

# Meta-Analysis of PTNS for Urinary Disorders

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*Produced for Uroplasty, Inc. by:*

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## Abstract

**INTRODUCTION:** Percutaneous Tibial Nerve Stimulation (PTNS) has been used clinically since 2000 to treat symptoms associated with urinary disorders: urinary urgency, urinary frequency (daytime or nighttime), and urge incontinence. To date, the studies that have been published have been of modest size, with the largest studies including about 50 patients. We conducted a meta-analysis of these studies to strengthen the conclusions that could be drawn from them.

**METHODS:** Seventeen (17) papers were reviewed for inclusion in the meta-analysis; seven (7) met the inclusion criteria of: (1) PTNS therapy and (2) treatment of any of the following symptoms: urinary urgency, urinary frequency (daytime or nighttime), and urge incontinence. Of these papers, six were studies of patients before and after treatment with PTNS – they were not randomized to a control and treatment group. One was a randomized-control trial with an active pharmaceutical control; only the before-and-after treatment data in the PTNS arm was used. Seven objective responses to therapy were analyzed:

- Number of voids per day
- Voiding volume
- Nighttime voiding
- Number of incontinence episodes per day
- Incontinence quality-of-life (I-QoL)
- Overall quality-of-life (SF-36)
- Percent of patients improved

Not all of the papers included all seven of the responses. Urodynamic measurements were included in too few papers meeting the inclusion criteria to be meta-analyzed. Fixed- and random-effects meta-analysis models were analyzed for each of the seven results.

**RESULTS:** The responses to therapy and the number of patients evaluated under each criteria were:

- Number of daily voids - 244 patients improved an average of 23% (7 papers,  $p < 0.001$ )
- Nighttime voiding - 151 patients improved 41% (5 papers,  $p = 0.002$ )
- Voiding volume - 182 patients improved 43% (5 papers,  $p < 0.001$ )
- Incontinence episodes - 167 patients improved 45% (4 papers,  $p = 0.023$ )
- Incontinence QoL - 122 patients improved 17% (3 papers,  $p = 0.033$ )
- Overall QoL - 75 patients improved 17% (2 papers,  $p = 0.25$  NS)
- Percent of patients improved - 174 of 244 (71%) patients improved (7 papers,  $p < 0.001$ )

All of the variables showed significant heterogeneity of effect size and required a random-effects model except percent of patients improved, which was analyzed using a fixed-effects model as there was a similar effect across all the studies (No adjustments were made for multiple inference).

**DISCUSSION:** The published literature provides strong evidence for the effectiveness of PTNS for the treatment of urinary urgency, urinary frequency, and urge incontinence. Over two-thirds of patients show improvement.

## 1. Introduction

### 1.1 Percutaneous Tibial Nerve Stimulation

Percutaneous Tibial Nerve Stimulation (PTNS) has been used in clinical practice since 2000 to treat symptoms associated with urinary disorders: urinary urgency, daytime or nighttime urinary frequency, and urge incontinence. The Urgent PC Neuromodulation System (Figure 1) is a minimally invasive neuromodulation system from Uroplasty, Inc. (Minnetonka, MN). It is designed to deliver retrograde access to the sacral nerve plexus through percutaneous electrical stimulation of the posterior tibial nerve (Figure 2). The Urgent PC Neuromodulation System consists of the Urgent PC Stimulator and the Urgent PC Lead Sets (with percutaneous stimulation needle electrode) and has been cleared by the U.S. FDA for the treatment of urinary urgency, urinary frequency and urge incontinence.



Figure 1

In recent years, a number of papers have been published on the use of PTNS for pelvic-floor conditions. Many of these papers have been of modest size, ranging from a dozen to several dozen patients. The amounts of stimulation and the methods for measuring responses have varied to some degree. These issues have caused some in the medical community to question whether there is adequate, consistent evidence of the effectiveness of PTNS therapy.

### 1.2 Meta-Analysis

Meta-analysis is a method of statistical analysis for combining results from a few or many studies to produce aggregate conclusions about the effect of a treatment, sometimes compared to another. We conducted a meta-analysis of PTNS studies to strengthen the conclusions that could be drawn from them.

It is well accepted among meta-analysts and reviewers at major journals that meta-analyses do not require every patient in all studies to receive identical treatment, or even that their responses to the treatment are measured in precisely the same way. Rather, it is only required that the therapies be similar enough that the audience for meta-analysis (in the medical field, usually physicians or healthcare payers) would acknowledge them as the same clinical therapy. The response measurements are required to measure the same concept, although they can use different scales to do so. The responses are converted into the standardized difference of means (SDM), a number which measures how many standard deviations the average treatment response is from the control or no-treatment response. Then all of the SDMs are averaged.

For example, it would be acceptable in most circumstances to meta-analyze the effect of an analgesic on fever reduction if some studies used tablets and others used capsules or liquids in varying doses and if some studies measured the fever reduction in degrees Fahrenheit and others in degrees Celsius. Although the amount of fever reduction may be affected by the dose or method of administration, a general conclusion about the effectiveness of the analgesic on fever would still be possible. Also, the two scales for measuring temperature can be converted into a single scale by using the SDM.

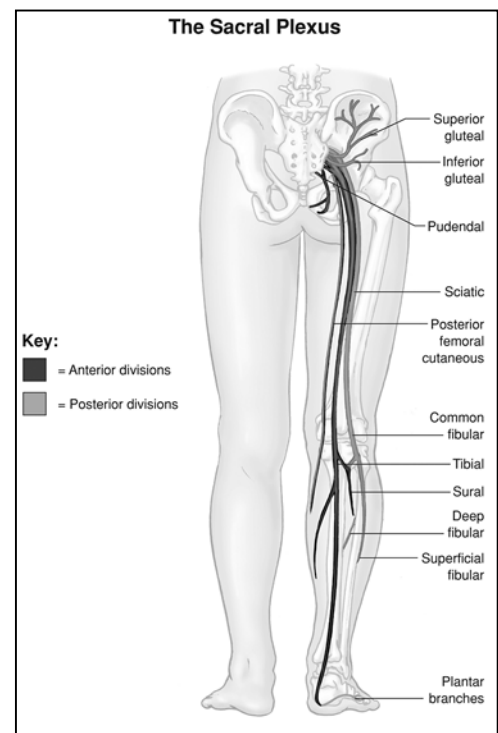


Figure 2

In analyses in which the treatments or patients in the included papers are not very similar, the amount of change caused by the treatment can be highly variable from study to study. This is known as “heterogeneity of effect size” or simply “heterogeneity.” When there is evidence of heterogeneity in the analysis, a random-effects meta-analysis must be used. If there is no evidence of heterogeneity, it is permissible to use a fixed-effects analysis. These terms are analogous to the analysis of variance (ANOVA) terms; in a fixed-effects model, the assumption is that each subject (article) provides an estimate of the same effect size. In a random-effects model, the assumption is that there is a population of different effect sizes from which the subjects (articles) are sampled.

The results of a meta-analysis are the global p-value for the effect of the treatment and an estimate of how effective it is (the effect size). The estimate of the effect size, however, is usually in standard deviations, and so must be converted back to the original measurement units. In this paper, we have reported effect size as percent improvement.

## 2. Methods

### 2.1 Inclusion/Exclusion Criteria

The manufacturer has maintained a library of journal articles on PTNS and related therapies over several years. This entire set of articles was used for this analysis, from which 17 complete references utilizing percutaneous posterior tibial nerve stimulation were available. These 17 papers were reviewed for inclusion in the meta-analysis and were included if they met the following criteria:

- Patients were diagnosed with pelvic-floor conditions including one or all of the following: urinary urgency, urinary frequency, and urge incontinence.
- Patients’ symptoms were measured before and after therapy.
- The therapy delivered was PTNS; transcutaneous tibial nerve stimulation (TTNS), transcutaneous electrical nerve stimulation (TENS), sacral nerve stimulation (SNS) and other modalities were excluded.

Additionally, a single abstract (Peters et al. 2008) presented at the 2008 AUA Late Breaking Science Forum was included in this meta-analysis because it reported the first results from a multi-center, randomized controlled study of PTNS. Articles were excluded if the patients appeared to be a subset of those in another publication by the same group of authors. Appendix 2 contains the complete references of papers included in this analysis and those studies that were considered but not included based on the above criteria.

### 2.2 Analysis Methods

From the articles that met the inclusion and exclusion criteria, symptom and urodynamic data were extracted. The data were meta-analyzed with the program Comprehensive Meta Analysis v2.2 ([www.Meta-Analysis.com](http://www.Meta-Analysis.com)). Each of the response variables that were present in at least two source articles was meta-analyzed.

Each variable was first meta-analyzed with a fixed-effects model. The model was then tested for heterogeneity of the effect; if this test was statistically significant, a random-effects meta-analysis was used.

## 3. Results

### 3.1 Articles Included in the Analysis

Seven of the 17 papers met the inclusion/exclusion criteria. Of these papers, six were single-arm studies of patients before and after treatment with PTNS. One was a randomized-control trial with an active pharmaceutical control; only the before-and-after treatment data in the PTNS arm was used. Only one paper contained urodynamic

data, so it was not possible to meta-analyze these data. Seven symptomatic responses to therapy were present in two or more articles and were analyzed:

- Number of voids per day
- Voiding volume
- Number of voids per night
- Number of incontinence episodes per day
- Incontinence quality-of-life (I-QoL)
- Generic quality-of-life (SF-36)
- Percent of patients improved.

### 3.2 Patient Characteristics

The seven papers included a total of 244 patients treated with PTNS. The number of PTNS-treated patients per paper ranged from 15 to 51. Between two-thirds and all of the patients in these studies were female; overall, 87% were female. Their average ages ranged from 51 to 63 years, with an overall average of 56 years. Although two papers did not report the duration of the patients' symptoms, the five reporting papers had an overall average duration of nearly seven years.

### 3.3 Response to PTNS Therapy

Table 1 shows the mean responses to therapy for each of the seven variables that were analyzed. It also lists the p-values for the fixed- or random-effects model used, and the p-value for the test for heterogeneity (the "Q" test). In all cases except the percent of patients improved, the test for heterogeneity was significant, indicating the true effect sizes appear to differ among the studies. The random-effects models are therefore the appropriate ones for the other six variables. For the percent of patient improved, the effect size was similar among studies.

The responses to therapy and the number of patients evaluated under each criteria were:

- Number of daily voids: 244 patients improved an average of 23% (7 studies,  $p < 0.001$ )
- Nighttime voiding: 151 patients improved 41% (5 studies,  $p = 0.002$ )
- Voiding volume: 182 patients improved 43% (5 studies,  $p < 0.001$ )
- Incontinence episodes: 167 patients improved 45% (4 studies,  $p = 0.023$ )
- Incontinence QoL: 122 patients improved 17% (3 studies,  $p = 0.033$ )
- Overall QoL: 75 patients improved 17% (2 studies,  $p = 0.25$  NS)
- Percent of patients improved: 174 of 244 (71%) patients improved (7 studies,  $p < 0.001$ )

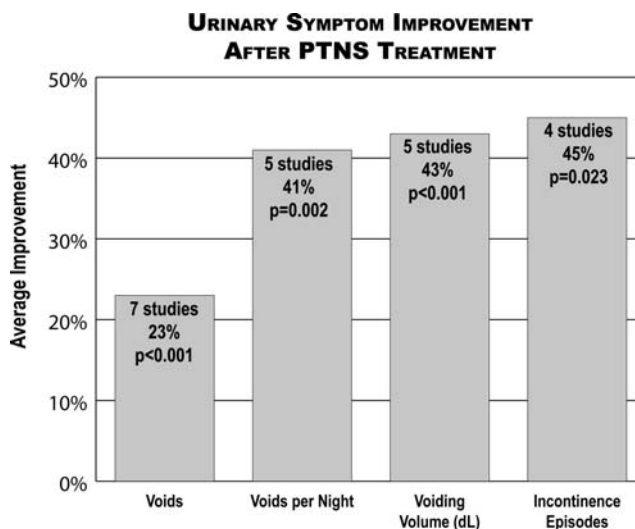


Figure 3

**TABLE 1: Summary of Results of Meta-Analysis Reported as Mean Response to Therapy**

<b>RESPONSE (PATIENTS)</b>	<b>ARTICLES</b>	<b>RESULTS</b>	<b>MODELS AND P-VALUES*</b>
VOIDS (N=244)	Congregado-Ruiz Govier Kim Klingler Peters Van der Pal Vandoninck	PRE: 12.3 POST: 9.5 IMPROVEMENT: 2.8 PERCENT: 23%	RANDOM: p < 0.001 Q FOR RANDOM p = 0.002
VOIDS PER NIGHT (N=151)	Congregado-Ruiz Kim Klingler Peters Van der Pal	PRE: 2.9 POST: 1.7 IMPROVEMENT: 1.2 PERCENT: 41%	RANDOM: p = 0.002 Q FOR RANDOM p < 0.001
VOIDING VOLUME (ML) (N=182)	Congregado-Ruiz Klingler Peters Van der Pal Vandoninck	PRE: 137 POST: 196 IMPROVEMENT: 59 PERCENT: 43%	RANDOM: p < 0.001 Q FOR RANDOM p < 0.001
INCONTINENCE EPISODES (N=167)	Congregado-Ruiz Peters Van der Pal Vandoninck	PRE: 4.1 POST: 2.2 IMPROVEMENT: 1.9 PERCENT: 45%	RANDOM: p = 0.023 Q FOR RANDOM p < 0.001
I-QoL (N=122)	Govier Van der Pal Vandoninck	PRE: 57 POST: 67 IMPROVEMENT: 9.9 PERCENT: 17%	RANDOM: p = 0.033 Q FOR RANDOM p < 0.001
SF-36 (N=75)	Van der Pal Vandoninck	PRE: 57 POST: 67 IMPROVEMENT: 9.9 PERCENT: 17%	RANDOM: p = 0.25 Q FOR RANDOM p < 0.001
PERCENT OF PATIENTS IMPROVED (N=244)	Congregado-Ruiz Govier Kim Klingler Peters Van der Pal Vandoninck	POST: 71%	FIXED: p < 0.001 Q FOR RANDOM p = 0.11

\* The p-values are unadjusted for multiple inference.

All of the variables showed significant heterogeneity of effect size and required a random-effects model except percent of patients improved, which was analyzed using a fixed-effects model (No adjustments were made for multiple inference). Figure 3 shows the average improvement for each of these variables. Note: Positive improvement means that patients exhibited a decrease in voids, voids/night and incontinence episodes and an increase in voiding volume.

The criteria used for “percent of patients improved” included an improvement of a minimum percent in incontinence episodes or frequency of voids (Vandoninck, Govier, Klingler, Van der Pal), patient self-evaluation (Congregado-Ruiz), an assessment by the physician (Peters), and other (Kim).

Appendix 1 provides the details of the seven meta-analyses, including the standard graphical representation of the results of each analysis. These are: Table A-1: Number of Voids; Table A-2: Voids per Night; Table A-3: Voiding Volume; Table A-4: Incontinence Episodes; Table A-5: I-QoL; Table A-6: SF-36; and Table A-7: Percent of Patients Improved.

## 4. Discussion

All of the response variables included in this analysis indicated that they were improved by PTNS therapy. All were significant in the fixed-effects models. In the random effects models, all were significant (when p-values unadjusted for multiple inference were considered) except SF-36. Interestingly, this had the smallest available sample size of 75 patients. Given the variability of quality-of-life data, this sample size may simply be too small to have provided the power needed to detect a real difference in overall quality of life. There is no indication that QoL decreased following PTNS therapy.

Three of the response variables -- number of voids, void volume, and voids per night -- were highly significant even in the random-effects model ( $p < 0.001$  in each case). It is important to note that although the improvements may seem modest in terms of the percentage, the improvement was enough to reduce the symptoms to the normal range. For example, the average number of voids per day was about 12 before treatment and about 9.5 after treatment. The number of daily voids conservatively considered to be normal is eight (8). The reduction of about 2.5 voids, which is a seemingly modest 23% improvement, represents an elimination of 65% of the *excess voids* these patients were experiencing.

The papers included in this analysis were based on single-arm studies of patients' symptoms before and after PTNS (the Peters 2008 study also included a randomized, active pharmaceutical control). A potential critique of this work is that patients are capable of influencing their symptoms by their behaviors and beliefs; this is the “placebo effect.” Consequently, the influence of patients' behaviors and beliefs are not separable from the effect of therapy. However, one might infer that the patients included in these studies were resistant to the placebo effect. On average, the duration of their symptoms was nearly seven years, so it is likely that they had tried several other therapies with no success over the life of their condition. For this reason, it seems reasonable to conclude that all or part of their improvement was due to a physiologically based treatment effect.

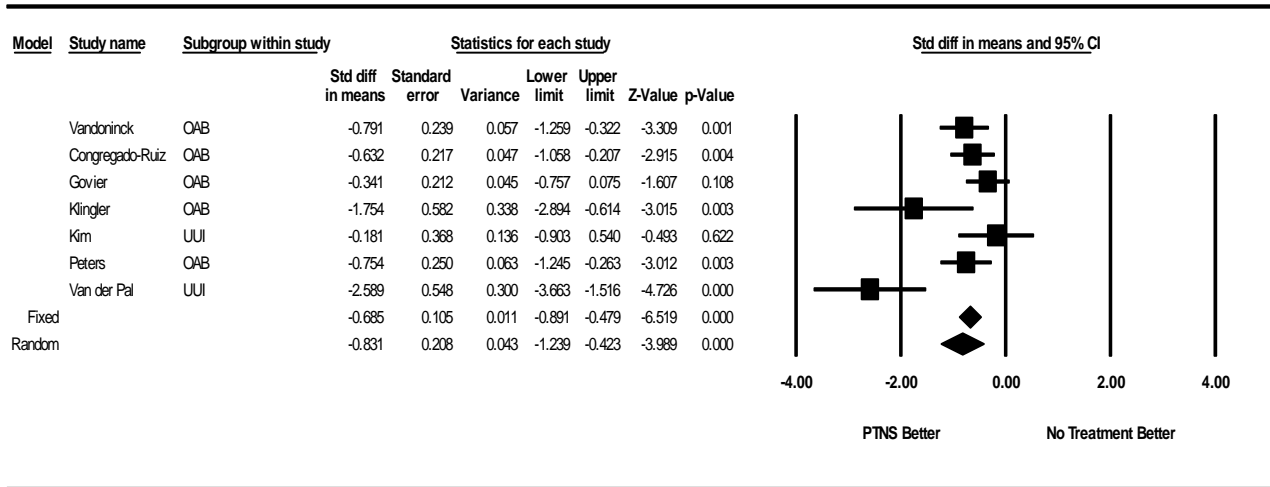
The published literature provides strong evidence for the effectiveness of PTNS for the treatment of urinary urgency, urinary frequency, and urge incontinence.

## Acknowledgements

This study was funded by Uroplasty, Inc. The analysis was performed by independent contractor Technomics Research, with no financial ties to the sponsor. The sponsor was not involved in the analysis or in the conclusions drawn from it. The sponsor supplied their complete library of electrostimulation articles from which the articles in this meta-analysis were selected. A short biographical sketch of the author, Melissa Martinson, MS PhD is provided in Appendix 3.

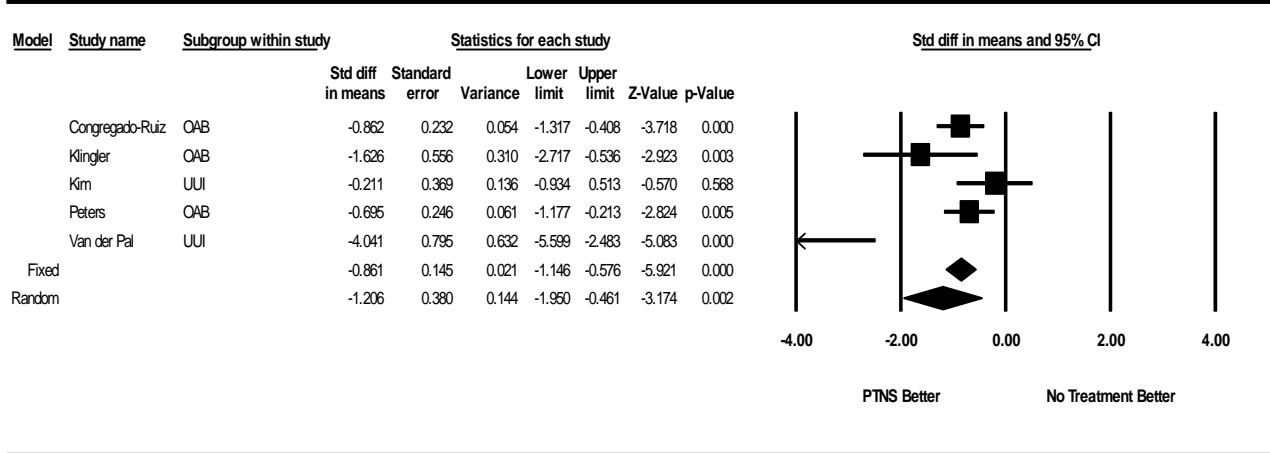
## APPENDIX 1: META-ANALYSIS DETAILS

Table A-1 **Number of Voids**



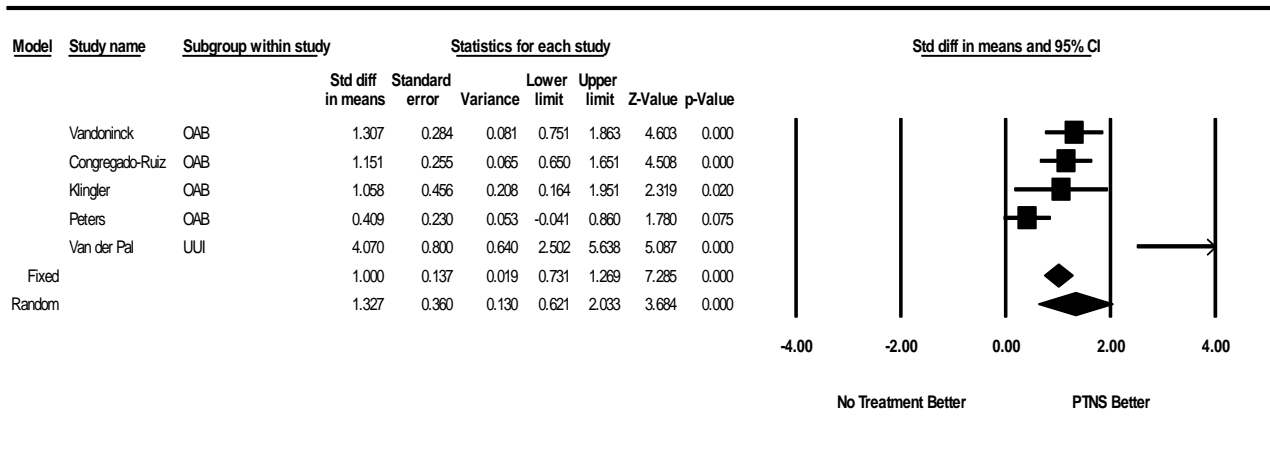
Meta Analysis

Table A-2 **Voids per Night**



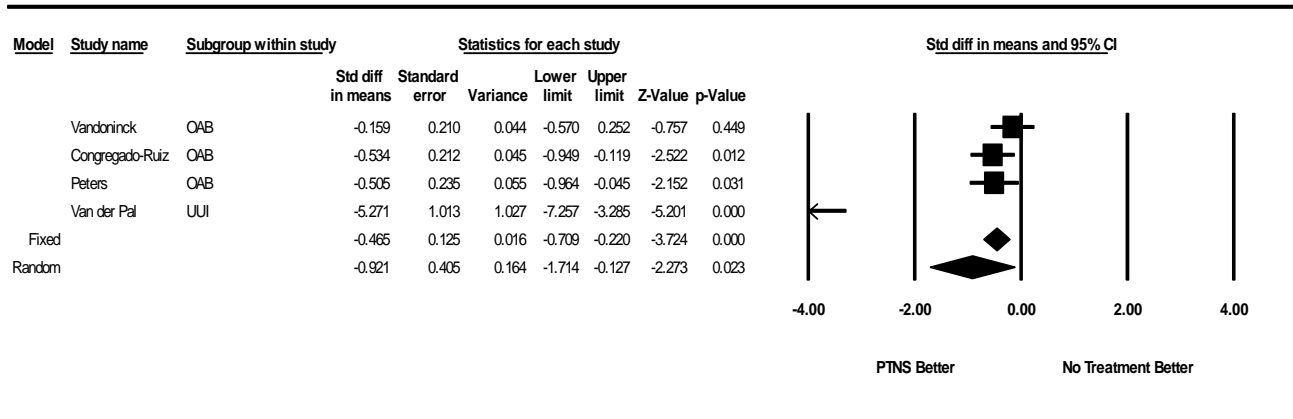
Meta Analysis

Table A-3 **Voiding Volume**



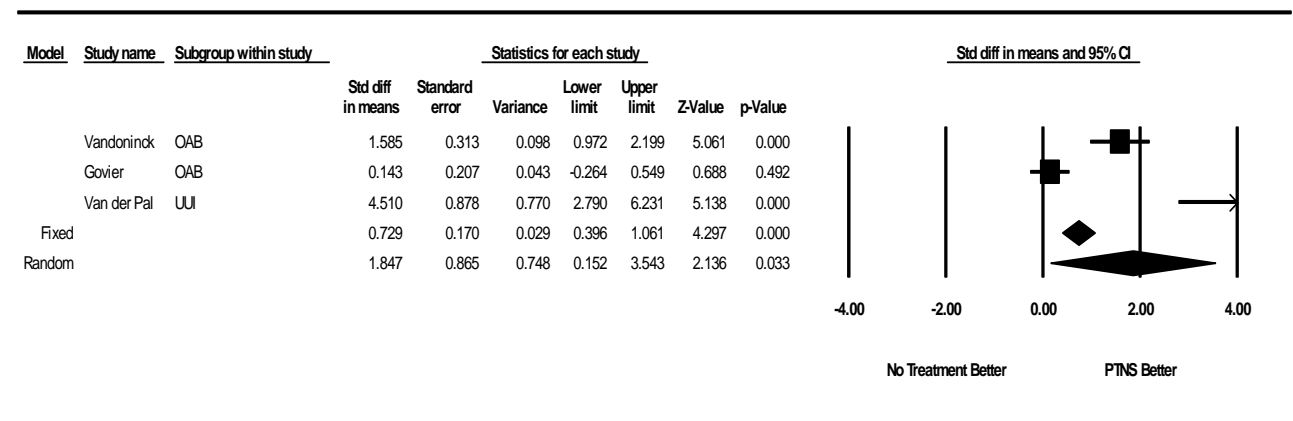
Meta Analysis

Table A-4 **Incontinence Episodes**



**Meta Analysis**

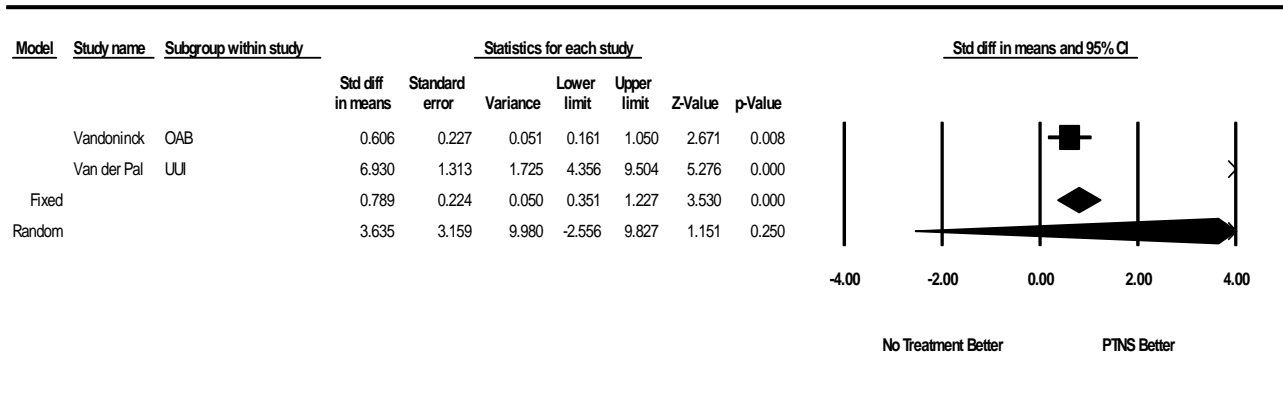
Table A-5 **I-QoL**



**Meta Analysis**

Table A-6

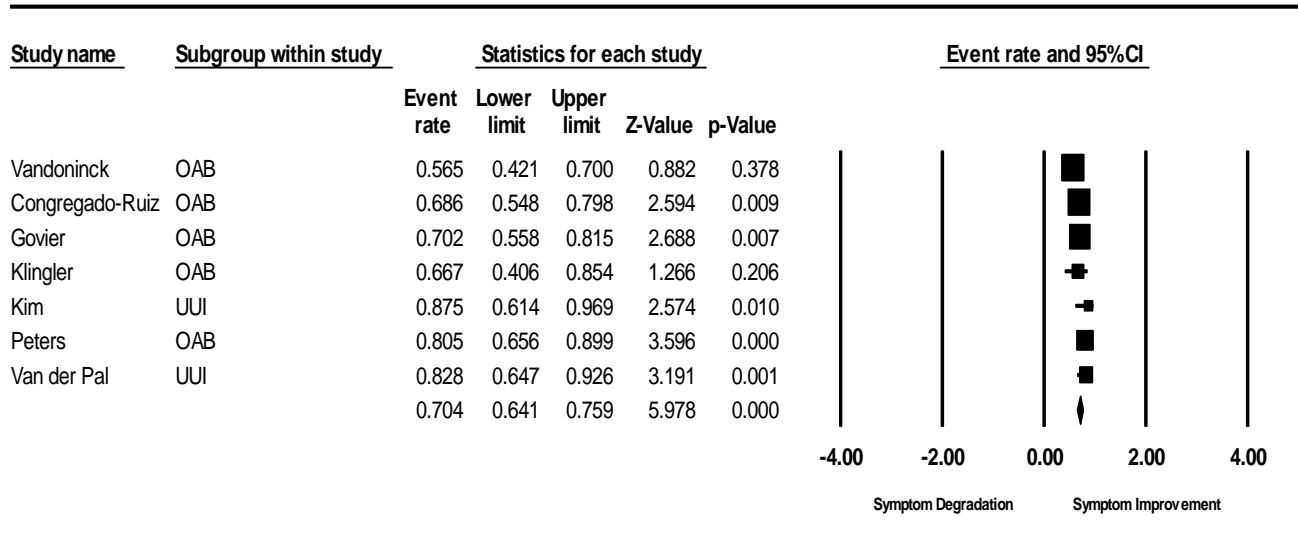
SF-36



Meta Analysis

Table A-7

Percent of Patients Improved



Meta Analysis

## APPENDIX 2: REFERENCES

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## APPENDIX 3: DR. MARTINSON BIOGRAPHICAL SKETCH

Dr. Martinson's commercial experience includes 20 years of clinical trials, health economics and outcomes studies in both medical device and pharmaceutical companies. She is co-founder of Technomics Research, LLC, with John Nyman, MS PhD, a professor of health economics at the University of Minnesota School of Public Health. The company provides statistical and health-economics consulting to the medical device, pharmaceutical, and managed care industries.

Dr. Martinson holds a B.A. in Biology from Swarthmore College, and both an M.S. in Statistics and a Ph.D. in Health Services Research from the University of Minnesota. She holds an Adjunct Associate Professorship at the University in the School of Public Health, where she teaches graduate-level economic modeling. Her publications include meta-analyses and economic models with cost-effectiveness analyses.

She recently published the meta-analysis:

Johnson, M. & Martinson, M. (2007). Efficacy of electrical nerve stimulation for chronic musculoskeletal pain: A meta-analysis of randomized controlled trials. *PAIN*, 130, 157-165.

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Urgent PC is indicated for Urinary Urgency, Urinary Frequency and Urge Incontinence. **CONTRAINDICATIONS:** Treatment with Urgent PC is contraindicated for patients with pacemakers or implantable defibrillators, patients prone to excessive bleeding, patients with nerve damage that could impact either percutaneous tibial nerve or pelvic floor function, or patients who are pregnant or planning to become pregnant during the duration of the treatment. **PRECAUTIONS:** Exercise caution for patients with heart problems related to pacing. Most common side-effects include transient mild pain or skin inflammation at or near the stimulation site. **CAUTION:** Federal law (USA) restricts this device to sale by or on the order of a physician. For complete instructions for use, storage, warnings, indications, contraindications, precautions, adverse reactions and disclaimer of warranties, please refer to the insert accompanying each Urgent PC product.

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