Neuromodulation for refractory overactive bladder in men

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Male incontinence is an important and often neglected medical problem that has a huge impact on quality of life. Men who are refractory to medications are considered for minimally invasive second-line measures such as botulinum toxin A and neuromodulation. In this article the authors discuss the use of neuromodulation in men with refractory overactive bladder, its place in current guidelines, efficacy and potential adverse events.

Although men experience incontinence less commonly than women, it is still a significant problem and they are often reluctant to seek help. It is estimated that approximately 17% of men aged over 60 experience urinary incontinence. Overactive bladder (OAB) is defined as urgency with or without urgency incontinence, which is often associated with increased daytime frequency, and nocturia, assuming local pathology in the bladder such as urinary tract infection (UTI) has been excluded. The EPIC study suggested that the prevalence of OAB in men is 10.8%. OAB can be divided into dry (no incontinence) or wet (with urgency incontinence). After a thorough work-up and evaluation with a focused history, examination, midstream urine sample (MSU), renal function blood test, frequency voiding chart and OAB validated questionnaires, treatment is often instigated with lifestyle changes, dietary and fluid advice, and bladder drill. The next line will include pharmacotherapy such as antimuscarinics and beta-3 agonists, or a combination. If medication is ineffective, botulinum toxin A and neuromodulation can be tried. Neuromodulation can be broken down into two broad categories: sacral nerve stimulation (SNS) and percutaneous tibial nerve stimulation (PTNS).

Sacral nerve stimulation
SNS has been in use for several decades. It involves the transmission of electrical pulses via a generator to an electrode implanted next to the sacral nerves (ideally S3). SNS of the lower urinary tract was first developed by Tanagho and Schmidt in the 1980s. In the late 1990s approval for SNS was gained from the Food and Drug Administration (FDA) in the United States. The FDA approved SNS in managing refractory urge incontinence in 1997 and chronic urinary retention and frequency/urgency syndrome in 1999.

The mechanism through which SNS works is not fully understood. The likelihood is that there are multiple contributory mechanisms to modulate abnormal sensations and involuntary reflexes. The stimulator causes an alteration in neural activity
by providing an electrical charge to an area near the sacral nerve. There is an activation of somatic afferent nerves that, in turn, inhibit bladder sensory pathways and reflex bladder hyperactivity. The electrical stimulation has an effect on both the afferent and the efferent nerve fibres. There is likely to be a contributory effect from multiple levels of the neural pathway, for instance at the level of the spinal afferents, at the spinal cord level and in the brain centres. Voluntary voiding is maintained during SNS and the hypothesis is that this reflects the inhibition of the ascending pathway of the reflex, as well as an element of induced adaptive changes (neural plasticity). There is also a hypothesis that an activation of the hypogastric sympathetic pathways has a contributory effect.

There are two well established techniques for the first stage of implantation. In this stage, temporary leads are implanted and the patient evaluated to determine if there is any improvement in their symptoms. The first technique is peripheral nerve evaluation, which can be performed as an outpatient, with the leads remaining in place for one to two weeks. The second technique is the first stage tined lead (FSTL) procedure, where leads are placed under sedation or general anaesthetic. In FSTL, the leads are better anchored to tissues due to the tines and are therefore associated with less lead migration (Figure 1). FSTL allows for prolonged testing, typically two to four weeks, and translates into a better full implant rate. It is important to ensure that the leads are correctly placed. This is done by testing motor responses at S2–S4, with the aim being to get the leads positioned at S3, where the motor response promotes inward movement of the intergluteal fold due to contraction of the levator ani (Bellows’ reflex) and plantar flexion of the great toe. Prior to a decision to move onto the second stage (permanent implant), the patient must demonstrate a subjective benefit and, typically, at least a 50% improvement in bladder diary variables.

**Evidence**

Initial robust evidence for the use of SNS for OAB came from a multicentre international randomised study that was the basis of the recommendation for approval by the FDA. Seventy-six patients (19.4% male and 80.6% female) were randomised to receive an implant or have conservative treatment for six months. The latter group were offered an implant after six months. The study found that in the implant group there was a significant reduction in leaking episodes, severity of leaking episodes and number of pads used per day. The patients with implants had their stimulators temporarily turned off at six months. At this point there was a significant increase in urge incontinence symptoms.

A systematic review included 34 primary studies, four of which were randomised controlled trials, with the rest being case series. The review authors were critical of the case series, stating that they did not have a comparison group and did not take account of possible confounding factors. They were also critical of the randomised controlled trials, as these could have been affected by performance and attrition biases. The authors summarised the evidence from the randomised controlled trials as: ‘80% of patients achieved continence or exhibited an improvement of >50% in their main incontinence symptoms after SNS. There was a similar improvement in the case series studies (67%), although this data was less reliable’. They concluded that the results were consistent with SNS reducing symptoms, but that the impact on quality of life needed further investigation. The benefits were found to still be present at three to five years after implantation.

An important paper was published by Groenendijk et al in 2008, which evaluated urodynamics in patients six months after implantation of a sacral nerve stimulator. This showed a significant improvement in first sensation of filling and maximum void in all patients with urge urinary incontinence following implantation, independent of whether or not they had detrusor overactivity on their initial urodynamics test.

The most recent study that supports the use of SNS for OAB was published in 2018 by Siegel et al and was a multicentre, prospective five-year follow-up of patients. 91 per cent of the participants were female. The study evaluated therapeutic success as well as quality of life measures, and found a statistically significant improvement in symptoms (leaks and/or voids). There was also a statistically significant improvement in quality of life measures using the ICIQ-OABqol questionnaire.

A recent systematic review published in European Urology in 2018 included 21 studies with at least 20 patients with six months of follow-up for both SNS and PTNS. There is no available information on the percentage of male participants in these studies. As well as an overall success/improvement rate (decreasing incontinence episodes, pad use, voiding frequency, improving bladder capacity and/or volume voided) for SNS, ranging from 61% to 90%, there was a long-term benefit for urgency incontinence, urgency frequency syndrome and idiopathic retention refractory to conservative treatment.

In the majority of these studies, in particular the most recent five-year multicentre follow-up, there are low percentages of male participants. This reflects the predominance of the condition in women and makes it difficult to fully assess their relevance to the male OAB population.
Adverse effects
The FDA approval studies also looked at the safety of SNS implantation, with adverse events grouped as either device-related (lead or device problems) or therapy-related (pain, infection or change in bowel function). The FDA approval incorporates an analysis of safety where all patients from the three indications were pooled, including 581 patients who had 914 temporary tests (repeat tests were performed for a variety of reasons) and 219 implants. There was an overall adverse event rate of 23.2%. 18.2% of test stimulations had adverse events; approximately half (50.8%) of these required no intervention and only one (0.6%) required surgical intervention. There was an adverse event rate of 51.3% for implants; 38.3% of these required non-surgical intervention and 53.7% required hospitalisation or surgical intervention. There was a 33.3% surgical revision rate. 91% of the adverse events were resolved by the end of the study. Seven (3.1%) had permanent explants due to pain at the implant site, infection, new pain or change in bowel function.5

A systematic review states that approximately half of the patients who underwent SNS experienced adverse events.16 These included pain at the implantation site, lead migration, relocation, replacement or permanent explant of the implanted pulse generator, wound problems, adverse effects on bowel function, infection and generator problems. There was a 33% rate of surgical revision, the most common reasons for this being pain, revision of the lead system and infection. The authors noted that there is no evidence of the long-term efficacy and safety of the procedure, and felt that over time more revisions would be needed. However, in the conclusion, the authors state that improvement in technique over time has resulted in a decrease in complication rates.15

In the recently published five-year prospective study, there was a 22.4% re-operation rate after full implantation. In subjects with a fully implanted system an undesirable change in stimulation occurred in 22%, followed by implant site pain in 15% and lack of efficacy in 13%.17 The permanent explantation rate was 19%. The authors conclude that the rate and type of adverse events were consistent with the published literature.

In the recently published systematic review the failure rate reported was 4–64% and the surgical revision rate was 9–33%.18 The authors felt that the adverse event rate has been overstated and conclude that the overall safety is good but that the reintervention rate remains high.

Percutaneous tibial nerve stimulation
PTNS has been under investigation since 1966, where cat models were used to demonstrate that peripheral nerve stimulation inhibited bladder contractions.19 PTNS was first developed for humans by Dr Marshall Stoller in 1999 as a less invasive alternative to SNS,20 The exact mechanism of action is poorly understood; however, it is thought that it acts by interrupting the abnormal reflex arcs that are present in OAB.21 Some of the nerve roots of the posterior tibial nerve are the same as the nerves that control the bladder. By stimulating these large-diameter somatic afferent fibres, there is thought to be a central inhibition of the micturition reflex pathway. A recent study in cat models by Tai et al demonstrated that short, repeated stimulation of the tibial nerve induced a post-stimulation inhibitory effect that persisted.22 This differs from SNS, which only induces a change while the stimulator is turned on.23,24

The main advantage of PTNS is that it can be provided in an outpatient setting, and there is even scope for it to be set up in a primary care setting. A needle electrode is placed above the medial malleolus, posterior to the tibia, with a surface electrode on the arch of the foot (Figure 2). A treatment lasts for 30 minutes and is initially repeated weekly for 12 weeks. After this treatment intervals are based on the patient’s symptoms.25

An alternative to the percutaneous approach for PTNS is the transcutaneous approach. This might be appealing as it is non-invasive; however, there is limited evidence on its benefits published to date.

Evidence
A review article by Staskin et al in 2012 identified over 30 studies of PTNS in the published literature.24 These ranged from case series through to randomised controlled trials, two of which are long-term follow-up studies. The review concluded that PTNS provides an option for patients who are refractory to anticholinergic therapy, and is less invasive and less costly than SNS.24 The SUmIT trial provides the best available data for PTNS.26 This consisted of a randomised, double blinded, sham-controlled study performed in the USA. Two hundred and twenty adults (mixed male and female) were randomised to 12 weeks of treatment with weekly stimulation.
PTNS or to sham therapy. The participants filled out OAB and quality of life questionnaires, as well as bladder diaries. 54.5% of patients who received PTNS reported a moderate or marked improvement in bladder symptoms, compared with 20.9% of patients who received sham therapy. There was a reduction in number of voids per day (-2.4 versus -1.5 in sham group) and a decrease in the number of episodes of urge incontinence. The authors conclude that they have provided level 1 clinical evidence that PTNS is safe and effective in treating OAB.

In a recent systematic review, benefit from PTNS ranged from 54–79%. The authors concluded that PTNS therapy has shown good results with fewer side-effects in the short term; however, it has not been tested in the long term. PTNS has a higher failure rate (between 40% and 44%) compared to SNS but is less invasive. The authors concluded that in clinical practice PTNS should be offered to those who are unwilling or who are not fit to undergo SNS.

There are currently no large, randomised trials of good quality on the use of transcutaneous tibial nerve stimulation for treatment of OAB in the adult population. This is an area of ongoing interest.

Adverse effects
The adverse effects of PTNS include bruising or bleeding at the needle site, tingling and mild pain. These were mild, transient and relatively uncommon (1–2%).

Conclusion
OAB is an important cause of urinary incontinence in men, and is associated with high levels of morbidity and costs for the NHS. Current first-line management consists of conservative measures followed by pharmacological management. If men with OAB are refractory to these measures, there is no clear consensus on the most clinically effective and cost-efficient management. Neuromodulation clearly plays a role in these patients and has been shown to be clinically effective as well as cost effective. The advantage of PTNS is that it is minimally invasive and low risk, although the evidence for clinical efficacy is weaker than that of SNS. SNS has good quality data to suggest it is effective. It is a costly procedure with a reasonably high rate of surgical revision, however long-term data suggests that over time it is as cost-efficient as other treatments for overactive bladder. Both PTNS and SNS should be considered in the treatment algorithm of men with OAB who are refractory to optimised medical management.

Declaration of interests:
Arun Sahai and Sachin Malde have received funding to promote sacral nerve stimulation services from Medtronic; Dudley Robinson has spoken on PTNS for Cogentix.

Key points

**Sacral nerve stimulation (SNS)**
- Requires surgical implantation of device
- Good efficacy (61–90%)  

**Percutaneous tibial nerve stimulation (PTNS)**
- Less invasive than SNS – can be done as outpatient procedure
- Less effective than SNS (54–79%)
- Less studies and longer term follow up compared to SNS

Both PTNS and SNS should be considered in the treatment algorithm of men with OAB who are refractory to optimised medical management.

**References**
9. van der Pal F, Heesakkers JP, Bemelmans BL. Current opinion on the
Overactive bladder