Mechanism and Priority of Botulinum Neurotoxin A versus Sacral Neuromodulation for Refractory Overactive Bladder: A Review

Yanping Zhang Fengping Ji Erpeng Liu Jian Guo Wen

First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

Keywords

Botulinum toxin A · Sacral neuromodulation · Mechanism · Priority · Refractory overactive bladder

Abstract

Background: The treatment of common overactive bladder (OAB) has reached a consensus, but there is not a clear answer to the treatment of refractory OAB (ROAB). ROAB is defined as nonresponsive to treatment with behavioural and oral therapies. The disease can influence the physical and mental health of patients, cause poor quality of life, and create an urgent socio-economic burden. With the advancement of medical treatment, the treatment of OAB has improved significantly in the last 2 decades, especially ROAB, by the usage of botulinum neurotoxin A (BoNT-A) and sacral neuromodulation (SNM). Many studies have demonstrated their effectiveness and safety. However, which therapy is the optimal method remains unclear for patients with ROAB, and the exact mechanism involved in the procedures is still unknown. **Summary:** This review is to clarify the mechanisms, advantages, and disadvantages of SNM and BoNT-A in treatment of ROAB, and determine whether there is an order effect of SNM and BoNT-A in managing ROAB. **Key Messages:** BoNT-A and SNM mainly act on the peripheral nervous system and central nervous system, respectively. But BoNT-A and SNM may partly act on the central and peripheral nervous systems, separately. SNM may be a better choice than BoNT-A in the long time. At the same time,

BoNT-A and SNM can treat the ROAB as the first and next steps, and the sequence of both would not affect the effectiveness of each other.

© 2021 S. Karger AG, Basel

Introduction

Overactive bladder (OAB) is defined by the International Continence Society (ICS) as urgency with or without urge urinary incontinence but usually with urinary frequency and nocturia in the absence of urinary tract infection [1]. Many diseases can induce OAB, such as Parkinson's disease, cerebral infarction, diabetes, and benign prostatic hyperplasia. OAB can be divided into neurogenic OAB and idiopathic OAB according to whether nerve impairment is present.

OAB is highly prevalent worldwide. Irwin et al. [2] found that its overall prevalence was 11.8%, which is similar in men and women and increases with age. The prevalence of OAB in adults aged ≥ 18 years was 16% in men and 16.9% in women in the USA [3], and in adults aged ≥ 40 years, it was 15.6% for men and 17.4% for women in Europe [4]. In Asia, the prevalence of OAB was lower, but it was still 6.0% overall, 5.9% among men, and 6.0% among women according to the fifth nationwide population census of China [5]. In mainland China, the overall prevalence of OAB was 2.1%, with OAB-dry accounting for 1.0% and OAB-wet accounting for 1.1%; OAB was

Table 1. Mechanism of BoNT-A injection

BoNT-A target	Mechanism
Peripheral nerve	1. Decline of neurotransmitter release in the presynaptic membrane 2. Reduces receptors in the postsynaptic membrane 3. Improves the sensation of the bladder by decreasing ATP in the suburothelial space
Central nerve	1. Impairs the sensory fibres on terminals in the spinal cord dorsal horn
BoNT-A, botulinum toxin A.	

more common in men than in women older than 60 years [6]. Therefore, knowing how to treat OAB and decrease its prevalence is becoming urgent.

Behavioural therapy, for example, health education, delayed urination, bladder training, fluid intake modification, reduced coffee consumption, moderate physical activity, and pelvic floor muscle retraining, is the first step for a new OAB patient. However, such modifications usually have a poor response because most patients have low compliance with outpatient service, and OAB requires a longer time to show an improvement. Next, the process comes into second-line treatment, oral drugs. Anticholinergic medication and β -adrenergic agents are common, and evidence has confirmed that they have clinical efficacy in patients with OAB [7]. However, the adverse effects of β -adrenergic agents (increased blood pressure, nasopharyngitis, urinary tract infections, and urinary retention) and anti-muscarinic agents (dry mouth, dry eyes, constipation, blurred vision, dyspepsia, urinary retention, and impaired cognitive function) limit the usage of medicines. Due to adverse effects, more than 70% of patients quit pharmacotherapy within 6 months to 3 years [8]. In addition, some patients are insensitive to oral medicine. Although different results indicate shut-off of second-line treatment, only 3.5% of patients (men and women) were treated with third-line therapy [9]. Once behavioural therapy and oral drugs are both determined to be ineffective, the patient enters the refractory OAB (ROAB) stage [10].

ROAB is defined as the failure of behavioural therapy after 8–12 weeks and the failure of at least 1 anti-muscarinic agent administered for 4–8 weeks by the 2019 AUA/SUFU guidelines [11]. The prevalence rate of ROAB is unknown but most likely represents a small portion of the total OAB population [12]. When the patients meet the ROAB diagnosis, third-line treatment is considered. Third-line treatment consists of botulinum neurotoxin A (BoNT-A) injection, sacral neuromodulation (SNM),

and percutaneous tibial nerve regulation. In recent years, the effectiveness of SNM and BoNT-A has been proven, and the success rates of both are approximately 80% [13] and 60% [14], respectively. Although SNM and BoNT-A have high success rates, the mechanisms of both remain unknown. In addition, which treatment is better or more appropriate remains unclear. In this review, we will discuss what roles BoNT-A injection and SNM play and which method can be chosen preferentially.

Botulinum Neurotoxin A Injection

History of BoNT-A Injection

BoNT-A, the most potent biological toxin known to humans, has a light chain and heavy chain associated with function [15]. It is used to treat strabismus, blepharospasm, muscular dystonia, hyperhidrosis, and migraine and is widely used for cosmetic purposes [16]. By the end of 1967, botulinum toxin was first shown to inhibit the bladder in rats by Carpenter [17]; in 2011, botulinum toxin was finally approved for the treatment of urinary incontinence, secondary to neurogenic detrusor overactivity [18]. Because many studies have proven its effectiveness, the US Food and Drug Administration (FDA) approved the use of botulinum toxin for the treatment of OAB in 2013 [19]. Thus, it is necessary to understand the mechanism of action.

Mechanism of BoNT-A

The mechanisms of BoNT-A in the treatment of OAB mainly include several parts shown in Table 1. BoNT-A can inhibit neurotransmitter release not only from efferent but also possibly from afferent nerve terminals [14, 20]. At the same time, BoNT-A influences both the release of presynaptic neurotransmitters and the density of postsynaptic membrane receptors. In the presynaptic membrane, there is a synaptic vesicle associated protein-2 pro-

Table 2. Mechanism of SNM

SNM target	Mechanism
Central nerve	1. Somatic afferent nerve activates the central inhibitory pathway 2. Visceral sensory nerve activates the central inhibitory pathway
Peripheral nerve	1. Activates the motor nerve pathway
SNM, sacral neuromodulation.	

tein that binds with the heavy chain of BoNT-A and enters the presynaptic membrane [21]. Then, catabolism is processed inside the synaptic vesicles, and the 2 chains are separated, leaving the light chain as the active part [10, 13]. Next, the actual active moiety, the light chain, recognizes and cleaves synaptosome-associated protein 25, which is vital in binding vesicles to the cell membrane and prevents neurotransmitter release [17]. On the other hand, Schulte-Baukloh et al. [22] first examined postsynaptic muscular changes in receptor profiles after injection of onabotulinum toxin A. There was a significant decrease in M2, M3, P2X2, and P2X3 receptors. The receptors of M3 and M2 directly and indirectly play a key role in bladder contractility. P2X2 and P2X3, purinergic receptor proteins that may be involved in motor signalling in neurogenic OAB [18], are highly expressed in OAB patients [23, 24]. Thus, a decrease in receptors might contribute to the reduced contractility of the urinary bladder after BoNT-A injections. In addition to the abnormal motor function, excessive sensitivity of the bladder also needs to be stopped. BoNT-A works by decreasing the sensitivity of the bladder at 2 levels. A previous study proved that ATP can mediate the sensation of bladder fullness and has a role in the pathophysiology of OAB [25]. In a laboratory, neurogenic detrusor hyperactivity in rats with chronic spinal cord injury showed increased release of ATP, while NO release was reduced [26]. This suggests that disorder of these transmitters can lead to OAB and that the prevalence rate shows a positive correlation with changes in ATP. Therefore, ATP can become one of the targets to treat OAB. On the peripheral nerve, intravesicular BoNT-A injections have been shown to significantly inhibit the release of ATP from urothelial cells [13], and ATP in the suburothelial space declines, resulting in decreased bladder sensation, owing to a lack of sensory fibre activation. In the central region, BoNT-A, radiolabelled with technetium-99, was detected in the dorsal root ganglia 6 h post-injection [27], and some data revealed that BoNT-A significantly impaired sensory fibres through a mechanism involving cleavage of synaptosome-associated protein 25 at termi-

nals in the spinal cord dorsal horn [28]. Above all, BoNT-A injections improve not only the feeling of urgency but also the behaviour of voiding.

Sacral Neuromodulation

History of SNM

SNM was developed more than one hundred years ago as a treatment for OAB. In 1988, Tanagho and Schmidt [29] first introduced an electrode implant placed in the S3–S4 sacral foramen to produce chronic electric stimulation of the sacral nerves and restore normalcy to voiding habits. After this development, many urologists proved the effectiveness of SNM, prompting the FDA approval of Inter-Stim (Medtronic, Minneapolis, MN) for urge incontinence in 1997 and for urgency, frequency, and non-obstructive urinary retention in 1999 [30]. Subsequently, SNM achieved substantial progress and has been introduced all over the world. Now, the SNM operation has been perfected. The procedure has 2 stages, an experience period and a permanent period, to assess effectiveness before implantation of a permanent pulse generator. This process is also a minimally invasive procedure, and Bartley et al. [30] described the SNM operation in detail in their article.

Mechanism of SNM

SNM mainly functions in the central nervous system, differing from BoNT-A, which mainly acts on the peripheral nervous system. SNM and BoNT-A injections have emerged as third-line treatment options for patients with ROAB to initial treatment. Groen et al. [31] investigated women with idiopathic detrusor overactivity incontinence and thought SNM can suppress OAB but cannot exert the effect on urethral resistance and bladder contraction strength. However, the detailed mechanism of SNM in treating OAB is still unclear. The mechanism of SNM treatment of ROAB is shown in Table 2, which includes 2 parts of the central and peripheral nervous systems. In the matter of the central nervous system, most

studies conclude that afferents may play a vital role in the mechanism of SNM [32, 33]. Considering spinal cord injury, a loss of control from the brain to the bladder and activation of the spinal micturition reflex pathway lead to changes in afferent nerve activity and abnormal reflex mechanisms [34], followed by the appearance of OAB. In inflammatory disorder, C fibres play a significant role. C fibres are unresponsive in normal but activated in OAB [35]. After SNM treatment, the number of uninhibited contractions decreased, indicating that the contraction of the bladder was controlled and that OAB was alleviated [30]. Exploring the reasons, SNM may electrically stimulate somatic afferent nerves in a sacral spinal root and send signals to the central nervous system, which may restore normal bladder function [36]; in addition, activation of somatic afferent nerves inhibits bladder sensory pathways by blocking C fibres and reflex bladder hyperactivity [37]. Malaguti et al. [32] also found that SNM acts at the cortical site level by the afferent pathway, and it is specific from the sacral area to the somatosensory cortex. In addition, SNM also activates the visceral sensory nerves. This is proven by a study in which Fowler et al. [38] demonstrated that anal sphincter contraction observed during SNM is the result of an afferent-mediated response because the response is stronger with direct motor nerve stimulation. However, there are other theories that SNM can stimulate the motor nerve pathway and retrograde spinal motor neurons [33]. This is proved by a study which suggests that pelvic floor muscle contractions are due to stimulation of direct efferent during SNM testing [39].

Priority of SNM and BoNT-A

As third-line treatments for OAB, SNM and BoNT-A have extensive applications in ROAB. Currently, the data indicate that the rate of success of SNM in treating OAB is 70% [40], and 80% of patients who receive BoNT-A injection show improvement in urinary symptoms [41]. However, we still have no answer regarding which therapy is more suitable. Many factors influence the selection of procedure. BoNT-A is a simple operation that is performed under cystoscope guidance using intravenous sedation as an outpatient procedure [42], so it is minimally invasive. However, reinjection every 6 months may be needed because of its self-limited duration of effect. SNM is complex and requires a two-step surgery. This is difficult to manage and evaluate but has a longer duration compared with BoNT-A. After SNM implantation, it can

last 4–6 years, or even longer. Currently, the possible injury and complexity of surgery are acceptable based on the use of more technical advances, and it is not the main consideration. Thus, a longer duration may be valued by the patients.

Beyond operation and duration, safety and effectiveness are essential aspects in selection. Usually, the efficacy and safety of BoNT-A injection and SNM are evaluated through successful treatment rates (symptoms of OAB improvement >50%) and adverse events, respectively. The efficacy and safety of BoNT-A injection and SNM to treat OAB have been evaluated in some studies [43, 44]. The studies revealed that the rate of success between BoNT-A injection and SNM was similar. However, BoNT-A injection is faced with a high rate of adverse events, particularly urinary retention. In the cohort study [45], because of the BoNT-A injection, the incidence rate of urinary retention was up to 34.9%, followed by the need for clean intermittent self-catheterization. At the same time, clean intermittent catheterization can also cause urinary infection. For SNM, local pain and infection are common and easily handled. Thus, BoNT-A injection has a disadvantage in safety compared to SNM. Moreover, there are opposite views about the efficacy of both options. The study discovered that patients implanted with SNM had a higher success rate than those who received BoNT-A injection in the short term [46]. More studies need to be carried out to assess which one has a more effective impact. Today, the first opinion is more recognizable. According to the first view, we think the SNM has a priority. However, when we introduce cost-effectiveness, the suggestion would be overturned. In a study in which the cost-effectiveness of SNM and BoNT-A injection was assessed, the authors thought that BoNT-A injection would be a cost-effective option in the first 2 years [47]. However, with the increasing duration of therapy, the cost accumulates in terms of BoNT-A injection, but that of SNM remains unchanged. Therefore, SNM may become more cost-effective. This was proven by a study [48] that deemed SNM to be cost-effective compared with BoNT-A over 10 years. Therefore, SNM would be the best option in the long term.

In addition, with regard to the non-responder who received treatment with SNM or BoNT-A injection initially, we have no conclusion whether we can choose the other therapy and how effective it will be. In recent studies, some standpoints have been proposed. Baron et al. [49] evaluated the tolerance and efficacy of BoNT-A injection after the failure of SNM for iOAB and identified that BoNT-A injection can be used in SNM non-responders

and has a success rate of 43.4%. Moreover, a systematic review and meta-analysis suggested that patients who fail or are dissatisfied with BoNT-A can select the SNM, and the effectiveness is not significantly different [50]. It can be seen from this evidence that both SNM and BoNT-A injection can be considered the first or next step in treating ROAB, and their effects would not be influenced by each other. There are still small numbers of patients who are insensitive to both treatments; combining SNM and BoNT injection may be more effective, although further study is needed to confirm this hypothesis.

In summary, both SNM and BoNT-A injection are good choices in treating ROAB, and their mechanism still needs to be further investigated. SNM may be cost-effective in the long term and have minor side effects. With regard to the sequence of administering both, their effectiveness would not be influenced when one fails and then the other is performed. Moreover, multiple factors should be taken into consideration, especially the will of patients. Before making a decision, the patient must be informed about the operation, duration, cost, and effect of both.

References

- Abrams P, Artibani W, Cardozo L, Dmochowski R, van Kerrebroeck P, Sand P. International continence society: reviewing the ICS 2002 terminology report: the ongoing debate. *Neurourol Urodyn*. 2009;28:287.
- Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. *Eur Urol*. 2006;50(6):1306–5.
- Stewart WF, Van Rooyen JB, Cundiff GW, Abrams P, Herzog AR, Corey R, et al. Prevalence and burden of overactive bladder in the United States. *World J Urol*. 2003;20(6):327–36.
- Milsom I, Abrams P, Cardozo L, Roberts RG, Thüroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU Int*. 2001;87(9):760–6.
- Wang Y, Xu K, Hu H, Zhang X, Wang X, Na Y, et al. Prevalence, risk factors, and impact on health related quality of life of overactive bladder in China. *Neurourol Urodyn*. 2011;30(8):1448–55.
- Wen JG, Li JS, Wang ZM, Huang CX, Shang XP, Su ZQ, et al. The prevalence and risk factors of OAB in middle-aged and old people in China. *Neurourol Urodyn*. 2014 Apr;33(4):387–91.
- Nambiar A, Lucas M. Chapter 4: guidelines for the diagnosis and treatment of overactive bladder (OAB) and neurogenic detrusor overactivity (NDO). *Neurourol Urodyn*. 2014;33(Suppl 3):S21–5.
- Szymański JK, Słabuszewska-Józwiak A, Zaręba K, Jakiel G. Neuromodulation: a therapeutic option for refractory overactive bladder. A recent literature review. *Wideochir Inne Tech Maloinwazyjne*. 2019 Dec;14(4):476–85.
- Moskowitz D, Adelstein SA, Lucioni A, Lee UJ, Kobashi KC. Use of third line therapy for overactive bladder in a practice with multiple subspecialty providers: are we doing enough? *J Urol*. 2018;199(3):779–84.
- Ziegelmüller BK, Sommer A, Bauer RM. Botulinumtoxin bei überaktiver Blase. *Urologe*. 2020;59(8):963–72.
- Lightner DJ, Gomelsky A, Souter L, Vasavada SP. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment 2019. *J Urol*. 2019;202(3):558–63.
- Atiemo HO, Vasavada SP. Evaluation and management of refractory overactive bladder. *Curr Urol Rep*. 2006 Sep;7(5):370–5.
- Spinelli M, Sievert KD. Latest technologic and surgical developments in using InterStim Therapy for sacral neuromodulation: impact on treatment success and safety. *Eur Urol*. 2008;54(6):1287–96.
- Brubaker L, Richter HE, Visco A, Mahajan S, Nygaard I, Braun TM, et al. Refractory idiopathic urge urinary incontinence and botulinum A injection. *J Urol*. 2008;180(1):217–22.
- Jiang YH, Liao CH, Kuo HC. Current and potential urological applications of botulinum toxin A. *Nat Rev Urol*. 2015 Sep;12(9):519–33.
- Cruz F. Targets for botulinum toxin in the lower urinary tract. *Neurourol Urodyn*. 2014;33(1):31–8.
- Carpenter FG. Motor responses of the urinary bladder and skeletal muscle in botulinum intoxicated rats. *J Physiol*. 1967;188:1–11.
- Cruz F, Herschorn S, Aliotta P, Brin M, Thompson C, Lam W, et al. Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial. *Eur Urol*. 2011;60:742–50.
- Raju R, Linder BJ. Evaluation and treatment of overactive bladder in women. *Mayo Clin Proc*. 2020 Feb;95(2):370–7.
- Kanai A, Zabarova I, Oefelein M, Radziszewski P, Ikeda Y, Andersson KE. Mechanisms of action of botulinum neurotoxins, β 3-adrenergic receptor agonists, and PDE5 inhibitors in modulating detrusor function in overactive bladders: ICI-RS 2011. *Neurourol Urodyn*. 2012;31(3):300–8.
- Dong M, Yeh F, Tepp WH, Dean C, Johnson EA, Janz R, et al. SV2 is the protein receptor for botulinum neurotoxin A. *Science*. 2006;312(5773):592–6.

Conflict of Interest Statement

There is no conflict of interest.

Funding Source

Henan Province Medical Science Provincial-ministerial Co-construction Project (No: SBGJ2018059); National Science Foundation of China, U1904208.

Author Contributions

Yanping Zhang: project development, data collection, manuscript writing, and editing. Fengping Ji: manuscript writing and editing. Erpeng Liu: editing. Jian Guo Wen: project development and editing.

- 22 Schulte-Baukloh H, Priefert J, Knispel HH, Lawrence GW, Miller K, Neuhaus J. Botulinum toxin A detrusor injections reduce post-synaptic muscular M2, M3, P2X2, and P2X3 receptors in children and adolescents who have neurogenic detrusor overactivity: a single-blind study. *Urology*. 2013;81(5):1052–7.
- 23 O'Reilly BA, Kosaka AH, Knight GF, Chang TK, Ford AP, Rymer JM, et al. P2X receptors and their role in female idiopathic detrusor instability. *J Urol*. 2002;167:157–64.
- 24 Brady CM, Apostolidis A, Yiangou Y, Baecker PA, Ford AP, Freeman A, et al. P2X3-immunoreactive nerve fibres in neurogenic detrusor overactivity and the effect of intravesical resiniferatoxin. *Eur Urol*. 2004;46(2):247–53.
- 25 Cockayne DA, Hamilton SG, Zhu QM, Dunn PM, Zhong Y, Novakovic S, et al. Urinary bladder hyporeflexia and reduced pain-related behaviour in P2X3-deficient mice. *Nature*. 2000;407(6807):1011–5.
- 26 Smith CP, Gangitano DA, Munoz A, Salas NA, Boone TB, Aoki KR, et al. Botulinum toxin type A normalizes alterations in urothelial ATP and NO release induced by chronic spinal cord injury. *Neurochem Int*. 2008;52(6):1068–1075.
- 27 Malde S, Fry C, Schurch B, Marcelissen T, Averbeck M, Digesu A, et al. What is the exact working mechanism of botulinum toxin A and sacral nerve stimulation in the treatment of overactive bladder/detrusor overactivity? ICI-RS 2017. *Neurourol Urodyn*. 2018 Jun;37(S4):S108–16.
- 28 Coelho A, Oliveira R, Cruz F, Cruz CD. Impairment of sensory afferents by intrathecal administration of botulinum toxin A improves neurogenic detrusor overactivity in chronic spinal cord injured rats. *Exp Neurol*. 2016 Nov;285(Pt B):159–66.
- 29 Tanagho EA, Schmidt RA. Electrical stimulation in the clinical management of the neurogenic bladder. *J Urol*. 1988 Dec;140(6):1331–9.
- 30 Bartley J, Gillera J, Peters K. Neuromodulation for overactive bladder. *Nat Rev Urol*. 2013;10(9):513–21.
- 31 Groen J, Ruud Bosch JL, van Mastrigt R. Sacral neuromodulation in women with idiopathic detrusor overactivity incontinence: decreased overactivity but unchanged bladder contraction strength and urethral resistance during voiding. *J Urol*. 2006;175(3 Pt 1):1005–9.
- 32 Malaguti S, Spinelli M, Giardiello G, Lazzeri M, Van Den Hombergh U. Neurophysiological evidence may predict the outcome of sacral neuromodulation. *J Urol*. 2003;170(6 Pt 1):2323–6.
- 33 Gill BC, Pizarro-Berdichevsky J, Bhattacharyya PK, Brink TS, Marks BK, Quirouet A, et al. Real-time changes in brain activity during sacral neuromodulation for overactive bladder. *J Urol*. 2017;198(6):1379–85.
- 34 Shi P, Zhao X, Wang J, Lan N. Effects of acute sacral neuromodulation on bladder reflex in complete spinal cord injury rats. *Neuromodulation*. 2013;16(6):583–9.
- 35 Elkelini MS, Pravdiviy I, Hassouna MM. Mechanism of action of sacral nerve stimulation using a transdermal amplitude-modulated signal in a spinal cord injury rodent model. *Can Urol Assoc J*. 2012 Aug;6(4):227–30.
- 36 Leng WW, Morrisroe SN. Sacral nerve stimulation for the overactive bladder. *Urol Clin North Am*. 2006 Nov;33(4):491–501.
- 37 Jones J, Van de Putte D, De Ridder D, Knowles C, O'Connell R, Nelson D, et al. A joint mechanism of action for sacral neuromodulation for bladder and bowel dysfunction? *Urology*. 2016 Nov;97:13–9.
- 38 Fowler CJ, Swinn MJ, Goodwin RJ, Oliver S, Craggs M. Studies of the latency of pelvic floor contraction during peripheral nerve evaluation show that the muscle response is reflexly mediated. *J Urol*. 2000;163(3):881–3.
- 39 Vagane D, Franssen E, Voorham J, Van de Borne S, Voorham-van der Zalm P, De Wachter S. Behind the scenes: an electromyographic interpretation of the pelvic floor contractions seen by the naked eye upon stimulation in sacral neuromodulation patients. *Neurourol Urodyn*. 2019;38:S446–9.
- 40 Vasdev N, Biles BD, Sandher R, Hasan TS. The surgical management of the refractory overactive bladder. *Indian J Urol*. 2010;26(2):263–9.
- 41 Yokoyama T, Kumon H, Smith CP, Somogyi GT, Chancellor MB. Botulinum toxin treatment of urethral and bladder dysfunction. *Acta Med Okayama*. 2002;56(6):271–7.
- 42 Rapp DE, Lucioni A, Katz EE, O'Connor RC, Gerber GS, Bales GT. Use of botulinum-A toxin for the treatment of refractory overactive bladder symptoms: an initial experience. *Urology*. 2004;63(6):1071–5.
- 43 Amundsen CL, Komesu YM, Chermansky C, Gregory WT, Myers DL, Honeycutt EF, et al. Two-year outcomes of sacral neuromodulation versus onabotulinumtoxinA for refractory urgency urinary incontinence: a randomized trial. *Eur Urol*. 2018;74(1):66–73.
- 44 He Q, Li B, Zhang C, Zhang J, Luo D, Wang K. Treatment for refractory overactive bladder: a systematic review and meta-analysis of sacral neuromodulation and onabotulinumtoxinA. *Int Urogynecol J*. 2021;32(3):477–84.
- 45 Singh R, El Nashar SA, Trabuco EC, Klingele CJ, Gebhart JB, Occhino JA. Comparison of short term outcomes of sacral nerve stimulation and intradetrusor injection of onabotulinumtoxinA (Botox) in women with refractory overactive bladder. *Female Pelvic Med Reconstr Surg*. 2015;21(6):369–73.
- 46 Singh R, El Nashar SA, Trabuco EC, Klingele CJ, Gebhart JB, Occhino JA. Comparison of short term outcomes of sacral nerve stimulation and intradetrusor injection of onabotulinumtoxinA (Botox) in women with refractory overactive bladder. *Female Pelvic Med Reconstr Surg*. 2015;21(6):369–73.
- 47 Siddiqui NY, Amundsen CL, Visco AG, Myers ER, Wu JM. Cost-effectiveness of sacral neuromodulation versus intravesical botulinum A toxin for treatment of refractory urge incontinence. *J Urol*. 2009;182(6):2799–804.
- 48 Arlandis S, Castro D, Errando C, Fernández E, Jiménez M, González P, et al. Cost-effectiveness of sacral neuromodulation compared to botulinum neurotoxin A or continued medical management in refractory overactive bladder. *Value Health*. 2011;14(2):219–28.
- 49 Baron M, Perrouin-Verbe MA, Lacombe S, Paret F, Le Normand L, Cornu JN. Efficacy and tolerance of botulinum toxin injections after sacral nerve stimulation failure for idiopathic overactive bladder. *Neurourol Urodyn*. 2020;39(3):1012–9.
- 50 Yang G, Xu Y, Qu G, Zhang Y. Refractory overactive bladder patients who chose sacral neuromodulation therapy after failed OnabotulinumtoxinA treatment: a systematic review and meta-analysis. *PLoS One*. 2020;15(3):e0230355.