Evolution of neuromodulation for lower urinary tract dysfunction

VALORISATION ADDENDUM

Introduction

Chronic lower urinary tract dysfunction (LUTD) is a common disorder that has a significant impact on quality of life. As described in the introduction of this thesis, the term 'dysfunction' refers to an abnormality in the physiology of the lower urinary tract, including the detrusor muscle, urinary sphincter, bladder neck and the associated peripheral and central nervous system. According to the type of dysfunction, different clinical symptoms can arise. The Overactive Bladder Syndrome (OAB) is the most common disorder, and is defined as the presence of urinary urgency, usually accompanied by frequency and can occur with or without urinary incontinence. In contrast, lower urinary tract dysfunction (LUTD) can also result in the inability to evacuate urine. Insufficient contraction of the detrusor can lead to difficult elimination or urinary retention: the underactive bladder. Suffering from LUTD can be very bothersome and has significant effects on many aspects of an individuals' life, representing a particularly impactful health burden to quality of life and productivity.

Epidemiology of lower urinary tract dysfunctions

According to the EpiLUTS study, a large population-based, cross-sectional internet survey, conducted in the UK, Sweden, and the USA, OAB and other lower urinary tract symptoms are problems many people suffer from. In the USA, 31,588 respondents completed the survey, making EpiLUTS one of the largest population-based epidemiological studies specifically focusing on OAB.[1,2] Defined by the presence of urinary urgency of at least 'sometimes' and/or urge-urinary incontinence, 43% of female and 27% of male respondents reported OAB. With a more restrictive definition of at least 'often', the prevalence of OAB was 33% for women and 16% for men.

For the OAB Physical and Occupational Limitations (OAB-POLL) study 10,000 US adults were recruited to complete an internet survey regarding their OAB symptoms, demographic and clinical characteristics, and physical activity

data, in order to estimate the prevalence of OAB and LUTS and the effects of OAB on work productivity and physical functioning.[3] The authors defined OAB similarly to the EpiLUTS study, as urgency at least 'sometimes' and/or the presence of urge urinary incontinence. Based on this definition, the overall prevalence of OAB in the total US population was 23.3%, with women reporting OAB almost twice as frequently as men (30.0 vs. 16.4%, respectively).

Socio-economic relevance

Individuals with OAB report significant impairment to overall quality of life: OAB interfered with daily activities, including symptoms that caused them to stay at home, decreased physical activity because of OAB and even gaining weight because of an inability to exercise. Women with OAB were also significantly more likely than those without OAB to report disturbed sleep, decreased self-esteem, decreased sexuality, and feelings of overall declining health. Findings from the NOBLE study also demonstrated significant effects of OAB on health-related quality of life as measured by validate surveys.[4]

From a patient's perspective, the costs associated with OAB tends to be for routine care, such as incontinence pads, diapers, and laundry, generally reflecting the burden of urinary incontinence.

Estimates of the individual and societal costs for the management of OAB continue to rise. In 2007, average annual per capita costs of OAB in the United States were $1925 ($1433 in direct medical, $66 in direct nonmedical, and $426 in indirect costs). Applying these costs to the 34 million people in the United States with OAB results in total national costs of $65.9 billion. Average annual costs in 2015 and 2020 would be $76.2 billion and $82.6 billion, respectively.[5]

People with symptoms of OAB often delay seeking treatment until increased symptom severity or bother appear. An important aspect of OAB is that it remains difficult to treat effectively. Pharmacotherapy is generally effective based on individual clinical trials but often only modestly superior to placebo.

In chapter 8 (general discussion) we describe that SNM has been shown to be both more effective and cost saving, or at least acceptably cost-effective compared to other therapies (PTNS or BoNT-A).

Autiero et al. compared SNM with optimal medical therapy, BoNT-A and PTNS in the UK. At 5 years, SNM was more effective and less costly than PTNS. Compared with ongoing medical therapy at 10 years, SNM was more costly and more effective, and compared with BoNT-A, SNM with PNE was less costly and more effective, and SNM with TLP was more costly and more effective.[6] The costs for SNM mainly involve device acquisition and implantation. All other

treatments involve on-going drug costs and physician visits for maintenance treatment.

Recently the results of the ROSETTA trail were presented. In this multicenter open-label randomized trial to assess whether BoNT-A is superior to SNM 369 women with refractory urgency urinary incontinence were treated, and 364 were available for the primary outcome analyses. The BoNT-A group reported significantly greater mean reduction in incontinence episodes per day compared to the SNM group. The BoNT-A group was significantly more likely to experience complete resolution of urgency incontinence, report greater improvements in overactive bladder symptom bother. Urinary tract infections were higher in the BoNT-A group (35% vs.11%, $p<0.001$). Self-catheterization was required in 8% and 2% of the BoNT-A group at one and six months, respectively and neuromodulation device revisions/removals occurred in 3%.[7]

It has to be notified that most studies regarding cost effectiveness for SNM received financial support by the manufacturer of SNM devices, which possibly introduces a bias.

Target population

The results of this manuscript are relevant to patients with symptoms of lower urinary tract dysfunction such as frequency, urgency-incontinence or urinary retention. Some of our results are also important for patients who suffer from the combination of urinary tract dysfunctions as well as fecal problems (incontinence and/or constipation). For example patients can be better informed on what results and possible complications to expect and patients can benefit from longer battery life.

Furthermore our study data can be relevant for medical device corporations who want to develop less costly devices then the ones that are used today. These devices should be small, rechargeable and MRI compatible.

Products

Although no new products have been developed with the results of this thesis directly, we showed that changes made in the way of implantation are safe and effective (chapter 4). We also found that patients prefer to have control over the devices used in SNM (chapter 5), the possibilities for self control can be expanded in future designs. The size of the implantable pulse generator is already reduced for better patient comfort, and another company introduced a smaller and rechargeable device for more patient comfort and efficacy.

Innovation and future
In our view, the improvement of SNM should be targeted at:

- Increase in treatment efficacy
- Increase of patient comfort
- Reduction of adverse events and re-interventions

We estimate this can be reached by better patient selection and therefore a good test phase is most important. The test phase is preferably performed by a tined lead test phase while this gives more reliable results than testing with a PNE.

We showed that patients who are dissatisfied with BoNTA or when BoNTA treatment fails can be treated successfully with SNM.

Further improvement of patient comfort can be reached by using on-demand stimulation, with the positive side effect of more patient controlled therapy, or by conditional stimulation as we explained in chapter 8.

For patients with urinary as well as fecal problems we advise a combined work-up in a center were treatment options such as SNM, PTNS and BoNTA can be used and treatments for functional problems of the lower urinary tract and of the bowel tract can be combined for more (cost) effectiveness.

References

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