

Sacral neuromodulation in overactive bladder: a review and current perspectives

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Abstract: Overactive bladder (OAB) symptoms of urgency, frequency, and urge incontinence currently affect a substantial portion of the population, especially as age increases. Sacral neuromodulation has become a popular option for refractory OAB symptoms over the past 2 decades. Studies have demonstrated that it is an effective treatment for OAB and urge incontinence as indicated by decreased number of voids, increased bladder capacity, and fewer leakage events. In addition, the effects have proved to be durable to multiple years following implantation. These benefits come at the expense of a high rate of adverse events, although with comparable long-term cost-effectiveness to botulinum toxin A. We aimed to review the literature that demonstrates that sacral neuromodulation continues to be an efficacious treatment for refractory OAB wet and dry patients, with continuously expanding indications.

Keywords: urge incontinence, sacral neuromodulation, overactive bladder, refractory, voiding dysfunction

Introduction

Overactive bladder (OAB) was first described in 1996 as a cluster of both bladder storage symptoms and symptoms consisting of urinary urgency, frequency, nocturia, and incontinence.¹ The field of neurourology continued to expand, and a subcommittee of the International Continence Society differentiated OAB, the grouping of these symptoms without a diagnosis, from detrusor overactivity, which was the objective urodynamic finding of involuntary detrusor activity.² OAB was defined to be urinary urgency with or without urge incontinence, nocturia, and/or frequency. OAB wet is defined as an involuntary loss of urine associated with a strong desire to void.³ OAB wet encompasses a vast gradient of severity and can have a significant negative impact on quality of life due to significant bothersome symptoms and unanticipated loss of urinary control.⁴

OAB, specifically OAB wet, symptoms currently affect a substantial portion of the population, and the overall prevalence of OAB has been shown to be relatively similar between men and women. One US-based study demonstrated 16% prevalence of OAB in men and 16.9% in women.⁴ Milsom et al⁵ confirmed these findings in the European population, with an estimated OAB prevalence of 15.6% in men and 17.4% in women on surveys completed by patients older than 40 years. A correlation has been found between increasing age and prevalence of OAB wet symptoms. Stewart et al⁴ discovered that the prevalence of OAB wet symptoms increased with age for both men and women, with substantial increases after the age of 44 years for women

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and 64 years for men. Stress and mixed urinary incontinence are more prevalent with advanced age as well, but purely OAB wet patients have a higher likelihood of necessitating treatment. Urge incontinence composes a higher percentage of incontinence in males, with estimates ranging from 40% to 80% of patients.⁶ The social and psychological impact of these disease processes is enormous. For females, there is a prevalence of moderate or severe bother scores among ~3%–17%.⁷ The National OAB Evaluation study found that OAB wet and dry individuals had significantly lower 36-Item Short Form Health Survey quality-of-life scores, higher Center for Epidemiological Studies – Depression scores, and poorer quality of sleep.⁴ In addition to the personal impact, the economic burden of urinary urge incontinence in the US is enormous, as it was estimated to approach US\$76.2 billion in 2015.⁸

The treatment options for the condition start with conservative therapies, as recommended by the American Urological Association guidelines, such as biofeedback and behavioral therapy. First-line medical therapies tend to be anticholinergics and beta-3 agonists before potentially considering invasive surgical treatments such as urinary diversion. These therapies have proven to be effective and safe in a number of clinical trials as detailed extensively by the resources and handbooks of the International Continence Society. When medical therapies have been inadequate, neuromodulation therapies, particularly sacral neuromodulation (SN), are considered. The US Food and Drug Administration approved SN in September 1997 for the treatment of urge urinary incontinence for those patients who have not had success in managing their symptoms with more conservative therapies. In 1999, they subsequently approved SN for urinary retention and frequency urgency syndrome.⁹ Since its approval, SN has become an increasingly utilized intervention for urinary urge incontinence due to sustained long-term benefits, particularly in the setting of refractory symptoms after the use of anticholinergics or beta-3 agonists.

However, prior to considering SN, the exact etiology of the incontinence should be determined by complete evaluation as detailed by the American Urological Association guidelines with history, physical examination, and a postvoid residual to assess for urinary retention. Urodynamics is an optional test that may be performed in carefully selected patients. SN has the best effect when the patients are carefully chosen, and it provides the greatest benefit to OAB wet patients. Substantial efficacy has not been demonstrated for patients with mixed urinary incontinence or solitary stress

urinary incontinence. In addition, it has been suggested that SN has greater benefit to those of younger age or with less severe cognitive deficits.¹⁰ There continues to be an ongoing evaluation of the usefulness of SN, including for new nonurologic indications such as fecal incontinence and constipation. We aimed to review the current literature on the safety and efficacy of SN as a therapeutic option, specifically for the indication of refractory OAB.

Pathophysiology/mechanism

Urinary tract dysfunction often involves abnormalities in the central nervous system. Several medical conditions and/or procedures that disturb central or peripheral S2–S3 nerves can also disturb the lower urinary tract balance and lead to a compensatory response by the central nervous system. The excessive response by the central nervous system can lead to unwarranted overactivity or inhibition of the bladder.¹¹ OAB wet and dry symptoms are generally thought to be caused by intermittent spasms of the pelvic floor musculature and/or bladder.¹¹ In summary, OAB can be attributed to four different specific etiologies: 1) phasic smooth muscle detrusor contractions; 2) activation of sensory afferent nerves; 3) enhanced excitatory transmission in the CNS; and/or 4) reduced CNS central inhibition.

SN is a newer surgical therapy for refractory OAB wet individuals designed to allow patients to retain their native bladder and experience relief without the morbidity of more invasive operations such as augmentation cystoplasty. In 1988, Tanagho and Schmidt¹² first introduced an electrode implant to be placed in the S3–S4 sacral foramen to produce chronic electric stimulation of the sacral nerves and restore normalcy to voiding habits. Initially, neuromodulator placement was a one-stage process, but this was altered in 2003 to create a two-step algorithm for permanent implantation. The permanent tined lead implant has allowed for longer patient testing periods of at least 14 days and fewer episodes of lead migration. In addition, it was shown to increase the percentage of patients receiving benefit during the testing period, improve tolerability, and reduce technical failures.¹³ Another change that was made was to reposition the neuromodulator to a buttock location. A lower anterior abdominal wall location was initially described, but Scheepens et al¹⁴ found that buttock placement lead to fewer adverse events, ability to avoid patient repositioning, and shorter operative times.

Sacral nerve stimulation can lead to excitatory or inhibitory reflexes on the bladder, depending on the force and rate. Despite the substantial usage of SN over the past two decades, the exact mechanism remains poorly elucidated. Studies have

evaluated multiple sites for neuromodulation, such as the sacral, tibial, pudendal, and genital nerves. However, the most commonly described site of neuromodulation for treatment of OAB is the third sacral nerve root (S3). In addition, this location has the largest amount of long-term data on safety and efficacy.¹⁵ There has also been comparison of unilateral lead placement and bilateral lead placement. Pham et al placed unilateral stage 1 S3 leads in 55 patients and bilateral leads in 69 patients with refractory voiding dysfunction. Stage I trials were successful in 32/55 (58%) and 53/69 (76%) of unilateral and bilateral cohorts, respectively ($P=0.03$), with no statistically significant difference in complications.¹⁶ Scheepens et al evaluated unilateral versus bilateral stimulation in patients with chronic voiding dysfunction. No statistically significant improvement was observed between bilateral stimulation and unilateral stimulation, but the authors did conclude that in some individuals, bilateral stimulation may be more effective in improving symptoms.¹⁷

Although the exact mechanism of action is incompletely understood, it is theorized that SN moderates the normal micturition reflex by stimulating the somatic afferent inhibition of sensory processing of the bladder within the spinal cord. The most well-accepted hypothesized mechanism, and the suspected mechanism by these authors, is that the effect derives from stimulation of the alpha myelinated afferent fibers and unmyelinated C fibers in the S3 and S4 pelvic and pudendal nerve roots that affect the micturition reflex.¹⁸ SN uses electrical stimulation to stimulate the pacemaker for the bladder, which are the sacral nerves that innervate the musculature of the pelvic floor and lower urinary tract. Using the electrical stimulation, it is able to either inhibit or incite neural reflexes.¹³ Another theory of mechanism is direct inhibitory input to the bladder, which then suppresses bladder overactivity. In this mechanism, SN causes direct inhibitory signals to the bladder, which can cause inhibition of the guarding reflex and decrease the pelvic floor spasticity, leading to improvement in both urinary retention and bladder overactivity.¹⁹

Outcomes

Urge incontinence

Since SN was first approved for OAB wet patients in 1997, multiple studies have demonstrated its efficacy for the short and long term. When Latini et al²⁰ looked at the effects on urge incontinence, they found that 90% of the patients had $\geq 50\%$ improvement in symptoms and signs of urge incontinence as evidenced by voiding diaries. The frequency of incontinence episodes for these patients decreased significantly from a

mean of 8.8 per day to 2.3 per day at 6-month follow-up. The amount of pads and diapers was also subsequently reduced in patients with the neuromodulator. At baseline, the patients saturated 4.7 pads/diapers/day compared to 0.8 pads/diapers/day at follow-up.

van Kerrebroeck et al found that there was a decrease in urge incontinence episodes from 9.6 prior to implantation to 4.7 at 1-year follow-up. This improvement was persistent even at 5-year follow-up with an average of 3.9 episodes.²¹ The severity of these leaks was improved as well. The number of leaks per day classified as heavy decreased from 2.6 prior to implantation to 1.2 after 1 year and 0.8 at 5 years. The decrease in incontinence corresponded to reduction in pads used per day to 1.8 at 5-year follow-up from 5 pads/day prior to the sacral neuromodulator.

Siegel et al followed up a group of 41 urge incontinent patients for a period of ~3 years following sacral neuromodulator placement. They corroborated the perseverance of the results noted by van Kerrebroeck et al. After 3 years, 59% of the patients had a greater than 50% decrease in the amount of incontinent events each day and 46% of the patients did not have any leakage.¹¹ The patients reported an average of 11.6 leaks/day with 6.7 pads/day at baseline, which had decreased to 5 leaks/day with 3.6 pads/day after 3 years. All studies reviewed demonstrated statistically significant reductions in leakage events and pad usage with neuromodulator placement. The clinical significance of the reduction of incontinence episodes in some of the studies by one fewer leak per day is still unclear. However, even if it is a small numerical change, it likely does make an impact on the individual's quality of life, given that this person has had incontinence refractory to all previously tried methods.

Urgency/frequency

In terms of exclusive impact on urgency and frequency symptoms, similar benefits have been demonstrated for those experiencing urge incontinence. Chartier-Kastler et al²² conducted one of the first studies to look at efficacy of the device for urinary frequency and found that the voids per day decreased from 16.1 per day to 8.2 per day. The maximum bladder capacity improved significantly from a baseline of 244 mL to 377 mL. In addition, the patients were able to hold a greater volume in between voids and OAB events, as the volume at the first uninhibited contraction increased from 214 mL to 340 mL. A multicenter study by Hassouna et al²³ demonstrated significant improvements in water cystometry and quality of life based on the 36-Item Short Form Health Survey. It was also shown that the effects seen were attributable to the neuromodulators

because when the stimulators were deactivated, their patients' symptoms returned to baseline. Following reactivation, the benefits were seen again and were durable at 1 year and 2 years following the implantation.

Siegel et al followed up 29 patients for 2 years following placement of the neuromodulator implant. At baseline, there was a mean of 17.7 voids per day with an average voided volume of 132 mL. After 2 years, this was still significantly reduced to 10.6 voids per day with a mean voided volume of 225 mL.¹¹ In all, 56% of the patients had a greater than 50% reduction in the amount of voids per day and 32% of individuals reverted to a normal range of four to seven voids per day. At 2 years, 69% of the patients reported improved voided volumes and same or reduced amount of urgency compared to baseline.

van Kerrebroeck et al²¹ found that the average number of daily voids decreased from 19.3 to 13 at 1-year follow-up and was still significantly decreased at 5-year follow-up with 14.8 voids per day. The average voided volume increased to 170 mL after 1 year from a baseline of 92 mL, with a very similar average void volume of 165 mL after 5 years. There was less of an effect noted with regard to the amount of urgency episodes, with a decrease from 2.3 times to 1.9 times per day after 1 year and 2.1 times per day after 5 years.

One might hypothesize that there may be differences in response based on whether symptoms were due to neurologic disorders such as stroke, Parkinson's disease, multiple sclerosis, or spinal cord injury. However, there does not appear to be a significant dichotomy. The symptoms appeared to improve for patients after 2 years regardless of whether their symptoms were associated with a neurologic disorder. One report had patients fill out questionnaires at baseline and at 2 years following the placement. Both neurologic and nonneurologic etiology groups had statistically significant improvements on the Interstitial Cystitis Symptom and Problem Index, Overactive Bladder Questionnaire symptom severity, and Health-Related Quality of Life measures. There was no significant difference in urgency, frequency, and number of incontinence episodes per day between patients without a neurologic disorder and those with a neurologic disorder.²⁴ However, there was likely a clinically significant larger decrease in frequency of three fewer voids per day compared to one fewer void per day, respectively, for non-neurologic disorder patients than neurologic disorder patients. Nevertheless, the impact of the sacral nerve stimulator appeared generalizable to patients regardless of whether their voiding dysfunction had an underlying neurologic component or not.

There have been other studies performed to elucidate the factors that may help to predict response to SN and facilitate the process of identifying patients who have the highest chance of success. One prospective study of 55 patients with refractory urge incontinence who responded to SN found that the cure rate was associated with age. The patients who were younger than 55 years had a statistically significant higher cure rate of 65%, while patients older than 55 years had a cure rate of 37%.¹⁰ In addition, the number of chronic conditions and neurologic states appeared to negatively affect the outcome. Another cohort study by Sherman et al looked at 34 patients experiencing refractory urinary urge incontinence after surgery for stress incontinence who underwent neuromodulator placement. They found that 59.1% of patients who had improvement were aged >55 years, while 100% of patients who did not experience improvement were aged <55 years. Another positive predictor of response was the presence of pelvic floor muscle activity.²⁵ However, there is not a clear consensus as all studies do not agree. Starkman et al²⁶ found that there were no significant differences in success rates at 7-month follow-up when looking at the risk factors of age and urodynamic variables.

Complications

Although SN has been shown to have short-term and long-term efficacy, there are a number of complications that can occur in a significant portion of patients. Out of the studies reviewed, there was generally a 30%–40% rate of complications within the first 5 years. This has a substantial impact on the patients when the cost of a revision of removal surgery potentially combined with the need to implant a new device. Siegel et al found no difference between the need for surgical intervention due to adverse effects (AEs) between neuromodulators implanted for urgency/frequency symptoms versus urge incontinence. In all, 33% of the 219 patients with a sacral neuromodulator device implanted need surgical correction by 1 year.¹¹ Typically, the surgical modification involved relocating the device due to pain from the subcutaneous pocket or amending the leads due to suspected migration. Overall, the most common AEs were 15.3% with pain at the stimulator site, 9.0% with new pain, 8.4% with suspected lead migration, 6.1% with infection, and 5.5% with transient electric shock. Of note, they did not consider elective removal, an AE, which would lower the overall complication rate.

Other studies looked at the longer term durability and complication rate for the devices.^{21,27,28} At a mean follow-up of ~3 years, White et al found that 30.3% in their cohort had experienced AEs requiring surgical intervention. These

complications spanned issues such as pain, device malfunction, infection, postoperative hematoma, and lead migration. Of the complications noted, 3.5% experienced infections, 2.7% experienced pain related to the device, and 5.9% experienced lead migration. They considered patients who had the device removed due to lack of efficacy, battery expiration, or electively for other causes as having experienced AEs. Using this classification, they found an overall complication rate of 30.3% and felt that this would represent the upper end of complication percentage.²⁷ The authors also found that the timing of the adverse events was dependent on the type of complication. The mean length of time from sacral neuromodulator implantation to hematoma was 0.3 days, to infection was 16.5 days, to lead migration was 24.6 months, to modulator-related pain was 15.2 months, and to traumatic disruption was 16.7 months. This timeframe is consistent with other surgeries in that hematoma and infection tend to be more acute postsurgical complications. Interestingly, they also looked at patient risk factors for AEs. They found that significant predictors of AEs included a history of trauma, a change in body mass index class, enrollment in a pain clinic, the duration of follow-up, and a history of AEs.

van Kerrebroeck et al followed up 163 patients with sacral neuromodulators for an even longer period of 5 years. They found that after 1 year, 19.9% of patients had experienced AEs that required surgical intervention.²¹ After 5 years, this figure had jumped to 42.1% of patients who experienced AEs requiring intervention. In addition to these patients, 3.5% had it removed due to lack of efficacy, 2% had it revised due to battery expiration, and 5% desired elective removal.

Finally, there is the uncertainty of whether sacral neuromodulators are safe in pregnant patients. One question that continues to be unanswered is whether there is a teratogenic effect of the device, especially in the first trimester. Wiseman et al looked at six case studies of pregnant patients with implanted devices that were not deactivated for the first trimester of pregnancy. They found that in one of the six cases, the delivery was premature by 6 months but there were no fetal abnormalities seen in any of the cases.²⁸ Even in the case of the premature infant, the patient had multiple urinary tract infections after deactivation of the device, and urinary tract infections have been shown to be a risk factor for premature delivery. This was promising evidence that neuromodulators have no harmful effects and may even provide some benefit. However, it is difficult to extrapolate many conclusions from such a small number of patients. Thus, the manufacturers still recommend that the implant be deactivated after discovery of pregnancy.²⁹

Contraindications to placing the device would include failure to respond to the test device, patient's inability to operate the device, and patient's planning to undergo diathermy or magnetic resonance imaging in the future.

Cost-effectiveness

Cost is a significant factor when deciding whether to pursue SN because it can be an expensive surgery. One study that examined health care expenditure in the US for 1 year following neuromodulator placement found that there was a 73% reduction in the average yearly office visit expenses from US\$994 to US\$265 per patient with a significant decrease in diagnostic and therapeutic procedures leading to US\$674 in savings per patient for these procedures.³⁰ Drug costs were also significantly decreased from US\$693 to US\$483 per patient. These cost savings represent a 92% reduction in outpatient doctor visits and diagnostic and procedure costs, in addition to a 30% reduction in drug expenditures.

There is not only the question of whether placing a neuromodulator versus not placing a neuromodulator is fiscally responsible, but whether the implant compares favorably to other surgical interventions financially. In a study from Duke University, the authors Siddiqui et al³¹ found that sacral nerve stimulation was more expensive (US\$15,743 vs US\$4,392) but was also more effective (1.73 vs 1.63 quality adjusted life-years) than botulinum toxin A during a 2-year treatment period. However, once they factored in traditional cost-effectiveness ratios of US\$50,000 and US\$100,000 per quality adjusted life-year, sacral nerve stimulation was found to be less cost-effective than botulinum toxin A for the treatment of refractory urge incontinence. However, given that the treatment period evaluated was only 2 years, it is difficult to determine whether this advantage would remain persistent in the long term with repeated botulinum injections. It is still unclear whether it is the most economically wise therapy for refractory OAB.³⁰

A study out of England used scenario analysis to evaluate the cost-effectiveness of botulinum toxin A compared directly to SN and found that botulinum toxin A was dominant to SN.³² Other studies out of Europe appear to show that SN is economically favorable over botulinum toxin A in the medium- to long-term period. Bertapelle et al found that higher initial costs of SN were balanced out by excellent long-term outcomes. It was found to be cost-effective after 3 years and more cost-effective, with both lower cost and higher efficacy, than botulinum toxin A at 10 years.³³ In Spain, the authors used incremental cost-effectiveness ratios to determine the incremental cost per quality-adjusted life year gained. They found that the cost per quality-adjusted life year gained for SN

over botulinum toxin A was €3,775 at 5 years and €9,830 at 7 years.³⁴ This was deemed to be substantially cost-effective using a previously established threshold of €30,000 per quality-adjusted life year as efficient for Spain.³⁵ At 10 years, the cumulative costs of SN, botulinum toxin A, and medical therapy were €29,166, €29,458, and €29,370, respectively. In addition, SN had a cumulative quality-adjusted life year of 6.89 compared to 6.38 for botulinum toxin A and 5.12 for medical therapy.³⁴ Owing to the lower cost in combination with higher efficacy, they deemed SN the superior option at 10 years. There appears to be a trend toward superiority of cost-effectiveness of SN for long-term management, although for periods less than a decade, it still remains murky. Ultimately, the choice between botulinum toxin A and SN is the one that belongs to the patient, with consideration of the efficacy, cost, and time commitment.

Conclusion

SN has become an increasingly utilized option for refractory OAB symptoms. Over the past two decades, SN has continued to gain popularity to relieve refractory OAB symptoms with studies demonstrating that it is an effective treatment with potentially long-term enduring benefits. However, these benefits have been shown to come at the expense of a high rate of adverse events although with comparable long-term cost-effectiveness to botulinum toxin A. SN continues to play a role in the management of carefully selected refractory OAB wet and dry patients, with continuously expanding indications.

Disclosure

The authors report no conflicts of interest in this work.

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