Neuromodulation Techniques: A Comparison of Available and New Therapies

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Neuromodulation has become ever more common in the fields of urology and voiding dysfunction. Many therapeutic alternatives have emerged to increase effectiveness of these therapies and reduce morbidity and invasiveness. Each new modality needs to prove its efficacy in common indications for voiding dysfunction such as refractory urgency–frequency, urge incontinence, and perhaps urinary retention, as well as in select patient populations and subgroups. We need more information to broaden the applicability of neuromodulation to larger numbers of patients and conditions.

Introduction
The field of neuromodulation has grown significantly in recent years. Initial developments in the 1800s led to interest in the delivery of electrical stimulation to achieve responses in nerves and muscles throughout the body. In neuromodulation, however, electrical stimuli to nerves has been developed to alter neurotransmission processes in cases of nonneurogenic, as well as neurogenic conditions, resulting in tremendous therapeutic opportunities in patients with refractory conditions. Over time, we have refined many of these techniques to achieve best clinical results with the least degree of morbidity. This paper reviews the application and clinical outcomes of neuromodulation therapies for the treatment of pelvic organ dysfunction, focusing on the role of pelvic neuromuscular physiology in translational innovations (Fig. 1).

Several therapeutic methods have been developed to treat refractory voiding dysfunction. We address each therapy and discuss its current role in patient management.

Transcutaneous Electrical Stimulation
Strictly speaking, transcutaneous electrical stimulation (TENS) stimulates the sacral nerves; the desired clinical effects, however, are more neuromodulatory. This therapy seems to occupy a place midway between sacral root stimulation and anal, vaginal, and perineal stimulation. TENS devices have been used to limited degrees to enhance tolerability to bladder filling and may offer some avenue for therapy in postponing voiding. Fall et al. [1] described TENS use suprapubically in patients with interstitial cystitis and subsequent studies have advanced the use of this modality [2,3]. The exact stimulation parameters are not quite agreed upon as different frequencies have been used. Two Hz may stimulate pudendal afferents, whereas 50 Hz may stimulate striated paraurethral musculature. Similarly, low-frequency TENS units may have some use in eradicating detrusor contractility [4]. This technology is easy to use, however, it may require extended time to gain treatment-related benefits. TENS unit therapy directed toward S2 or S3 may make sense because direct transcutaneous stimulation of this area may yield better results than suprapubic stimulation alone. Positive results have been demonstrated based on urodynamic data, with improved bladder capacity, delay in first urge to void, and reduced detrusor instability [5]. For adequate maintenance of this therapy’s benefits, its use must continue for longer durations, which is probably the reason it is not widely used in current practice.

Noninvasive magnetic stimulation
Noninvasive magnetic stimulation of the sacral roots inhibits bladder contractions and causes effects that persist for a short time beyond the stimulation period. This type of stimulation cannot be applied for prolonged periods
and is currently unsuitable for long-term treatment, although it may be helpful for preliminary assessment of candidates for chronic sacral root neuromodulation. Extracorporeal magnetic innervation provided by a specially modified chair (NeoControl Pelvic Floor Therapy System; Neotonus, Marietta, GA) is being studied for potential use in overactive bladder, stress incontinence, and pelvic pain. It is unclear if the exact mechanism of action is magnetic, nerve root, peripheral nerve, or intramural nerve stimulation. No prospective randomized studies to date have been performed to demonstrate this therapy’s use in larger groups of urge incontinence or stress incontinence.

Selective Nerve Stimulation

**Pudendal nerve**

Because the bladder afferent reflex works through sacral interneurons that activate storage through pudendal nerve efferent pathways directed towards the urethral sphincter, the pudendal nerve is a logical target for developing neuromodulation therapies. Early attempts to manipulate this reflex through electrical stimulation were based on direct pelvic floor muscle stimulation and then led to the subsequent development of the first implantable and external pelvic floor stimulators, anal plug stimulators [6, 7], and intravaginal pessary stimulation [8, 9]. To deliver optimal stimulation to the nerve directly, Vodusek et al. [10] introduced selective pudendal nerve stimulation (PNS) that showed micturition reflex inhibition.

Recent neurophysiologic studies reveal that selective nerve stimulation (SNS) works for bladder storage disorders by a similar inhibition of the micturition reflex as a result of electrical stimulation of sensory afferent fibers, depolarizing Aβ and Aγ somatomotor fibers that affect the pelvic floor and external sphincter and thus inhibit detrusor activity [11]. Because many sensory afferent nerve fibers contained in the sacral spinal nerves originate in the pudendal nerve, the pudendal nerve afferents are important targets for neuromodulating the inhibitory reflex on the micturition cycle. Direct pudendal nerve neuromodulation stimulates more pudendal afferents than SNS and may do so without the adverse effects of off-target stimulation of leg and buttock muscles. Thus, techniques for direct pudendal nerve stimulation at alternative locations to the sacral foramen are being developed. Spinelli et al. [12] recently modified existing sacral neuromodulation