, 30 were enrolled to receive the drug while 34 patients underwent biweekly 30-minute TTNS sessions for 12 weeks. The stimulation was set to 20 Hz, with a pulse width of 200 µs and the amplitude was set just above the motor threshold. One electrode was placed posterior to the medial malleolus and the return electrode was placed on the sole of the foot. Participants were asked to complete a 3-day bladder diary and quality of life questionnaire before and after the treatment. This team noticed a significant reduction of 70% and 60% between TTNS and ERO respectively.

3.4 Pre-clinical research in OAB

Recent preclinical animal work is being done to uncover the physiological mechanisms and different neural pathways that may contribute to the therapeutic effects of TNS. Tai et. al. placed 3 transcutaneous electrodes around a cat’s foot in order to stimulate the tibial nerve to demonstrate the suppression of bladder activity [40]. The neural pathway that they stimulated to activate the TN was by stimulating the medial and lateral plantar nerves at the same time since these are peripheral branches of the TN. As published by Kovacevic and Yoo, selective electrical activation of the medial and lateral plantar nerves can independently control bladder function [28]. Using anesthetized rats, it was shown that acute bladder inhibition was most effectively achieved by activating the medial plantar nerve; whereas prolonged bladder inhibition was most effectively obtained by electrically activating the lateral plantar nerve. More recently, using the same anesthetized rat model, Moazzam and Yoo found that saphenous nerve stimulation can also be used to reflexively inhibit bladder function. The saphenous nerve stimulation can cause bladder inhibition with minimal nerve stimulation (up to 1.5 times the nerve stimulation threshold) [29], [43]. Although the precise role of the central nervous system circuits remains unclear, animal models suggest that bladder-inhibitory reflexes can be evoked by multiple nerves located within the lower leg.
3.5 Comparison between PTNS and TTNS

Table 3.1: Comparison table - PTNS vs. TTNS [11], [15], [44]

<table>
<thead>
<tr>
<th></th>
<th>PTNS</th>
<th>TTNS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stimulation Frequency</strong></td>
<td>20 Hz</td>
<td>5-20 Hz</td>
</tr>
<tr>
<td><strong>Pulse width</strong></td>
<td>200 µs</td>
<td>200 µs</td>
</tr>
<tr>
<td><strong>Intensity (Amplitude)</strong></td>
<td>• 0 – 10 mA</td>
<td>• 0-100 mA</td>
</tr>
<tr>
<td></td>
<td>• Around the motor threshold</td>
<td>• Slightly below motor threshold</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Slightly below pain threshold</td>
</tr>
<tr>
<td><strong>Stimulation Protocols</strong></td>
<td>12 stimulation sessions total, weekly or monthly</td>
<td>Daily, biweekly, 3 times a week, weekly</td>
</tr>
<tr>
<td><strong>Location of electrode 1</strong></td>
<td>5 cm above medial malleolus and posterior to tibia</td>
<td>• 3-10 cm above medial malleolus &amp; posterior to tibia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Behind medial malleolus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Sole of the foot</td>
</tr>
<tr>
<td><strong>Location of electrode 2</strong></td>
<td>• Sole of the foot</td>
<td>• 5-15 cm above medial malleolus</td>
</tr>
<tr>
<td></td>
<td>• Arch of the foot</td>
<td>• Below medial malleolus &amp; posterior to tibia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Sole of foot</td>
</tr>
<tr>
<td><strong>Response Rates</strong></td>
<td>37 – 82%</td>
<td>0 – 83%</td>
</tr>
</tbody>
</table>

Although PTNS and TTNS have varying response rates and therapy parameters / protocols they have both been shown to be effective therapies. A cost effectiveness study conducted by Martinson et. al. in 2013 [35] reported that PTNS is a significantly cheaper alternative than Botox, augmentation cystoplasty or SNS therapies. Although this supports the feasibility of using PTNS as a long-term therapy, it still requires repeated clinical visits. Since TENS is a non-invasive method to deliver nerve stimulation, it becomes a target for a potential at-home therapy which would further decrease the cost of treatment [45]. Scaldazza et. al. suggested that due to the low cost, PTNS should be considered as first line of treatment rather than third [34]. Similarly, Schreiner et. al. thought that due to the cost effectiveness of TTNS, it should be changed to a first line of therapy. Further investigation is necessary to understand the underlying mechanism, refine the parameters and determine the most effective protocols used in these therapies.
Chapter 4

4 Materials and Methods

4.1 Study 1

In accordance with the protocol approved by the Research Ethics Board (REB) of the University of Toronto, in the study participants consisted of 15 healthy participants (10 female, age = 23.9 ± 2.5 years, range = 19 – 28 years) who provided written consent at the beginning of the experiment. Participants were recruited using recruitment materials approved by the REB of the University of Toronto, including posters posted around the campus, emails sent to the student body at the University of Toronto and word of mouth publicity. This study involved determining the feasibility of selectively activating the four target nerves using a conventional TENS device.

4.1.1 Experimental Methods

The experiment involved a one-hour session, during which a total of 11 stimulation trials were conducted. Following skin sterilization with alcohol wipes, a pair of 5 cm x 5 cm self-adhesive surface electrodes (STIMCARE, DJO Global, Vista, California) were placed on the lower leg to activate different neural targets (Figure 4.1): tibial nerve (TN), medial plantar nerve (MPN), the lateral plantar nerve (LPN), and the saphenous nerve (SAFN). Both electrodes were connected to a hand-held TENS unit (Empi Continuum™, DJO Global, Vista, California), where the stimulation frequency (20 Hz) and pulse width (200 μs) were set at constant values.
4.1.1.1 Inclusion/Exclusion criteria

Participants were included or excluded from the study based on the criteria below:

**Table 4.1: Inclusion / Exclusion criteria for the feasibility study**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can tolerate transcutaneous stimulation of the posterior tibial nerve trunk and branches, and saphenous nerve: at or above the threshold for foot twitch, and at frequencies between 10 Hz and 20 Hz.</td>
<td>Degenerative Neurological Disease of the CNS (e.g., Parkinson’s Disease, Multiple Sclerosis)</td>
</tr>
<tr>
<td>Between the age of 18 to 35</td>
<td>Cardiac pacemaker or other surgically implanted device(s)</td>
</tr>
<tr>
<td>Ability to read, write, speak, and verbally understand English</td>
<td>Pregnant or planning on becoming pregnant</td>
</tr>
<tr>
<td>Mentally competent, willing and able to understand and comply with all study related procedures during course of study</td>
<td>Cognitive dysfunction</td>
</tr>
<tr>
<td></td>
<td>Skin allergies to surface electrodes</td>
</tr>
<tr>
<td></td>
<td>Severe cardiopulmonary disease</td>
</tr>
<tr>
<td></td>
<td>Lower extremity pain or injury (joint, open wound, or otherwise)</td>
</tr>
</tbody>
</table>
Figure 4.1: Electrode Placement of the TENS device for all 4 neural targets. (A) The tibial nerve (TN) was electrically activated by placing the cathode 3 finger widths above and 1 finger width posterior to the medial malleolus and the anode at the midsole of the foot. (B) The medial plantar nerve (MPN) was targeted by placing both electrodes along the medial side of the plantar foot surface: cathode is placed at the base of the hallux and the anode is placed 2 finger widths from the cathode. (C) Similarly, the lateral plantar nerve (LPN) was targeted by placing both electrodes along the lateral side of the plantar surface. (D) The saphenous nerve (SAFN) was activated by positioning both electrodes on the medial side of the lower leg. The cathode was placed approximately 2 finger widths below the medial condyle of the tibia, and the anode was placed 2 fingers widths below the cathode.

4.1.1.2 Stimulation Protocol

The electrical activation of each neural target involved a series of three stimulation trials, where the amplitude was increased from 0 mA up to a pre-defined endpoint. The first trial was terminated at the cutaneous sensory threshold felt at the surface electrode ($T_{\text{skin}}$), the second trial was terminated at the threshold for activating the target nerve ($T_{\text{nerve}}$), and the third trial was terminated at the threshold for maximum tolerance ($T_{\text{limit}}$). Any carry-over effects were minimized by
alternating successive trials between each leg. The nerve activation threshold ($T_{\text{nerve}}$) was confirmed by either a foot motor response (TN, LPN, and MPN) or a cutaneous sensation that radiated down the medial aspect of the lower leg (SAFN). Immediately following each trial, questionnaires were handed out asking the participant to quantify the perceived intensity of surface stimulation using a visual to analog scale (VAS, range = 1 to 5), where 1 indicated the least comfortable sensation and 5 the most comfortable sensation. The questionnaire also instructed each participant to indicate the perceived area of stimulation by shading in an anatomical grid of the lower leg (Appendix A).

### 4.1.2 Statistical Methods

The stimulation amplitudes that achieved threshold activation of the skin ($T_{\text{skin}}$), target nerve ($T_{\text{nerve}}$), and maximum tolerance ($T_{\text{limit}}$) were summarized across all participants and represented as the mean ± standard deviation. Due to variability in thresholds among participants, both $T_{\text{nerve}}$ and $T_{\text{limit}}$ were normalized with respect to each participant’s $T_{\text{skin}}$. Data obtained from the questionnaire were used to summarize the perceived intensity of stimulation (VAS scores), and generate anatomical plots that show the spatial distribution of stimulation-evoked ‘sensation’. An anatomical plot for each neural target was created by summing the total number of participants that shaded in a particular pixel within the grid (maximum = 15), and then assigning a color intensity that was proportional to the frequency with which participants perceived stimulation in that particular pixel (figures 5.1 & 5.2).

Statistical analysis was conducted by performing a one-way ANOVA followed by a pair-wise Tukey-Kramer multi-comparisons (JMP, SAS Institute Inc.©, Cary, NC). A p-value less than 0.05 was considered statistically significant. To determine whether ANOVA was the correct analysis method, normality was confirmed by having the data undergo a normality test using JMP (SAS Institute Inc.©, Cary, NC).

### 4.2 Study 2

In accordance with the protocol approved by the research ethics board (REB) at the University Health Network (UHN), patients were asked to perform an at home stimulation protocol over 3 months to help determine the potential therapeutic effects of SAFN therapy for treating OAB. All
patients provided consent prior to beginning the study. SAFN therapy by TENS was offered as an alternative to drugs and other electrical neuromodulation techniques.

4.2.1 Materials

The TENS device used in this study (Phase 5 Combo, Canadian Medical Products Inc., Scarborough, ON) contains 2 channels from which stimulation can be delivered. Stimulation was delivered at 20 Hz and with a pulse width of 200 µs while the amplitude varied among participants based on their comfort levels. Two self-adhesive reusable rounded square electrodes of 5cm x 5cm (PROFLEX AgF electrodes, Canadian Medical Products Inc., Scarborough, ON) were used to deliver the stimulation. They were placed below the knee on the medial surface of the lower leg, the first electrode was placed two finger widths below the medial condyle of the tibia and the second electrode was placed two finger widths below the first one (figure 4.1).

4.2.2 Experimental Methods

All participants were referred to Dr. Magdy Hassouna as potential candidates for sacral neuromodulation. The urology clinic at Toronto Western Hospital is the main tertiary center for patients in Ontario, Canada. Those who could benefit from this TENS therapy are provided the option to participate in this study as an experimental treatment.
4.2.2.1 Inclusion/Exclusion Criteria

Participants were included or excluded from the study based on the criteria below:

Table 4.2: Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory overactive bladder (drugs such as anticholinergic medication)</td>
<td>Degenerative Neurological Disease of the CNS (e.g., Parkinson’s Disease, Multiple Sclerosis)</td>
</tr>
<tr>
<td>Frequency urgency syndrome</td>
<td>Cardiac pacemaker or other surgically implanted device(s)</td>
</tr>
<tr>
<td>Can tolerate transcutaneous stimulation of the lower leg</td>
<td>Pregnant or planning on becoming pregnant</td>
</tr>
<tr>
<td>Between the ages of 18 and 82</td>
<td>Cognitive dysfunction</td>
</tr>
<tr>
<td>Ability to read, write, speak, and verbally understand English</td>
<td>Skin allergies to surface electrodes</td>
</tr>
<tr>
<td>Mentally competent, willing and able to understand and comply with all study related procedures during course of study</td>
<td>Severe cardiopulmonary disease</td>
</tr>
<tr>
<td></td>
<td>Lower extremity pain or injury (joint, open wound, or otherwise)</td>
</tr>
</tbody>
</table>

4.2.2.2 Study visits and procedures

Participants underwent four visits throughout this study: (1) consent and screening visit, (2) baseline follow-up/device training, (3) 1-month follow-up and (4) 3-months follow-up and study exit. During the screening visit the participants were tested to make sure that SAFN activation was achieved with TENS. The second visit occurred one week after the first visit, where participants were trained to perform the stimulation treatment at home. Each visit was 30 – 60 minutes. All visits were conducted at the Urology clinic at Toronto Western Hospital.

4.2.2.2.1 Visit 1 – Consent & Screening visit

During the first visit, the study was described and the participants were asked to sign consent forms. The consent form was explained to the patients (about 15 minutes) along with two additional forms: (1) a screening form (Appendix B), and (2) a registration form which asked the subject’s age, gender, and their OAB treatment history (Appendix C).
Once written consent was received, participants were assigned a randomized code number (between B1 and B20). We continued to the screening process where participants were tested to determine whether the SAFN could be electrically activated with TENS. Participants were given a 4-day bladder diary (Appendix D) and a quality of life survey (Appendix E) to complete at home before the next visit. The bladder diary asks participants to track their bladder related activities such as, the number of trips to the bathroom and the urgency to urinate. A reminder email or phone call were sent prior to the second visit (e.g., ~ 4 days prior to the next visit).

4.2.2.2.2 Visit 2 – Baseline follow-up / Device training

Participants who returned a correctly filled out bladder diary and quality of life survey, underwent a stimulation protocol to demonstrate the sensation of the stimulation. During this visit, the SAFN stimulation was confirmed to ensure that the SAFN is correctly recruited, as indicated by a ‘tingling’ feeling radiating down to the ankle or foot.

**Stimulation protocol:**

1. An alcohol pad was used to clean the area of the lower leg, below the knee, where the two stimulation electrodes would be placed.
2. Two electrodes were placed on the participant’s leg and the strength of the stimulation was increased until there was either a sensation running from the electrode to the ankle/foot or the sensation became uncomfortable/painful.
3. If the participant began to feel pain before the sensation radiated down to the ankle/foot, then the electrodes were moved and the process was repeated 1 or 2 more times.

Patients with successful SAFN recruitment were stimulated for 30 minutes and the amplitude was set to a level just below the pain or discomfort threshold. These participants were invited to participate for the remainder of the study which involved at-home TENS therapy, applied at least three times a week for 12 weeks. If participants did not have successful SAFN recruitment or indicated that they did not want to continue were exited from the study. If the participant chose to continue with the study, they were asked to fill out a materials return agreement form.

Each participant was given a device kit which included:

a) The TENS device to take home with extra batteries, electrodes and connecting cables.
b) A set of instructions outlining the TENS device procedures which included the contact information of the graduate student in case of further clarification. (Appendix F)

c) A TENS device troubleshooting guide (Appendix G)

Each participant was provided with a folder that contained the following:

a) 1 set of study materials (1 set = 4-day bladder diary and 3-day quality of life questionnaire) to be filled out 26-30 days later (called “1-month study materials”)

b) A TENS stimulation calendar (Appendix H) with a page for each month on which patients will be asked to indicate dates of TENS treatments, the duration of the stimulation, the amplitude set on the device and location the stimulation was felt (calf, ankle or foot).

Participants were contacted on day 14 & 26 to answer any questions and to remind the participant to complete the study materials.

4.2.2.2.3 Visit 3 – 1-month follow-up visit

During the third visit, a completed bladder diary and quality of life questionnaire was collected from participants and the study staff reviewed the material to ensure it was filled correctly. Replacement set of materials were handed out to participants who didn’t complete or lost study materials. They were asked to mail the completed set to the urology clinic at Toronto Western Hospital.

During the visit, the participant briefly performed SAFN stimulation with the TENS device to confirm that treatment was being correctly self-administered. Incorrect steps were clarified and corrected. Participants were given another set of study materials to be completed at the end of the study after 12 weeks of stimulation.

Participants were contacted by phone one month after the third visit to answer any questions and to ask if they required extra supplies. Extra materials were mailed out to participants as needed.

4.2.2.2.4 Visit 4 – 3-month follow-up visit & study exit

Participants were contacted by phone 5 days prior to the fourth visit to remind them to complete the study materials. Participants returned the completed final set of study materials and the study staff reviewed the materials to ensure it was filled correctly.
Visit 4 also served as the end of study visit. During this visit, participants reviewed their study results with the study staff and discussed further treatment options with their urologist. A Study Exit form was completed by the participants. Participants who exited the study before its completion were asked to fill out the study exit form at that time.

4.2.3 Statistical Methods

Participants were asked to fill out bladder diaries and quality of life surveys (OABq) 3 times during the study. This occurred at baseline, at 4 weeks, and at 12 weeks of the study.

Baseline bladder symptom measures included: frequency, nocturia, number of urge incontinence episodes, and night time urge incontinence episodes [36], [46]. The effects of TENS therapy were determined by comparing these symptoms at baseline with those obtained at subsequent time points. A successful outcome was measured by a decrease of 50% or more of the symptom measures [22] [47]. The OABq has a total of 33 questions divided into two categories: (1) symptom severity/bother score, and (2) health related quality of life (HRQL) scale [48]. The first 8 questions cover the symptom severity/bother score and the remaining 25 questions cover the HRQL measures [48]. The HRQL questions are used to calculate 5 HRQL scores coping, concern, sleep, social and HRQL total [48]. Raw OABq values were transformed using the guidelines outlined by Coyne et. al. (Appendix I) [47], [48]. A change in the OABq transformed scores of 10 points or more indicated a clinically meaningful change in the subject’s quality of life [47], [48]. Clinical benefits to the patient were correlated with a decrease in the bother score, but with an increase in the remaining OABq measures.

Mean and standard deviation statistics were found for each time point using Microsoft Excel. Statistically significant improvements compared to the start of treatment were computed using repeated one-way ANOVA analysis in Microsoft Excel and JMP (SAS Institute Inc.©, Cary, NC). To determine whether ANOVA was the correct analysis method, normality was confirmed by having the data undergo a normality test using JMP (SAS Institute Inc.©, Cary, NC).
Chapter 5

5 Results

5.1 Study 1

Transcutaneous electrical activation of the 4 neural targets (TN, SAFN, MPN, and LPN) was achieved in all 15 participants. Each participant was able to indicate graphically the anatomical representation of electrical stimulation that was perceived at T<sub>skin</sub> and T<sub>limit</sub>. As shown in Figure 5.1 & 5.2, the perceived sensation of electrical pulses applied at T<sub>skin</sub> was spatially limited to the location of the surface electrodes. At T<sub>limit</sub>, the anatomical plots show notable spread of sensation radiating away from the surface electrodes. Participants receiving TN stimulation (figure 5.1) indicate the evoked sensation spreads up the medial aspect of the lower leg and also across a larger area of the ventral foot surface. Participants receiving SAFN stimulation indicated that the evoked sensation consistently radiated down to the medial malleolus (figure 5.2A). As shown in Figure 5.2B & 5.2C, electrical stimulation of the MPN and LPN at T<sub>limit</sub> resulted in perceived ‘sensations’ that were consistent with selective nerve activation (i.e., minimal spillover into adjacent innervation area).
Figure 5.1: Frequency of shaded squares among all the participants. It shows the areas where participants felt stimulation demonstrating the achieved selective activation during the cutaneous, nerve recruitment and tolerance threshold of the TN.
Figure 5.2: Similar to figure 5.1, this is a frequency of shaded squares among all the participants. Part A shows the cutaneous and tolerance threshold diagrams for the SFN. Part B shows the tolerance thresholds for the MPN and LPN.

As shown in Table 5.1, the average stimulation amplitude needed to evoke a cutaneous sensation using any of the 4 configurations ranged from 8.7 mA to 13.6 mA. The SAFN configuration exhibited the lowest $T_{skin}$, which was found to be significantly lower than those obtained by MPN and LPN stimulation ($p < 0.05$, ANOVA). The stimulation amplitude required to activate the
underlying target nerve (T_{\text{nerve}}) increased substantially in each stimulation configuration. At this level of stimulation, the threshold for activating the TN was significantly lower than that needed to activate the SAFN and LPN targets (p < 0.05, ANOVA). The average stimulation amplitude at which maximum tolerance was achieved (T_{\text{limit}}) ranged between 42.2 mA and 50.2 mA but there was no statistical difference between targets. It is noted that the maximum amplitude that could be tolerated by individuals were as low as 22 mA in the TN configuration to as high as 100 mA when targeting the MPN.

Table 5.1: Summary of stimulation results: mean ± SD (range)

<table>
<thead>
<tr>
<th>Target Nerve</th>
<th>T_{\text{skin}} (mA)</th>
<th>T_{\text{nerve}} (mA)</th>
<th>T_{\text{limit}} (mA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TN</td>
<td>10.2 ± 2.8 (6-17)</td>
<td>19.7 ± 4.4 (9-30)</td>
<td>42.2 ± 2.5 (22-64)</td>
</tr>
<tr>
<td>SAFN</td>
<td>8.7 ± 2.3 (6-15)</td>
<td>25.7 ± 7.4 (17-41)</td>
<td>47.7 ± 9.3 (28-62)</td>
</tr>
<tr>
<td>LPN</td>
<td>13.6 ± 3.7 (6-22)</td>
<td>25.5 ± 6.1 (19-41)</td>
<td>50.2 ± 15.5 (28-85)</td>
</tr>
<tr>
<td>MPN</td>
<td>11.6 ± 4.2 (3.5-19)</td>
<td>21.7 ± 5.9 (15-39)</td>
<td>50.1 ± 23.0 (25-100)</td>
</tr>
</tbody>
</table>

The normalized amplitudes for each threshold experienced by the participants are illustrated in figure 5.3. The limit thresholds are shown in terms of the skin and nerve recruitment thresholds for comparison. As seen in figure 5.3A, we found that the SAFN requires the largest multiple of T_{\text{skin}} to achieve T_{\text{nerve}} compared to the other nerve targets (p < 005, ANOVA). Figure 5.3B, shows that the T_{\text{limit}} of the SAFN has a much higher multiple of T_{\text{skin}} than the TN (p < 0.05, ANOVA) but is statistically similar to the T_{\text{limit}} values of the MPN and LPN. Although, the MPN and LPN
branch off of the TN, the higher $T_{\text{limit}}$ values could elude to the nature of the skin that the current must pass through as being calloused instead of smooth and thin.

![Graph](image)

**Figure 5.3:** (A) Average $T_{\text{nerve}}$ values plotted in terms of the individual’s $T_{\text{skin}}$ values, (B) Average $T_{\text{limit}}$ values plotted in terms of the individual’s $T_{\text{skin}}$ values

Figure 5.4 illustrates the participants $T_{\text{limit}}$ values in terms of their normalized $T_{\text{nerve}}$ values, there was no significant difference between the nerves. This suggests that the 4 target nerves require an average of 2.15 (range: 1.96-2.37) times of their respective nerve recruitment thresholds to achieve their limit thresholds.
Based on the qualitative assessments of electrical stimulation provided by each participant, we found that the perceived comfort level decreased with larger stimulation amplitudes (Figure 5.5). Although, there was a significant difference ($p < 0.01$, ANOVA) between the average comfort rating of each threshold, no significant difference of comfort levels was found between each nerve and their thresholds. This ensures that the stimulation protocol of this study was maintained throughout all the participants.

Figure 5.4: Average $T_{\text{limit}}$ plotted in terms of $T_{\text{nerve}}$ values
Figure 5.5: Comfort level curves show that the thresholds were taken at appropriate intervals. The average comfort levels were $4.8 \pm 0.42$, $3.8 \pm 0.89$ and $1.6 \pm 0.67$ on the VAS for the cutaneous, nerve recruitment and limit thresholds respectively. There is a notable significant difference between the average comfort levels of each threshold ($p < 0.05$, ANOVA) but not between the thresholds of each nerve.

5.2 Study 2

5.2.1 Population

10 patients provided consent to participate in the study. After the screening visit, we were able to successfully recruit 5 patients to participate in this pilot clinical study. Three patients completed the study while two were lost to at the 1-month follow up appointments. Therefore, we are unable to perform any statistical analysis on the results found but we can make notes about the progress of results so far. All on going participants have been able to provide detailed bladder diaries and
successfully complete the overactive bladder quality of life questionnaires. There were 11 patients who consented to participate in the study but only 5 qualified to participate in the study and completed their baseline study packages (Figure 5.6). The average age of these 5 patients was 54.4 ± 19.8 (range: 26 – 82). Two patients exited the study before completing the 1-month follow-up. One patient exited the study because they felt their symptoms were better managed with dietary (behavioural) changes while the second patient exited the study due to reasons unrelated to the study.

![Flow diagram of patients through the trial](image)

**Figure 5.6: Flow diagram of patients through the trial**

### 5.2.2 Bladder diary & OABq outcomes

There are many measures that were counted from the bladder diaries but only the most pertinent outcomes are displayed in table 5.2. The measures were chosen due to their prevalence in literature: frequency 24 hours, nocturia, severe urgent episodes, moderate-severe urgent episodes, urgency total, urgency night time, moderate incontinence episodes, severe incontinence episodes, urge-incontinence total, urge-incontinence night time. Table 5.3 shows the transformed OABq score
progression of each participant, it divides the data into 6 categories: bother, coping, concern, sleep, social and HRQL total. Patient SAFN-B18 and SAFN-B17 completed the trial and therefore have 3-time points on all graphs. SAFN-B5 and SAFN-B1 have 2-time points because they are in the process of undergoing the SAFN therapy. SAFN-B11 and SAFN-B8 exited the study before the 1-month follow-up and therefore, only have a baseline time point.

**SAFN-B18**

This patient is a 67 year old female who has had overactive bladder symptoms since her prolapsed bladder issues began in 2013 and has attempted various overactive bladder drug treatments with no success. She had not yet tried any electrical neuromodulation therapies. This patient began the SAFN stimulation protocol on April 27, 2017 and ended July 26, 2017. As seen in table 5.2, SAFN-B18 did not show any improvement in her total number of voids, but did have a notable change in her nocturia score (> 50%) between the 1 month and 3-month data collection points. By the end of the 3-month study, SAFN-B18 experienced a 53.8% decrease in the number of urge-incontinent episodes (Table 5.2). She also experienced a significant decrease in the number of severe urges but those urges seemed to have become less severe and have turned into moderate or weak urges thus causing the total number of moderate-severe urges to not have a significant decrease (Table 5.2). There was no change in the total number of urges or night time urges but there was an 86.4% decrease in the number of urge-incontinent night time episodes (Table 5.2). She maintained a stimulation protocol of undergoing the minimum of 3 stimulations / week (Table 5.4) therefore, this patient remained compliant throughout the course of the therapy.

It is important to note that during the patient’s 1-month visit, the patient reported that she was diagnosed with renal insufficiency, which suggests that any potential effects of SAFN therapy may be masked by this condition. As a result, this patient’s quality of life score was severely affected by this development in their health. The bother score had improved by decreasing by 20 points after the first month of stimulation, and further decreased by another 2.5 points at 3 months. However, all other OABq scores (Table 5.3) decreased to 0 by the end of the study. This patient did not choose to continue the SAFN therapy after the trial was completed.
SAFN-B17

This patient is a 40 year old female whose OAB symptoms first appeared in 2014 along with symptoms resembling a severe bladder infection. However, there was no diagnosis of an infection. Previously this patient has tried various OAB drugs with no success and stopped taking medication in 2016. She continues to take Phenazopyridine to reduce pain when she urinates. She has not tried any other bladder interventions including any neuromodulation therapies. She began stimulation on May 3, 2017 and completed the study on September 6, 2017. As shown in Table 5.2, there was no improvement in frequency, but nocturia showed a 37.8% improvement at 3 months. There was also a notable change in severe urgency (66.7% decrease). Even though there was a notable decrease in severe urgency, at the end of the 3 months, there was a 100% increase in moderate urgency causing the moderate-severe urgency total to not change. SAFN-B17 showed a 28 point improvement in the transformed social score (Table 5.3).

Although the participant maintained the minimum of 3 stimulations / week protocol during the first month, the frequency of TENS at-home treatment decreased to 2 stimulations/week during the remaining 8 weeks. During this latter period, she was unable to maintain full compliance (Table 5.4). Despite the reduced stimulation, the patient showed sustained decreases in severe urgency episodes (66.7% at 1 month; and 50% at 3 months). There was also a 37.8% decrease achieved in night time frequency at 3 months. However, the OABq scores did not show improvements at 3 months. In fact, the sleep score was lower than baseline. It is difficult to determine whether the loss of treatment compliance had a significant effect on treatment outcomes in this participant.

SAFN-B5

This patient is a 70 year old female whose OAB symptoms began 12 years ago. She experiences void frequency symptoms of having approximately 15 voids a day. This patient has tried many OAB drugs with no success. The participant stated that she takes sleep medication which contributes to the absence of nocturia. However, the patient does not report night time urge incontinence. She has not tried any electrical neuromodulation therapies. She began TENS therapy on June 5, 2017 and completed the study on September 20, 2017. This patient maintained the minimum stimulation protocol of 3 stimulation sessions / week and therefore, was compliant with the stimulation protocol. From the bladder diaries collected and summarized in table 5.2 there were no significant changes in any of her bladder metrics. In the first month, her OABq reported a 20
point increase in her sleep score but returned to baseline at the end of the study. At the end of the study there was clinically significant increase in her coping and social subscales of 10 and 12 points respectively.

**Table 5.2: Bladder Diary Summary**

<table>
<thead>
<tr>
<th>SAFN - #</th>
<th>B18</th>
<th>B17</th>
<th>B5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency 24 hr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B 1mo</td>
<td>3mo</td>
<td>B 1mo</td>
</tr>
<tr>
<td>Nocturia</td>
<td>28.3</td>
<td>24.8</td>
<td>21.0</td>
</tr>
<tr>
<td>Severe U</td>
<td>5.3</td>
<td>7.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Mod-</td>
<td>10.0</td>
<td>7.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Severe U</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U Total</td>
<td>20.0</td>
<td>15.8</td>
<td>10.5</td>
</tr>
<tr>
<td>U Night</td>
<td>7.0</td>
<td>3.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Mod I</td>
<td>4.5</td>
<td>0.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Severe I</td>
<td>0.5</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>UI Total</td>
<td>19.5</td>
<td>10.8</td>
<td>0.0</td>
</tr>
<tr>
<td>UI Night</td>
<td>5.5</td>
<td>0.8</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**Change > 25 %**  
**Change > 50 %**

*U = Urgency, I = Incontinence, Mod = Moderate, UI = Urge Incontinence*

**Table 5.3: OABq Summary**

<table>
<thead>
<tr>
<th>SAFN - #</th>
<th>B18</th>
<th>B17</th>
<th>B5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom</td>
<td>4w 12w</td>
<td>4w 12w</td>
<td>4w 12w</td>
</tr>
<tr>
<td>Bother</td>
<td>85.0</td>
<td>65.0</td>
<td>62.5</td>
</tr>
<tr>
<td>Coping</td>
<td>10.0</td>
<td>12.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Concern</td>
<td>8.6</td>
<td>11.4</td>
<td>0.0</td>
</tr>
<tr>
<td>Sleep</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Social</td>
<td>20.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>HRQL Total</td>
<td>9.6</td>
<td>7.2</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**Change > 10 points**

*4w = 4 weeks, 12w = 12 weeks*
Using the same protocol as Study 1, we measured the electrical recruitment of the SAFN with TENS in 4 of the 5 participants. Compared to young healthy individuals (Table 5.5), the T\textsubscript{skin} was 32.9% higher, T\textsubscript{nerve} was 3.5% lower, and T\textsubscript{limit} was 21.4% lower in the OAB group. We found a statistically significant difference (68.2%) in the normalized T\textsubscript{limit} (Figure 5.7), which suggested that OAB patients are not able to tolerate the same maximum levels of stimulation as the healthy participants. Figure 5.8 shows the limit thresholds normalized to the nerve recruitment thresholds, there was no significant difference between these values.

### Table 5.4: Patient Stimulation Protocol Compliance

<table>
<thead>
<tr>
<th></th>
<th>SAFN-B18</th>
<th>SAFN-B17</th>
<th>SAFN-B5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4 Weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of stim trials</td>
<td>12</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>Avg amplitude</td>
<td>43</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>Stimulation time (hr:min)</td>
<td>6:00</td>
<td>3:55</td>
<td>6:58</td>
</tr>
<tr>
<td>Protocol Frequency (/week)</td>
<td>2.5</td>
<td>2.5</td>
<td>3.5</td>
</tr>
<tr>
<td><strong>12 Weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of stim trials</td>
<td>39</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>Avg amplitude</td>
<td>40</td>
<td>21</td>
<td>34.5</td>
</tr>
<tr>
<td>Stimulation time (hr:min)</td>
<td>19:30</td>
<td>13:55</td>
<td>22:28</td>
</tr>
<tr>
<td>Protocol Frequency (/week)</td>
<td>3</td>
<td>2</td>
<td>3.5</td>
</tr>
</tbody>
</table>

**Table 5.5: Threshold Summary**

<table>
<thead>
<tr>
<th></th>
<th>TENS SAFN (n=4)</th>
<th>Healthy (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T\textsubscript{skin} (mA)</td>
<td>11.50</td>
<td>8.65</td>
</tr>
<tr>
<td>% difference = 32.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p = 0.061, ANOVA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T\textsubscript{nerve} (mA)</td>
<td>24.75</td>
<td>25.67</td>
</tr>
<tr>
<td>% difference = -3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p = 0.815, ANOVA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T\textsubscript{limit} (mA)</td>
<td>37.50</td>
<td>47.73</td>
</tr>
<tr>
<td>% difference = -21.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p = 0.054, ANOVA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 5.7: Average $T_{\text{nerve}}$ and $T_{\text{limit}}$ values plotted in terms of the individual’s $T_{\text{skin}}$ between OAB ($n = 4$) and healthy ($n = 15$) participants.

Figure 5.8: Average $T_{\text{limit}}$ values plotted in terms of the individual’s $T_{\text{nerve}}$ between OAB ($n = 4$) and healthy ($n = 15$) participants.
Chapter 6

6 Discussion

6.1 Study 1

In this study, we aimed to characterize the electrical recruitment of cutaneous afferents of the 4 nerve targets (TN, MPN, LPN and SAFN) as well as the upper limit (tolerance threshold) to TENS of the lower leg. We found that selective activation of the SAFN, MPN and LPN is possible even at maximum tolerance, but co-activation of the SAFN was confirmed during transcutaneous TN stimulation. There was no statistical difference between the cutaneous thresholds ($T_{\text{skin}}$) of the SAFN and the TN. This eludes to the co-activation of the tibial and saphenous nerves during TN stimulation. Elder et. al. showed, during PTNS the current trajectory activates both nerves since the needle electrodes passes the SAFN before reaching the TN [49]. Figure 5.1 shows that, initially the cutaneous fibers of the SAFN were recruited and then the TN fibers, as current increased the recruitment became stronger and the stimulation spread increased.

This study was motivated by the need for a non-invasive nerve stimulation therapy that could decrease the frequency of OAB symptoms. Previous studies have shown that TTNS has not been as effective as PTNS [44], [50]. Pre-clinical studies have shown that there are other nerve pathways (SAFN, MPN and LPN) that could be stimulated to cause bladder inhibition or OAB therapy. Multiple groups have tested an alternative technique involving the use of implantable tibial nerve stimulation devices [46], [51], [52]. Moazzam et. al. demonstrated that a wirelessly-powered implant could be used to stimulate the TN as a feasible stimulation approach in cats [53]. A subsequent study was conducted in rats which determined that long-term implants could be a viable option [51]. Urgent-SQ is the only commercially available implantable tibial nerve stimulator being used to deliver therapy [52]. TENS has the advantage of being a non-invasive and low risk technology that can help the patient manage their OAB symptoms long term. This type of an at-home therapy model would adapt to the patient’s lifestyle.

A simulation study was conducted in our lab to show what nerve fibers are activated with PTNS therapy explaining the variable therapeutic outcomes [49]. During stimulation a spill over of stimulation was found causing the SAFN fibers to activate since the active tip of the electrode is
very close to these fibers [49]. Pre-clinical trials conducted in our lab uncovered that the SAFN and the plantar nerves could serve as potential therapeutic nerve targets [28], [43]. Moazzam et.al. demonstrated robust bladder inhibitory effects by stimulating the SAFN using a nerve cuff electrode. The amplitudes necessary to induce inhibitory effects were lower than what was found to elicit the same response by stimulating the TN. Kovacevic et.al. demonstrated that bladder inhibition was attainable using the MPN and LPN. Using nerve cuff electrodes, it was found that the LPN elicits prolonged bladder inhibition when stimulation 6 times the rat’s foot EMG threshold. As these studies were done using nerve cuff electrodes it was not been determined whether selective activation of these nerves was possible using transcutaneous electrodes.

The current study shows evidence that stimulation spill over to saphenous cutaneous fibers occurs during TTNS. This is noted in the shaded frequency diagrams in figure 5.1. Therefore, with the current electrode configuration we are unable to attain selective tibial nerve activation. If the electrodes were both placed on the sole of the foot, as described by Tai et. al. in 2011, selective activation of TN would be achieved [40]. This study demonstrated that the SAFN has a lower cutaneous threshold and participants were able to tolerate this stimulation better than TN stimulation as described by the significant difference between their respective T_{limit} values (figure 5.3B). In this study, we found that even though the MPN and LPN are in close proximity, transcutaneous selective activation is possible to maintain at high amplitudes. This allows these new nerve targets to be explored as novel pathways for OAB therapy.

A major limitation to assessing whether TTNS therapy is an effective therapy involves the inconsistent electrode placement and stimulation parameters used in the various studies [32], [38], [39], [41], [45]. The first electrode placed behind the medial malleolus is common between most clinical trials, though, it is the placement of the return that tends to differ. A common electrode configuration involves one electrode posterior to the medial malleolus and the second 5-10 cm above the first. This configuration was used by Amarenco et. al, de Sèze et. al. and Ammi et. al. and their success rates were 50%, 83.3% and 53% respectively [32], [37], [39]. The second configuration placed two electrodes on the sole of the foot, to activate TN, this resulted in a 50% success rate [38]. The third configuration involves placing the electrode just above the medial malleolus and the second electrode was placed 5 cm higher than the first, this resulted in a 71% success rate [41]. In the final configuration, the TN stimulation technique of mimicking the placement of electrodes during PTNS [30], [45]. The placement of the electrodes has not been
consistent between studies which could be a contributing factor to the inconsistent success rates seen in these studies. Another factor could be the varying methods of measuring success can also raise question as to which method is the best; some studies used urodynamic changes instead of bladder diaries or incontinence related QoL survey [12], [32], [36], [37], [41], [54]. The TN stimulation electrode placement used in this study is the final configuration that was used by Peters et.al. and Manriquez et.al. [30], [45].

The clinical studies that test the use of TENS as a viable therapy for OAB do not clearly state the stimulation amplitude parameters used and duration of stimulation, nor do they state the thresholds used to provide this therapy as clear guidelines. The pre-clinical studies conducted by Tai et. al. indicates the stimulation threshold and the multiples of this threshold at which bladder inhibition is achieved (6T) [27], [55]. In the human trial that was conducted after the animal studies, stated that participants were stimulated to find the toe twitch [38]. The 90 minutes of stimulation administered to each participant was set between 25 and 60 mA but they did not characterize whether this value was close to the toe twitch threshold or not [27], [38]. In 2011, Tai et. al. reported that the stimulation intensity to inhibit the bladder was set to 2-4 times the toe twitch threshold; this is equivalent to our nerve recruitment threshold [27]. We identified that the average participant is not able to endure beyond 2.5 times the nerve recruitment threshold, which is \( T_{\text{limit}} \) (figure 5.4). This phenomenon is likely to be due to the size of the electrodes, as mentioned by Lyons et. al., larger electrodes are deemed more comfortable by patients since larger amplitudes are better tolerated [56].

6.2 Study 2

This study aimed to determine whether an at-home saphenous nerve TENS protocol provides effective treatment by having subjects record symptoms using a bladder diary and complete OAB quality of life questionnaires. Patients took part in a study where they ‘self-administered’ TENS therapy, 3 times a week for a total of 12 weeks (3 months). From the evidence collected, patients who applied stimulation more often showed the notable severe incontinence and severe urgency improvement. There was a clinically significant reduction (10 points or more) in bother scores. Of the patients that completed the study there was one compliant patient and one non-compliant.

This study was motivated by the evidence found in the feasibility study showing the saphenous nerve as a potential therapeutic target for TENS therapy in OAB patients. TENS devices are
commonly used for pain management [57] but, is still being explored as a potential use for treating OAB. We found that there wasn’t any notable change in the frequency data (number of trips in 24 hrs), table 5.2. This could have been due to the multitude of factors that could affect frequency overall such as loss of water from sweat, moisture lost in breathing or an increase of water intake from liquid in food consumption, diuretic consumption or caffeine. Many patients manage their symptoms by making behavioural changes in their day to day lives to accommodate for the urgency and frequency experienced to avoid incontinence. One common change that all patients made before stimulation began was to void before leaving the house so that they could reach their destination before feeling the urge to void again. TENS therapy does not alter this kind of behavioural changes, therefore even though this therapy may help decrease the number of urgent or incontinent episodes, the frequency of voiding does not decrease as seen with the results in table 5.2. Our results show some decrease in the urgent and incontinence episodes among the patients but they are not conclusive. TTNS studies conducted by de Sèze in 2011 demonstrated that there were significant outcomes experienced in 83% of patients [39]. They reported a significant decrease in the voiding frequency, severe urgency and incontinent episodes [39]. Patidar et. al. reported a significant change in the number of voids experienced by their participants at the end of the 12 weeks of therapy, from 11 voids per day to 7 [41]. Although these studies transcutaneously stimulated the TN, our study stimulated the SAFN using TENS and found similar results. In order to statistically determine the efficacy of TENS of the SAFN therapy, a subsequent study would need to be performed with more participants.

The patients recruited to this study were referred to a tertiary clinic that specializes in sacral neuromodulation. Published clinical studies show that these patients exhibit very severe OAB symptoms, such as frequencies between 9 and 26.3 [21], [58], which is consistent with the patients recruited in this study 11.5 - 28.3 voids per day. In contrast, PTNS and TTNS studies tend to recruit patients that are less severe [41], [59]. Patidar et. al. and Sharma et. al. had patients whose baseline voiding frequencies were between 8-14 voids per day. The implication of the higher voiding frequencies are that it may take longer for clinically significant changes to be noticed in the bladder symptoms or in the QoL questionnaires.

PTNS studies have demonstrated consistent therapeutic results compared to transcutaneous stimulation [11], [15]. Scaldazza et. al. found that PTNS had more significant results than compared to a treatment protocol of electrical stimulation combined with pelvic floor exercises.
In 2009 Peters et. al. demonstrated the consistent efficacy of PTNS therapy [30] responses were maintained for an additional 9 months by receiving weekly stimulation sessions [36]. Literature demonstrates that the treatment efficacy of transcutaneous stimulation has been inconsistent [44], one of the potential reasons for this is due to inconsistencies between interventions. In both cases, the target nerve was the TN and was stimulated near the ankle. In PTNS the needle electrode pierces through any edema present therefore, edema may not play a role in recruiting the target nerve. For the research conducted, patients whose SAFN we were able to recruit were invited to participate in the study. One of the reasons patients were screened out (3/5) was due to the edema present in their lower legs (below the knee), this has not been captured in any previous study as the SAFN has never been tested in humans as a potential OAB therapy target.

6.3 Challenges with TENS therapy

6.3.1 Electrode Placement

A major challenge of this study was to ensure that patients place the electrodes correctly for the therapy at home. We provided patients with a picture of where the electrodes were placed on during the screening / first day of stimulation visit. The electrodes were outlined on the patient’s leg so that they knew where the best placement was. After a few days, the outline of the electrodes began to fade and the patients were unaware of where they could move the electrodes to ensure maximum nerve recruitment. Unfortunately, this meant that the placement could not be rectified until the follow-up meeting scheduled and in the case of SAFN-B18 it was found that the placement may have been incorrect throughout the study. This highlights one of the technical difficulties in getting patients to self-administer TENS at home.

6.3.2 Edema

Another limitation noticed throughout the course of the study was the edema in their lower legs due to chronic venous insufficiency experienced by older adults. This made it harder for us to recruit the saphenous nerve during the screening process and that is why we had to exclude 5/10 patients.

Edema is defined as swelling or an abnormal enlargement in the body caused by fluid retention due to inefficient capillary fluid exchange [60]. In edema, the capillary filtration greatly exceeds
the absorption, which could be caused by an increase in hydrostatic pressure, a decrease in plasma protein or an increase in interstitial proteins [60]. Edema is a common sign of heart or liver failure, malnutrition or chronic venous insufficiency (CVI) [60], [61]. CVI occurs when the normal blood transport of one way valves in the veins is disrupted [62]–[64]. This disruption can be caused by incompetent venous valves and weakened calf muscles resulting in a high pressure system that ultimately leads to valve reflux [62]–[64]. CVI causes a “venous hypertension” that is responsible for most venous pathologies of the leg [62]–[64]. With the gradual deterioration of vessel walls over time, there is considerable evidence that the prevalence of venous diseases increases with age [62], [63], [65]. Beebe-Dimmer et. al. reported that the prevalence of CVI varies from <1% - 17% in men and <1% to 40% in women. The trend of CVI prevalence increasing with age was more pronounced in women compared to men in a 2001 study [64], [66]. There has not been consistent evidence that obesity or body composition is not a leading factor of CVI [62], [64]. This increase in fluid in the legs can act as an insulator to the electrical stimulation being applied which does not allow for proper therapy to be applied.

6.3.3 Patient Recruitment

A large challenge to this study was the patient recruitment process. Since this study was conducted in a tertiary clinic with patients coming from all over the province. The usual rate of follow-up appointments for each patient is every 6 months. Patients were not interested in participating in the study due to the frequency in which they needed to come to the clinic, leading to a slow recruitment rate.

6.3.4 Patient compliance

One roadblock to SAFN TENS therapy is patient compliance due to the highly repetitive nature of this therapy and the multiple clinic visits necessary to test this therapy. As many of the patients are travelling to the clinic from different areas across Eastern Ontario their compliance and dedication to this therapy has not been reaching the expected targets. Patients have dropped out of the study due to the distance that they needed to travel for this study and the number of times they needed to come to the clinic. There have also been patients who forget to do the stimulation or forget to take the stimulator with them on vacation causing the patients to prolong the therapy and potentially lose the bladder inhibitory / carry over effects of stimulation. Hasan et. al. found that throughout their study, they had to exclude 11/71 patients due to poor compliance [31].
Behavioural treatments are shown to be highly effective as a first line of therapy but outside the clinical trial setting there has been low compliance to keep up with the therapy [3].

It has been shown that therapies that require in-person visits to a clinic have higher compliance rates to the therapy but unfortunately this model is not accessible to many individuals who live in remote locations or cannot afford to come to clinics for multiple visits [57]. Thus, the at-home therapy model needs to be revised with non-invasive approaches that is more widely accepted by patients, especially those who do not want to take drugs or are averse to surgeries/minimally invasive procedures (i.e. PTNS). Ferroni et. al. was able to achieve a rate of 100% compliance in a 2 week study with tremendous results for enuresis / nocturia in children but they acknowledge that compliance could decrease with longer stimulation / treatment periods [54]. If primary care providers could prescribe minimally invasive nerve stimulation therapies, there could be higher compliance rates with patients as they are learning to make the behavioural changes necessary to manage their OAB.

6.3.5 Tertiary urology clinic

The SAFN TENS therapy study was conducted in a urology clinic at Toronto Western Hospital. Neuromodulation therapy is considered the 3rd line of treatment therefore there are not many clinicians who administer it. In Ontario, sacral neuromodulation therapy that is covered by provincial health insurance whereas, PTNS therapy is not. For patients to come to the urology clinic at Toronto Western Hospital, they must be referred to this clinic by their primary physician or urologist, in many cases the primary physician/urologist has already tried the 1st and 2nd line (behavioural and pharmaceutical therapy) of treatments with little or no success causing these patients to resort to the 3rd and final line of treatment. Of these patients, those that are not benefitting from SNS or are in the waiting list for SNS, are given the option to also try our experimental SAFN TENS therapy. This was one of the limitations of this study leading to the low recruitment rate.
Chapter 7

7 Conclusions & Future Work

Overactive bladder is an ongoing problem whose prevalence is growing with the current aging population in Canada [67]. Many individuals do not choose to report it because they are embarrassed or consider it a natural part of aging [3]. The goals outlined in this research are to (1) characterize the electrical recruitment of cutaneous afferent during TENS, (2) to determine the amplitude ranges at which patients can electrically activate each neural target using TENS and (3) determine whether an at-home TENS protocol provides effective treatment.

This research presents strong evidence supporting the feasibility of stimulating novel lower leg afferents for OAB therapy, with the LPN and SAFN being the most feasible targets. It also begins to determine whether an at-home SAFN TENS therapy protocol is effective or not. The therapy needs to be followed correctly for the effect to be maintained because this study suggests the therapy has a delayed effect. There were some bladder symptoms and quality of life measures that were improving over the course of the three months but it seems that the effect would have continued to grow as the therapy prolonged. It is possible that 3 months was not enough time to track the effect of this therapeutic model due to the challenge of compliance. There was a significant change in the cutaneous and limit thresholds between the healthy and OAB populations indicating that there may be some anatomical differences between these groups.

Further clinical studies are necessary to determine whether the most feasible nerve targets can be used as effective OAB therapy targets and if this model can be used to administer an at home therapy. Some of the clinical effects that we would like to further investigate and define are the stimulation parameters, the clinical efficacy of SAFN TENS therapy, comparing the SAFN TENS amplitudes between other demographics and a cadaver analysis to determine whether there is a significant difference between the lower leg composition and different ages. These investigations could shed light as to why, in literature, TENS therapy has had inconsistent results.

7.1 Stimulation Parameters

The stimulation parameters used in a TENS therapy have been widely tested but there is no standard procedure put in place. To standardize this therapy, the frequency, pulse width and
amplitude parameters needs to be refined. There have been some animal studies conducted on this topic but few studies pertaining to it’s effect in humans. Once these parameters have been defined it will allow researchers to continue to investigate afferents that could be stimulated at-home with using TENS devices.

7.2 Determining the clinical efficacy of SAFN TENS therapy

The SAFN TENS therapy tested in this thesis needs to be conducted on more participants to fully determine whether this therapy can attain clinically relevant efficacy. In this thesis, we have analyzed the preliminary data of the on-going study where we have seen that this therapy could be playing a crucial role in lowering the strength of symptoms but may not reduce the symptoms overall. Currently, there are more participants undergoing the therapy and we plan to recruit and test more patients in order to further determine its efficacy.

7.3 Comparing the SAFN thresholds between other clinically relevant groups

The premise for using a group of young healthy subjects in determining the cutaneous, nerve recruitment and limit thresholds is that theoretically the anatomy should not be any different between the various adult age groups. As shown in our SAFN TENS therapy study, there seems to be a difference in the measured thresholds between the two groups. As the number of OAB patient threshold collected is low (n=4), more participants should be tested to determine whether there is a statistical difference between the two groups. It would also be relevant to compare the thresholds found between a young healthy population, an older healthy population and the OAB population to see if there is a significant difference between the thresholds measured. This would determine whether the effect is due to ageing or due to OAB.

7.3.1 Cadaver analysis

Due to the lack of cross-sectional data available to infer a difference between the distance from the surface of the skin to the SAFN among all age groups, if a significant difference is found between the thresholds of young healthy, older healthy and OAB populations we would like to do a cadaver analysis. This would allow us to understand the potential limitations in this type of a therapy. It could also shed light onto why transcutaneous tibial nerve stimulation is more effective in younger populations compared to older adults who experience OAB.
References


[58] S. W. Siegel et al., “Long-term results of a multicenter study on sacral nerve stimulation


Appendices

Appendix A – Questionnaire of Study 1

Test #:

Rate your comfort level on a scale of 1 to 5:
1 = least comfortable
5 = most comfortable

Shade in the area where you feel stimulation:
## Appendix B – Participant Screening Form

### PARTICIPANT SCREENING FORM

<table>
<thead>
<tr>
<th>Study ID:</th>
<th>Date</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>QUESTIONS</th>
<th>CHECK ONE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong> Do you have refractory overactive bladder? In other words you were not helped by drugs such as anti-cholinergic medication?</td>
<td>Yes</td>
</tr>
<tr>
<td>If Yes, How long has it been since you have taken medication treatment for OAB?</td>
<td>No</td>
</tr>
<tr>
<td>_____ # Weeks _____ # Months _____ # Years</td>
<td></td>
</tr>
<tr>
<td><strong>2</strong> Do you have frequency urgency syndrome?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>3</strong> Can you read, write, speak, and verbally understand English?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>4</strong> Are you between the ages of 18-84?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>5</strong> Do you have a degenerative neurological disease? (For example, Parkinson’s Disease or Multiple Sclerosis)</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>6</strong> Do you have a cardiac pacemaker or other surgically implanted devices?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>7</strong> Are you pregnant or planning on becoming pregnant?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>8</strong> Do you have any cognitive dysfunction? (for example, memory trouble)</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>9</strong> Do you have severe cardiopulmonary disease?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>10</strong> Do you have lower extremity pain or injury?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

54
Appendix C – TENS Registration Form

TENS OF THE LOWER LEG FOR OAB TREATMENT
REGISTRATION FORM
(Please Print)

<table>
<thead>
<tr>
<th>Today's date:</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PATIENT INFORMATION</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study ID:</td>
<td>Birth date:</td>
<td>Age:</td>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>/ /</td>
<td></td>
<td>M</td>
<td>F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Email:</td>
<td>Phone no.:</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
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<td>( )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OAB BACKGROUND</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>When were you diagnosed with OAB?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of symptoms:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>List any treatments you have tried:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are you taking any Anticholinergic drugs?</td>
<td>Yes</td>
<td>No</td>
<td>If Yes please list:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IN CASE OF EMERGENCY</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of local friend or relative (not living at same address):</td>
<td>Relationship to patient:</td>
<td>Home phone no.:</td>
<td>Work phone no.:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>( )</td>
<td>( )</td>
<td>( )</td>
<td>( )</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The above information is true to the best of my knowledge. I authorize my insurance benefits be paid directly to the physician. I understand that I am financially responsible for any balance. I also authorize tens of the lower leg for oab treatment or insurance company to release any information required to process my claims.

Patient/Guardian signature ____________________________ Date __________

55
Appendix D – Bladder diary

Bladder Diary for Saphenous Nerve Study

Subject ID: ________  Day: **ONE**  Date: ___________

<table>
<thead>
<tr>
<th>Time</th>
<th>List drinks and how much</th>
<th>Trips to the Bathroom</th>
<th>Accidental Leaks</th>
<th>Did you feel urge to urinate?</th>
<th>What were you doing at the time?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approximate Time</td>
<td>What kind?</td>
<td>How much?</td>
<td>How many trips? (check for each trip)</td>
<td>How much urine?</td>
<td>How much?</td>
</tr>
<tr>
<td>7-8 am</td>
<td>Water</td>
<td>1 glass</td>
<td>√√</td>
<td>½ cup</td>
<td>I large leak</td>
</tr>
</tbody>
</table>

I used ______ pads today. I used ______ diapers today (write number).

Please list any Comments or Questions: ____________________________________________
# Appendix E – Overactive Bladder QoL Questionnaire

**Overactive Bladder Questionnaire (OAB-q)**

This questionnaire asks about how much you have been bothered by selected bladder symptoms during the past week. Please place a ✓ or ✗ in the box that best describes the extent to which you were bothered by each symptom during the past week. There are no right or wrong answers. Please be sure to answer every question.

<table>
<thead>
<tr>
<th>During the past week, how bothered were you by...</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>A great deal</th>
<th>A very great deal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Frequent urination during the daytime hours?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>2. An uncomfortable urge to urinate?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>3. A sudden urge to urinate with little or no warning?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>4. Accidental loss of small amounts of urine?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>5. Nighttime urination?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>6. Waking up at night because you had to urinate?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>7. An uncontrollable urge to urinate?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>8. Urine loss associated with a strong desire to urinate?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

The above questions asked about your feelings about individual bladder symptoms. For the following questions, please think about your overall bladder symptoms in the past week and how these symptoms have affected your life. Please answer each question about how often you have felt this way to the best of your ability. Please place a ✓ or ✗ in the box that best answers each question.
### Overactive Bladder Questionnaire (OAB-q)

<table>
<thead>
<tr>
<th>During the past week, how often have your bladder symptoms . . .</th>
<th>None of the time</th>
<th>A little of the time</th>
<th>Some of the time</th>
<th>A good bit of the time</th>
<th>Most of the time</th>
<th>All of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. Made you carefully plan your commute?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
<td>☐ 6</td>
</tr>
<tr>
<td>10. Caused you to feel drowsy or sleepy during the day?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
<td>☐ 6</td>
</tr>
<tr>
<td>11. Caused you to plan “escape routes” to restrooms in public places?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
<td>☐ 6</td>
</tr>
<tr>
<td>12. Caused you distress?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
<td>☐ 6</td>
</tr>
<tr>
<td>13. Frustrated you?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
<td>☐ 6</td>
</tr>
<tr>
<td>14. Made you feel like there is something wrong with you?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
<td>☐ 6</td>
</tr>
<tr>
<td>15. Interfered with your ability to get a good night’s rest?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
<td>☐ 6</td>
</tr>
<tr>
<td>16. Caused you to decrease your physical activities (exercising, sports, etc.)?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
<td>☐ 6</td>
</tr>
<tr>
<td>17. Prevented you from feeling rested upon waking in the morning?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
<td>☐ 6</td>
</tr>
<tr>
<td>18. Frustrated your family and friends?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
<td>☐ 6</td>
</tr>
<tr>
<td>19. Caused you anxiety or worry?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
<td>☐ 6</td>
</tr>
<tr>
<td>20. Caused you to stay home more often than you would prefer?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
<td>☐ 6</td>
</tr>
<tr>
<td>21. Caused you to adjust your travel plans so that you are always near a restroom?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
<td>☐ 6</td>
</tr>
<tr>
<td>22. Made you avoid activities away from restrooms (i.e., walks, running, hiking)?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
<td>☐ 6</td>
</tr>
</tbody>
</table>
## Overactive Bladder Questionnaire (OAB-q)

<table>
<thead>
<tr>
<th>Question</th>
<th>None of the time</th>
<th>A little of the time</th>
<th>Some of the time</th>
<th>A good bit of the time</th>
<th>Most of the time</th>
<th>All of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>23. Made you frustrated or annoyed about the amount of time you spend in the restroom?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>24. Awakened you during sleep?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>25. Made you worry about odor or hygiene?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>26. Made you uncomfortable while traveling with others because of needing to stop for a restroom?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>27. Affected your relationships with family and friends?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>28. Caused you to decrease participating in social gatherings, such as parties or visits with family or friends?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>29. Caused you embarrassment?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>30. Interfered with getting the amount of sleep you needed?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>31. Caused you to have problems with your partner or spouse?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>32. Caused you to plan activities more carefully?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>33. Caused you to locate the closest restroom as soon as you arrive at a place you have never been?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

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Appendix F – TENS at Home Use Instructions

TENS Application Instructions

Any questions or concerns, the research team can be contacted at:

For urgent inquiries please leave your phone number in the email and we will call you. All emails will be responded within 24 hours.

In this study you are expected to self-treat using at least 30 minutes of stimulation on at least 3 days each week. Please remember to write down on the calendar sheets which days or nights you provided yourself stimulation and also how long the stimulation lasted. The following guidelines are also suggested:

- Stimulation is best provided just before going to bed (especially if you have a history of nighttime bedwetting) and/or just after waking up. Subjects are highly encouraged to provide the 30 minutes of stimulation without interruption, while either sitting or reclining in bed.

- You should not walk while the stimulation treatment is provided: this may reduce the effectiveness of the treatment and is not advised.

- Spacing out the treatments to alternate days, for example, on Monday, Wednesday, and Friday or Tuesday, Thursday, Saturday is preferred.

- Although it is acceptable for you to provide yourself with treatment every day, you should not exceed 2 hours of stimulation per day: for example, 60 minutes in the morning and 60 minutes at night. Stimulating for more than 2 hours each day may increase the risk that your skin will become irritated.
TENS Use Instructions

1. Remove the device, lead wire and electrodes from the TENS case.

2. Apply the first electrode along the tibial bone of the inside of the leg below the knee. Place the second electrode 2 finger widths below the first electrode along the tibial bone.
3. Make sure the electrodes are properly connected to the lead wires and the lead wire is properly connected to the handheld device.

4. Turn on the TENS device.
5. Press the P button to scroll through the different programs until PC 18 appears on the screen.

6. Make sure that the program has been reset by pressing the S button.
7. To begin the program, increase the level of the device by pressing the + button until sensation is strong but comfortable.

8. Maintain the stimulation for 30 mins (or until the device stops automatically). If necessary, adjust the level of the device to keep the stimulation sensation strong but comfortable.
   a. If the device amplitude locks and does not increase, press the minus button to unlock the device and then adjust the amplitude accordingly.
9. Once the 30 minute of stimulation is complete turn off the device by pressing the off button.

10. Disconnect the lead wire from the device and disconnect the electrodes from the lead wire. Store the electrodes according to the instructions listed on the package. Put the lead wire and TENS device away in the bag provided.

11. On each date of the TENS calendar, please list the total time that the TENS was applied and the highest stimulation level (XX mA) that you used throughout the stimulation.
TENS Troubleshooting

Any questions or concerns, the research team can be contacted at:

For urgent inquiries please leave your phone number in the email and we will call you. All emails will be responded within 24 hours.

1.0 Battery replacement
The TENS device runs on a 9V battery.

1. When the battery goes low a small battery icon will appear on the screen of the device (Figure 1).

![Figure 1: Low Battery icon](image1)

2. To replace the battery, you must turn the device over and open the back cover of the device by sliding it down (Figure 2).

![Figure 2: Opening the back cover](image2)
3. Change the battery and make sure that when you insert the new battery, the plus sign is at the bottom of the device (Figure 3).

![Battery placement](image)

*Figure 3: Battery placement*

4. Replace the cover of the back onto the device (Figure 4). Slide the cover up in order to lock it in place.

![Closing the back cover](image)

*Figure 4: Closing the Back Cover*

5. Turn on the device and make sure that the battery icon has disappeared from the device LCD.
2.0 Electrode replacement and storage
The surface electrodes provided are re-usable. Please follow the “Removal & Storage” instructions listed inside the electrode package.

If your electrodes are no longer sticking to the surface of the leg after repeated use, please use a new pair of electrodes.

Carefully remove the electrodes from the lead (black and red tip) wires (Figure 5) and attach the new pair of electrodes (Figure 6). Make sure that the electrodes are connected properly to the lead wires by fully pushing the lead wires into the connector part of the electrodes (Figure 7).

![Figure 5: Lead Wires](image1)
![Figure 6: Electrodes](image2)

![Figure 7: Correct Electrode to Lead Wires connections](image3)

If your device is not functioning, please contact the research team at uoft.oabl@gmail.com.
Appendix H – TENS Calendar

June 2017
TENS Stimulation Schedule

<table>
<thead>
<tr>
<th>Sun</th>
<th>Mon</th>
<th>Tue</th>
<th>Wed</th>
<th>Thu</th>
<th>Fri</th>
<th>Sat</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>29</td>
<td>30</td>
<td>31</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>14</td>
<td>15</td>
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<td>16</td>
<td>17</td>
<td>18</td>
<td>19</td>
<td>20</td>
<td>21</td>
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<td></td>
<td>22</td>
<td>23</td>
<td>24</td>
<td>25</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>29</td>
<td>30</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix I – OAB-q transformed score calculation[47], [48]

Scoring Manual for the OAB-q

To calculate a symptom severity score, create a summed score from the listed items and use the formula below the table to transform the value. This will provide symptom scores where higher score values are indicative of greater symptom severity or bother and lower scores indicate minimal symptom severity.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Sum Item Values</th>
<th>Lowest and Highest Possible Raw Scores</th>
<th>Possible Raw Score Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom Severity</td>
<td>1 - 8</td>
<td>8,48</td>
<td>40</td>
</tr>
</tbody>
</table>

Transformation for Symptom Severity raw scores ONLY:

\[
\text{Transformed Score} = \frac{(Actual \ raw \ score \ - \ lowest \ possible \ raw \ score)}{Possible \ raw \ score \ range} \times 100
\]

For the HRQL subscales (coping, concern, sleep, and social), create summed scores of the listed items for each individual subscale. To calculate the HRQL total score, sum the value of each individual subscale (do not sum all the individual items). Use the formula below the table to transform all values. Higher scores will be indicative of better HRQL.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Sum Item Values</th>
<th>Lowest and Highest Possible Raw Scores</th>
<th>Possible Raw Score Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coping</td>
<td>9+11+16+21+22+26+32+33</td>
<td>8,48</td>
<td>40</td>
</tr>
<tr>
<td>Concern</td>
<td>12+13+14+19+23+25+29</td>
<td>7,42</td>
<td>35</td>
</tr>
<tr>
<td>Sleep</td>
<td>10+15+17+24+30</td>
<td>5,30</td>
<td>25</td>
</tr>
<tr>
<td>Social</td>
<td>18+20+27+28+31</td>
<td>5,30</td>
<td>25</td>
</tr>
<tr>
<td>HRQL Total</td>
<td>Sum of HRQL subscales (not individual items)</td>
<td>25, 150</td>
<td>125</td>
</tr>
</tbody>
</table>

Formula for transformation of HRQL raw scores:

\[
\text{Transformed Score} = \frac{(Highest \ possible \ score \ - \ Actual \ raw \ score)}{Possible \ raw \ score \ range} \times 100
\]

Missing Items

For the subscale analyses, if < 50% of the scale items are missing, the scale should be retained with the mean scale score of the items present used to impute a score for the missing items. If ≥ 50% of the items are missing, no scale score should be calculated, the subscale score should be considered missing. If a subscale score is missing, the HRQL Total score cannot be calculated