

Cost Utility Analysis of Sacral Neuro-Modulation vs Botox A in the Treatment of Overactive Bladder in Colombia

Abstract

Objectives: Cost Utility Analysis of Sacral Neuromodulation (SNM) vs. botulin toxin type A (BoNT-A) in Overactive Bladder (OAB) treatment in Colombia.

Methods: Through a HTA Consulting Discrete Event Simulation (DES) economic model adaptation, a cost-utility analysis of SNM vs. BoNT-A 100UI in the treatment of OAB in Colombia was done. The effectiveness data for SNM and BoNT-A, defined as more than 50% improvement in urinary parameters, was based on studies identified in systematic review Jaros 2013 conducted in Polish settings. Based in systematic search for quality of life (QoL) data, one health state for treatment success and one for treatment failure were defined. Costs data was obtained from Colombian Public Manual and urologist KOL which also adjusted the frequency of resources use. With 10 years horizon and a 3% discount rate deterministic and probabilistic sensitive analyses were done.

Results: SNM obtained 5.67 QALYs vs. 5.38 with BoNT-A with 0.28 incremental QALYs, with US\$27,828 vs. US\$28,906 total costs respectively. SNM was more effective and less costly, therefore been cost-saving. In the Probabilistic Sensitivity analysis 49.1% of the simulations fall in the NE quadrant, more effective and more costly, and 50.9% in the SE quadrant, more effective and less costly than BoNT-A, and 100% fall under the threshold of 3 Colombian GDP Per Capita.

Conclusion: SNM has higher effectiveness than BoNT-A in terms of QoL at a lower cost and compared to BoNT-A is cost-saving therapy for the treatment of OAB in Colombia. All the probabilistic results were cost-effective for Colombian Threshold.

Keywords: Electrical stimulation; Botulinum toxin; Overactive bladder, Quality of life; Urinary Incontinence

Research Article

Volume 3 Issue 6 - 2016

Juan C Castaño^{1*}, Adrian R Lopera² and John J Orozco³

¹*Uro-gynecology & Neuro- urology Department, Hospital Pablo Tobón Uribe, Colombia*

²*Department of Urology, Universidad CES Medellin, Colombia*

³*Health Economist Researcher, Center for HTA (CETES) CES University, Healthcare Economist Analyst, Medtronic PLC Latam, Colombia*

***Corresponding author:** Juan C Castaño, Uro-gynecology & Neuro- urology Department, Hospital Pablo Tobón Uribe, Calle 78 B # 69 – 240, Medellín, Colombia, Tel: +57 315 284 7681; Email: jcasta3@gmail.com

Received: February 04, 2016 | **Published:** December 12, 2016

Abbreviations: SNM: Sacral Neuromodulation; BoNT-A: Botulin Toxin Type A; OAB: Overactive Bladder; DES: Discrete Event Simulation; QoL: Quality of Life

Introduction

The treatment for overactive bladder (OAB) in children and adults is a real challenge to the urologist. Even knowing that this is not a malignant disease and does not affect the patients mortality rate, because its unpleasant symptoms, it does affect considerably their quality of life, including quality of sleep and mental health. Generally, the treatments are long lasting with many undesirable effects. Additionally, those treatments would have diminishing therapeutic effects over time. The International Continence Society defined OAB as symptoms of urinary urgency, with or without urge incontinence, usually accompanied by frequency and nocturia in the absence of urinary tract infection or other obvious pathology. There should not be any localized factors that can explain such symptoms (i.e. neoplasms, infections, foreign objects or cystolithiasis [1]).

Although etiologies for OAB could be related to infectious, neurologic, psychosomatic and mechanical, most are idiopathic. The physiopathology mechanism is related to over-activity of

detrusor smooth muscle, leading to urge need of micturition or urge incontinence. The 33% of patients with OAB are affected by urge incontinence, affecting social, psychological, occupational, domestic, physical, and sexual aspects of life and can lead to depression and low self-esteem [2]. In US, the prevalence is similar for women (16, 9%) and men (16%) although sex-specific prevalence differed by severity of symptoms.

There is a marked increased after 44 years in women and after 64 years in men [3]. Sex anatomic differences may increase the probability that OAB is expressed as urge incontinence among women. According to the American Urological Association [4], physicians should offer behavioral therapies as first line treatment for OAB. As second line treatments, clinicians should offer oral anti-muscarinics, including darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine or trospium. When behavioral and anti-muscarinic therapy fails or the patient is not candidate for them, botulinum toxin type A (BoNT-A), sacral neuromodulation (SNM) and tibial nerve stimulation could be offer by clinicians as third-line treatment in a carefully selected patient population characterized by severe refractory OAB symptoms.

BoNT-A and SNM are the most frequently used treatments when pharmacotherapy fails to reach and acceptable OAB

symptoms control. BoNT-A is a muscle relaxant that works by blocking nerve impulses to detrusor. The recommended BoNT-A dose is 100 U with an average of symptom control of 166 days, but some declining effect has been observed along the time. SNM consists of mild electrical impulses produced by an implantable neurostimulator and delivered through a lead to the sacral nerves in order to modulate the neural activity that act over pelvic floor, lower urinary tract, urinary and anal sphincters, and colon. Although the full SNM mechanism is no yet understood, it is possible that besides the sacral nerves stimulation it acts over the micturition center in the brain. In Colombia, BoNT-A and SNM are the most frequently used treatments for OAB that is not responding to Optimal Medical Treatment (OMT). Because both treatments have different effectiveness in urinary incontinence associated to OAB, as well as different adverse events and different costs, it is necessary to do a comparative cost-effectiveness analysis along with a cost-utility analysis to include the quality of life (QoL) reached for the patients with each therapy.

Methodology

Through the adaptation of a previously developed model by Gab et al from HTA consulting company [5], and previously data transferability analysis, a cost-utility analysis was done. Because the natural history of the events of urinary incontinence associated to OAB and its modification by the different treatments, including BoNT-A and SNM, are time dependent, a discrete event simulation (DES) model was considered as the most adequate to project in time the effectiveness, the utilities and the cost, further than the horizon considered in the data obtained from the clinical randomized trials (CRT). DES allows to model time dependent data and when events could happens more than once. In our analysis, time to treatment failure constitutes the main variable used to defined effectiveness of BoNT-A and SNM and for this, a Weibull distribution was used. Adverse events were defined according to its probability of occurrence. Costs were handled as discrete variables. (Figure 1) -DES OAB Model Diagram.

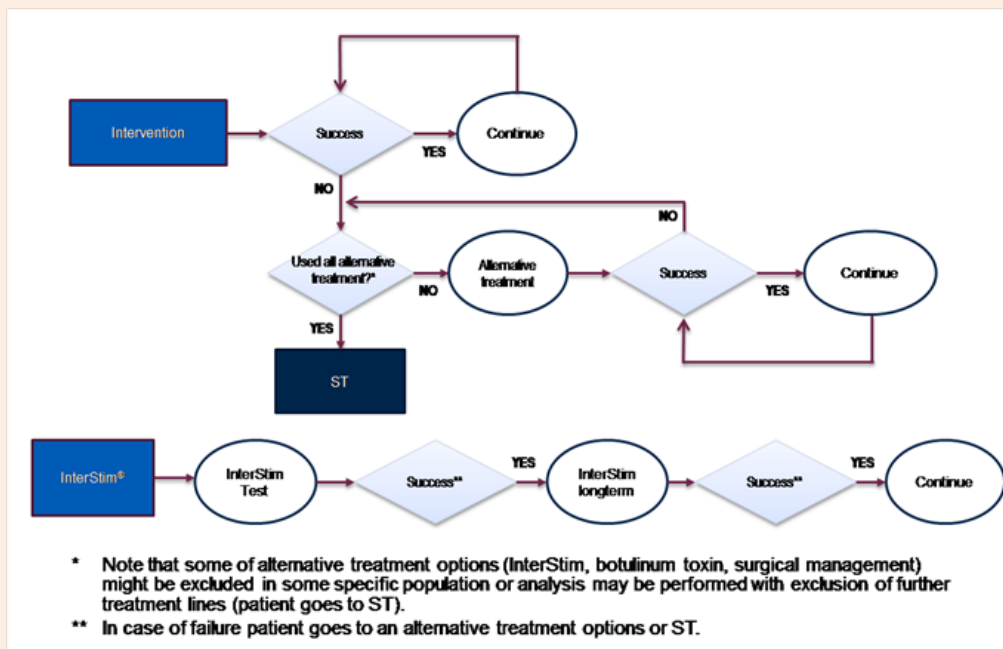


Figure 1: DES OAB Model Diagram.

Each patient is simulated separately and multiple simulations are run to generate the model results. For every simulated patient, the baseline characteristics are randomized given cohort baseline. A ten years horizon was assumed, with a discount rate for utilities and costs, of 3,5%. A third party payer perspective was defined. General mortality rates for Colombia were taken from WHO observatory and no specific mortality rates for OAB was considered. The costs were expressed in US Dollars and the market currency exchange rate of \$ 1.925 Colombian pesos for \$1 US Dollars for January 2015 was assumed.

Effectiveness and Population characteristic

The effectiveness data for OMT, SNM and BoNT-A 100 UI,

were based on studies identified in systematic review Jaros 2013 conducted for Medtronic in Polish settings for SNM. The effectiveness of test phase for InterStim was based on studies identified in Jaros 2013 review and additional Medline database search for clinical studies - RCTs and non-RCTs. The clinical end points are included in this analysis as “greater than 50% reduction in voiding and micturition symptoms in time” and “rates of adverse events occurrence”. For the first case, several time points were gather and time to treatment failure curve estimated. A Weibull distribution was assumed for time to event.

Table 1 - Keywords used in the search strategy. For the assessment of the safety of BoNT-A and SNM, only clinically significant or cost significant adverse events (AEs) were included.

They were categorized as short-time AEs and long-time AEs. Safety analysis of Inter Stim therapy was based on data from both RCTs and observational studies. Following adverse events (AEs) are included: leading to surgical revision; leading to electrode replacement; leading to device replacement; leading to device explantation. Adverse events that do not cause surgical intervention were not included. Based on Polish experts opinion there is no other adverse events than included in this analysis

which are associated with significant expenditures for patients or for public payer. For SNM, the battery life-time was included in the model. When the battery runs down, the whole device needs to be replaced and so these costs have to be included. This event has no impact on effectiveness treatment. For the economic analysis, the mean age and frequency of voiding symptoms per day of patients with OAB were taken from RCTs studies found in clinical analysis by Jaros 2013 [6].

Table 1: Keywords used in the search strategy.

Field		Keywords
Population		Lower urinary tract symptoms, urinary, urine, urination, bladder, voiding, incontinence, retention, symptom, symptoms, dysfunction, dysfunctions, overactive, underactive, instable, instability, detrusor, bladder, urgency, frequency
Intervention		Sacral, sacrum, neuromodulation, stimulation, electrostimulation, electric stimulation, interstim
Comparator		Botulinum, botulin, botox, botulinic, onabotulinum toxin a
Study Design ^a	RCT	Randomized controlled trial, random*, RCT, singl*, doubl*, trebl*, tripl*, blind*, mask*, single blind, double blind, triple blind, placebo, placebo-controlled, blinding, cross*over, crossover, trial, study, controlled clinical trial, random*, controlled, study*, random*, controlled, trial*, random, randomly, allocation, allocate*
	non RCT	Clinical, case control, family, longitudinal, retrospective, prospective, cohort, cohort, case control, case series, phase iv, post marketing, consecutiv*, follow up, observational, epidemiologic*, cross sectional, analysis, study, studies, patient, patients
Outcomes		x

Due to high number of results in EMBASE database limitation to RCT or observational studies was used.

Source: Gad B, et al. [5]. Sacral neuromodulation (InterStim®) in therapy of overactive bladder and urinary retention v 3. HTA Consulting 2013.

Utilities

Although the avoided incontinence episodes were include in the analysis, the main endpoint was utility, in terms of QoL, and direct medical costs. The QoL was calculated in terms of Quality Adjusted Life Years (QALYs), where 1 is considered as a perfect health and 0 as death. Negative values are sometimes accepted. This index is multiplied by the expected length of life, obtaining the amount of QALYs. The utilities in terms of QALYs were taken from a specific systematic literature search. Two health states were considered for utility value assignment, one for general population and the other in treatment failure state in a patient with OAB with urinary incontinence.

Costs

Direct medical cost for the treatment of patients with OAB and AEs were taken from local market prices and with the support of KOL. National Tariff Manuals were used when considered appropriate. The main costs concepts considered were device and drug costs, periprocedural costs such as urologist, anesthesiologist, nursing, and surgery room time per hour among others, as well as diagnostic costs, monitoring costs, hospitalization costs, and antibiotic, anticoagulation, analgesic and permanent explants and reoperation costs. Additionally, AEs cost were calculated. Because final costs are the results of unit costs by the amount of resource

use and the probability of use, a uncertainty adjustment was done. All cost were calculated in Colombian pesos (COP) and converted to USD at an exchange rate of 1925 COP by 1USD.

Incremental analysis

The cost-effectiveness analysis and the cost-utility analysis help to the policy maker to take informed decisions. In general, there is a high variability in the medical practice while new technology is emerging every day. When the new technology demonstrates a higher effectiveness and safety, the necessary question is how much will have to be paid by the patient, the third party payer or by the society. If the new technology compared to the former one or to the standard of care, is less effective and costlier, the decision is straightforward and should not be adopted. In the same sense, when is more effective and less costly it should be adopted. The problem comes when, this new technology is more effective but costlier. The question to ask, should be in the sense that how much should be paid in addition to the cost of the former technology by the additional effectiveness. In Health technology evaluation, this concept is call Incremental Cost Effectiveness ratio (ICER). The following formula illustrates the relation among costs and effectiveness of two technologies in order to know the ICER.

$$ICER = \frac{Cost^{New\ Tech} - Cost^{Old\ Tech}}{Effect^{New\ Tech} - Effect^{Old\ Tech}}$$

Sensitivity analysis

One way sensitivity and a probabilistic analysis were done. In the one way sensitivity analysis, the base case result for ICER was tested, changing the parameters of the main relevant variables and using for that the minimum and maximum range data. This allowed us to see the sensibility of the ICER result to changes on the parameters and to find to which variables is more sensible the ICER. For the probabilistic sensitivity analysis, it was allowed to change, at the same time, all the parameters in the more relevant variables, taken randomly any value among its probability density distribution. A Montecarlo simulation was done, with 10,000 iterations. All the simulations were plotted in the probabilistic cost-effectiveness plane to observe the robustness of the model, and to know the probability of to have a result in each quadrant according to effectiveness and cost.

Results

Effectiveness

After selection of studies based on abstract and titles, full text

analysis was performed. From this, 10 RCTs fulfilled inclusion criteria of the efficacy and safety analysis for SNM and 8 for BoNT-A 100 grs and were included in the analysis. In Table 2, it is shown the effectiveness for SNM patients for different times after implantation and for BoNT-A. Table 2 -SNM & BoNT-A Effectiveness. The effectiveness of SNM and BoNT-A in terms of positive clinical response, allows calculating the utility values for each health state along the time, in terms of Quality Adjusted Life Years (QALYs). The hypothetical cohort treated with SNM obtained 5,6673 QALYs compared to that with BoNT-A with 5,3830 QALYs, with 0,2844 incremental QALYs. At the same time, the SNM hypothetical cohort had 4,04 incontinence episodes per day per patient compared to BoNT-A hypothetical cohort with 4,68 incontinence episodes per day and per patient.

Costs

In the following (Table 3), the detailed micro-costing for both treatments can be observed in US\$. The total costs for SNM and BoNT-A to a 10 years horizon were very similar with US\$ 27.828,74 for SNM and US\$27.829,09 for BoNT-A, with an incremental cost of minus US\$0,35. Table 3 -Detailed costs results.

Table 2: SNM&BoNT-A Effectiveness.

Study	N° Patients		Effectiveness	Time after Implantation
	Total	With Clinical Positive Response		
C1InSite [7,8]	177	143	80.79%	3 Months
Schmidt 1999 [9]	58	43 ^a	74.14%	6 Months
	34	26 ^b	76.47%	
Weil 2000 [10]	16	15	93.75%	
In Site study [7,8]	187	142	75.94%	12 Months
Schmidt 1999 [9]	38	30	78.95%	
In Site study [7,8]	167	132	79.04%	
Schmidt 1999 [9] [11]	21	16	76.19%	18 Months
Cohen 2009 [12]	12	8	66.67%	
Nitti 2013 [13]	278	160	57.55%	
Chapple 2013 [14]	277	177	63.90%	
Mean	567	345	60.85%	

Adapted from Gad Barbara – Sacral Neuromodulation in therapy of OAB HTA Consulting

Effectiveness (>50% improvement in incontinence episodes) after SNM permanent implantation in clinical studies in patients with OAB (1-4).

Source: Gad B, et al. [5]. Sacral neuromodulation (InterStim®) in therapy of overactive bladder and urinary retention v 3. HTA Consulting. 2013.

Table 3: Detailed costs results.

Category	Sacral Neuromodulation			Botulinum Toxin type A		
	Deterministic	[Lower limit;	Upper limit]	Deterministic	[Lower limit;	Upper limit]
Devices and drugs costs	18.839,88	18.141,03	19.513,36	3.815,31	3.674,52	3.945,19
Periprocedural costs	2.148,57	2.090,96	2.201,69	7.000,35	6.227,42	7.924,94
Qualification costs	330,08	258,91	475,48	7.809,11	6.959,27	8.783,92
Monitoring costs	794,11	725,01	857,75	1.339,65	1.282,04	1.378,38
Hospitalization costs	0,00	0,00	0,00	152,11	134,20	173,04
Additional treatment costs	4.513,61	4.166,16	4.867,24	6.623,32	6.308,89	6.896,31
Other costs	211,13	158,96	267,01	0,00	0,00	0,00
Adverse events costs	991,35	797,44	1.206,90	1.089,24	916,62	1.291,49
Total costs	27.828,74	27.269	28.429	27.829,09	26.372	29.540

Incremental analysis – Deterministic results

Although SNM and BoNT-A had similar total costs, it was a bit lower for SNM, which produce more QALYs. Because it is less

costly and more effective, SNM was dominant over BoNT-A, and the criteria decision is straight forward. In this case, there is no need and does not make any sense to do the incremental analysis. Table 4-Deterministic Results.

Table 4: Deterministic Results.

Treatment	Total Costs	QALY	Incontinence Episodes (Per Day)
Sacral Neuromodulation	27.828,74 US\$	5,6673	4,04
Botulinum Toxin type A	27.829,09 US\$	5,3830	4,68
Incremental Sacral Neuromodulation vs Botulinum Toxin type A	-0,35 US\$	0,2844	-0,64
ICER Sacral Neuromodulation vs Botulinum toxin type A	SNM dominates BoNT-A		

Probabilistic Sensitivity Analysis

In order to assess the robustness of the model, a probabilistic cost-effectiveness analysis was done, using Montecarlo simulation with 1000 iterations. All the simulations falls under the WHO recommended Colombian threshold meaning SNM is a cost-effective intervention compared to BoNT-A. From all simulation, 51% were in the SW quadrant meaning that SNM has this probability of been cost-saving compare to BoNT-A. Figure 2 -Probabilistic Cost-Effectiveness Plane. The probabilistic sensitivity analysis shows a very robust model and it is coherent with the deterministic result.

Discussion

At the present moment there are no RCT or even observational data that allows us to know the health outcomes and costs in

the long term of SNM and/or BoNT-A in the treatment of OAB. Nevertheless, there is a need for informed decision making, which most of the times, are non-deferrable. The American Urology Association (AUA) guidelines for OAB, states that clinicians should offer behavioral therapies (e.g., bladder training, bladder control strategies, pelvic floor muscle training, and fluid management) as first-line therapy to all patients with OAB, with evidence strength Grade B [15]. Behavioral therapies may be combined with anti-muscarinic therapies with evidence strength grade C. As second line, with evidence strength Grade B, the pharmacotherapy with anti-muscarinics is recommended. Patients who are refractory to behavioral and medical therapy should be evaluated by an appropriate specialist if they desire additional therapy. In the third line, Sacral Neuromodulation or onabotulinumtoxinA therapy may be offered to the carefully selected patient with evidence strength grade C [16].

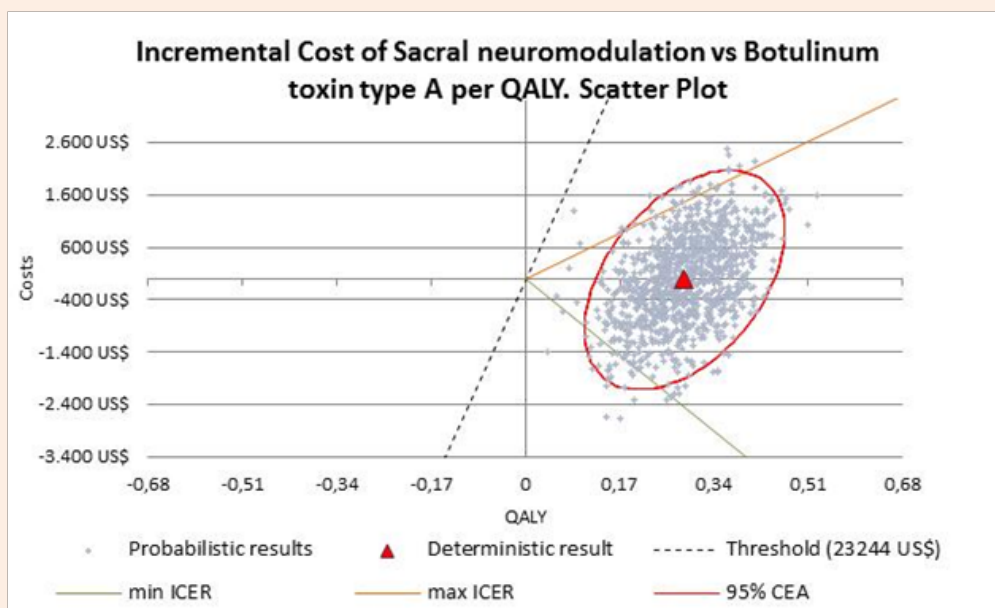


Figure 2: Probabilistic Cost-Effectiveness Plane.

To date, more than 100,000 patients around the world have had Sacral Neuromodulation as treatment for OAB and Fecal Incontinence and the results have been promising [17], even some outcomes reports high intervention rates. The symptoms improvement can be seen in one of the series with more prolonged patients follow up [18] (5 years) in which there was a 53% improvement in urgency and 58% in urinary incontinence episodes. Other clinical studies have been published with different success rates, but none above 50%. The highest success rates were published by Al Zahrani et al. [19], with a follow up of 14 years, with 84.8% for urgency and 87.5% for idiopathic retention.

On the other side, the injection of BoNT-A 100 mgrs. in patients with OAB has been widely used and the benefits are well known, as has been demonstrated in several clinical studies. There is a meta-analysis with identified 18 articles, where the conclusion was that the intra-detrusor injection of BoNT-A produces a significant improvement in patients with OAB refractory to anti-cholinergic drugs [20]. Those results are also seen in the urodynamic parameters. Schurch et al. [21] reported improvement after 24 weeks, in variables such as frequency of urinary incontinence episodes, maximum cistomanometric capacity, detrusor volume reflex and detrusor maximum pressure and quality of life with statistically significance values.

Therefore, although both treatments have demonstrated efficacy and effectiveness in OABD, their cost-effectiveness results are different. Arlandis et al. [17], in a cost-effectiveness analysis made in Spain, found similar effectiveness as in the present work, with 6.89QALYs for SNM and 6.38 QALYs for BoNT-A, with incremental QALYs of 0.51. The small differences between the two works in the amount of QALYs correspond to the differences in the demographic life tables of Colombia and Spain. Arlandis consider that although the initial costs for SNM are higher than those for the other treatments, decreasing follow-up costs coupled with

consistently greater effectiveness in the long term make SNM. Nazema et al. [22] did a cost-effectiveness analysis comparing the two interventions, obtaining that SNM was more effective than BoNT-A, but more costly. Nevertheless, the horizon was only two years, been too short for the comparison.

The importance of the horizon was confirmed in the work done by Randall et al. [23], who found that SNM was more cost-effective than BoNT-A after 5 years of follow up. This is coherent with the present work, where we used a 10 years projection through mathematical modeling. All cost-effectiveness analyses found in the literature are consistent with the statement that SNM is more effective than BoNT-A, and, in the long run are more cost-effective.

Conclusion

The present work allows demonstrating that SNM is more effective than BoNT-A, in terms of quality of life and avoided urinary incontinence episodes. In the long run, SNM is more cost-effective than BoNT-A. These results are consistent with other clinical studies and cost-effectiveness analysis published up to date.

References

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, et al. (2002) The standardization of terminology of lower urinary tract function: report from the Standardization Sub-committee of the International Continence Society. *Neurourol Urodyn* 21(2): 167-178.
2. Tubaro A (2004) Defining overactive bladder: epidemiology and burden of disease. *Urology* 64(6 Suppl 1): 2-6.
3. Stewart WF, Van Rooyen JB, Cundiff GW, Abrams P, Herzog AR, et al. (2002) Prevalence and burden of overactive bladder in the United States. *World J Urol* 20(6): 327-336.
4. Gormley A, Lightner D, Burgio K, Chai T, Clemens Q, et al. (2012)

- Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline. *J Urol* 188(6 Suppl): 2455-2463.
5. Gad B, Sekiewicz B, Nieszczyński G, Zerda I, Plisko R (2013) Sacral neuromodulation (InterStim®) in therapy of overactive bladder and urinary retention v 3. HTA Consulting.
 6. Jaros P, Rys P (2013) Clinical analysis. Sacral neuromodulation (InterStim®) in therapy of overactive bladder and urinary retention. HTA Consulting.
 7. Radziszewski P, Gugała A, Majewski M (2007) Overactive bladder. *PrzewLek* 10: 61-67.
 8. Radziszewski P, Baranowski W, Nowak-Markwitz E, Rechbeger T, Suzin J, et al. (2010) Expert panel recommendations on therapeutic and diagnostic management of urinary incontinence and overactive bladder in women. *Ginekol Pol* 81(10): 789-793.
 9. Rechbeger T, Kulik-Rechberger B (2010) Dysfunctions of the lower urinary tract-evaluation and therapeutical approach in family practice. *Forum Medycyny Rodzinnej* 4(6): 397-407.
 10. Pannek J, Blok B, Castro-Diaz D (2012) Guidelines on Neurogenic Lower Urinary Tract Dysfunction. *European Association of Urology*.
 11. Suskind AM, Smith PP (2009) A new look at detrusor underactivity: Impaired contractility versus afferent dysfunction. *Curr Urol Rep* 10(5): 347-351.
 12. Darda-Ledzion L, Członkowska A (2002) Lower Urinary Tract Dysfunction in Neurological Disorders. *Terapia* 4(3): 20-26.
 13. Darda-Ledzion L, Członkowska A (2002) Lower Urinary Tract Dysfunction in Neurological Disorders. *Terapia* 4(3): 20-26.
 14. Medtronic. About Sacral Neuromodulation.
 15. Gormley EA, Lightner DJ, Burgio KL, Chai TC, Clemens JQ, et al. (2012) Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. *The Journal of urology* 188(6): 2455-2463.
 16. Yehoshua A, Malone D, Gillard P, Globe D (2013) Cost-effectiveness analysis of refractory overactive bladder: A systematic literature review. *Value In Health* 16(3): A182.
 17. Arlandis S, Castro D, Errando C, Fernández E, Jiménez M, et al. (2011) Cost-Effectiveness of Sacral Neuromodulation Compared to Botulinum Neurotoxin A or Continued Medical Management in Refractory Overactive Bladder. *Value Health* 14(2): 219-228.
 18. Campbell JD, Gries KS, Watanabe JH, Ravelo A, Dmochowski RR, et al. (2009) Treatment success for overactive bladder with urinary urge incontinence refractory to oral antimuscarinics: a review of published evidence. *BMC Urology* 9(1): 18.
 19. NICE (2015) Urinary incontinence. The management of urinary incontinence in women.
 20. Allen F Interstim® for the treatment of urinary and faecal incontinence: a systematic review. *Abacus International*.
 21. Jaros P, Rys P (2013) Clinical analysis. Sacral neuromodulation (InterStim®) in therapy of overactive bladder and urinary retention. HTA Consulting.
 22. Siddiqui NY, Amundsen CL, Visco AG, Myers ER, Wu JM (2009) Cost-effectiveness of sacral neuromodulation versus intravesical botulinum A toxin for treatment of refractory urge incontinence. *J Urol* 182(6): 2799-2804.
 23. Leong RK, de Wachter SG, Joore MA, van Kerrebroeck PE (2011) Cost-effectiveness analysis of sacral neuromodulation and botulinum toxin A treatment for patients with idiopathic overactive bladder. *BJU Int* 108(4): 558-564.