Does deep brain stimulation improve Parkinson’s disease-related lower urinary tract symptoms and voiding dysfunction?

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Abbreviations used: AUA-SS, American Urological Association symptom score; CMT, conventional medical treatment; DanPSS, Danish prostate symptom score; DBS, deep brain stimulation; DO, detrusor overactivity; GPe, globus pallidus externa; GPI, globus pallidus interna; IPSS, international prostate symptom score; LC, locus coerules; LC-DBS, DBS of the LC; LUTS, lower urinary tract symptoms; MCC, maximal cystometric capacity; MPPT, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; OAB-q, overactive bladder questionnaire; OAB-SS, overactive bladder symptom score; QoL, quality of life; PAG, periaqueductal grey matter; PAG-DBS, DBS of the PAG; PD, Parkinson’s disease; PET, positron emission tomography; PDQ-8, Parkinson’s disease questionnaire; PMC, pontine micturition center; PnO, pontine reticular nucleus; PPN, pedunculopontine nucleus; PPN-DBS, DBS of the PPN; SHIM: sexual health inventory for men; STN, subthalamic nucleus; STN-DBS, DBS of the STN

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ABSTRACT

Parkinson’s disease (PD), caused by degeneration of dopaminergic neurons, leads to motor and autonomic symptoms. A large proportion of PD patients experience lower urinary tract symptoms (LUTS) and voiding dysfunction, associated with poor quality of life. Deep brain stimulation (DBS) is an adjunctive therapy used in combination with medication for Parkinsonian motor symptoms and is currently being explored to treat PD-related LUTS. This review discusses the current literature on the effects of DBS on lower urinary tract function and whether this modality can be used to modulate PD-related LUTS and voiding dysfunction.

Keywords: deep brain stimulation, lower urinary tract symptoms, neuromodulation, Parkinson’s disease, voiding dysfunction

INTRODUCTION

Parkinson’s disease (PD) is a debilitating disease caused by the degeneration of dopaminergic neurons within the basal ganglia of the brain, which play a role in controlling movement and autonomic processes, including micturition [1]. PD is traditionally characterized by motor symptoms including akinesia, rigidity, postural instability, and tremors [2,3]. Between 27% to 86% of PD patients will experience some type of lower urinary tract symptoms (LUTS) or voiding dysfunction [3]. Voiding dysfunction in PD may be due to poor vesicourethral coordination with delayed or incomplete urethral relaxation or impaired bladder contractility. PD-related LUTS adversely affect quality of life and may result in early institutionalization. Urinary symptoms can precede motor symptoms and may be an indicator of disease progression in those with early-stage PD [4].

In recent years, there has been significant interest on the impact of the deep brain stimulation (DBS) on PD-associated LUTS and voiding dysfunction and its possible utilization as a therapeutic tool. DBS first began as a technique in animal models to localize cerebral functions [5] but is now an established adjunctive treatment for improving motor symptoms in PD patients [6]. The use of DBS to improve urinary function was discovered incidentally in subjects undergoing DBS for other diseases [7]. Both animal and human studies have revealed promising results regarding the ability of DBS to modulate micturition in PD [1-3,5,7-21]. However, there is currently a paucity of original studies detailing the impact of DBS on LUTS and voiding dysfunction in PD patients.

In this non-systematic review, we summarize the current literature on the effects of DBS on the storage and voiding functions of the lower urinary tract in patients with PD and discuss the implications of these findings for future therapies.

MICTURITION IN PD PATIENTS

Overview of normal micturition

Normal micturition involves a complex series of neural networks within both the autonomic and central nervous systems, which coordinate...
both the storage and emptying of urine. The bladder is a hollow visceral organ with proprioceptors that sense bladder stretch. As the bladder fills and distends, detrusor stretch receptors sendafferent signals to the spinal cord, which incites sympathetic outflow and the activation of efferent motor neurons in Onuf’s nucleus. The sympathetic signaling triggers the release of norepinephrine, which stimulates β_{1}-adrenergic receptors in the detrusor, allowing for relaxation. The somatic signaling incites the release of acetylcholine, which stimulates nicotinic receptors allowing the rhabdosphincter to contract and maintain continence. During this process, parasympathetic activity is reciprocally inhibited [22].

When the bladder fills past its threshold, afferent receptors travel through the sacral spinal cord via the pelvic nerve to the periaqueductal grey matter (PAG), which is under the control of many high cortical centers including the prefrontal cortex, thalamus, and limbic structures. Neurons in the PAG then relay signals to the pontine micturition center (PMC) or Barrington’s nucleus [5]. The PMC integrates sensory information from the bladder with higher-level cortical structures [23]. When deemed appropriate to void by cortical input, the PMC initiates micturition by signaling to parasympathetic preganglionic neurons, which synapse in the sacral spinal cord with postganglionic neurons in the pelvic plexus. These neurons release acetylcholine, which activates M2 and M3 receptors in the urothelium to produce bladder contractions. In this phase of micturition, sympathetic and somatic pathways are inhibited, allowing for voluntary relaxation of the external urethral sphincter, thereby initiating voiding [23].

**PD-associated LUTS and voiding dysfunction**

LUTS are the most common autonomic symptoms in PD [1,24]. Storage LUTS (nocturia, urgency, frequency, and urgency incontinence) are more common in the early phase of the disease [2], whereas voiding symptoms are more apparent in the later phase [25]. The etiology of voiding dysfunction in PD is multifactorial [26]. One key aspect is the development of neurogenic lower urinary tract dysfunction secondary to degradation of suprapontine dopaminergic neural pathways involved in micturition. Other age-related pathologies affecting micturition are also common in PD patients. Over 36% of patients have bladder outlet obstruction, while many others experience symptoms secondary to pelvic organ prolapse, BPH, and hormonal deficiencies [26]. Furthermore, motor symptoms may prevent patients from toileting themselves appropriately in a timely manner.

Most patients with PD tend to have post-void residuals within “normal limits” (< 100 ml) [26,27]. On urodynamics, detrusor overactivity (DO), either terminal or phasic, is the most common urodynamic finding, but detrusor underactivity can also be observed [2,26]. Other common urodynamic abnormalities include high resting urethral pressures and uninhibited external sphincter relaxation [27]. Rarely, PD patients can demonstrate pseudo-detrusor-sphincter dyssynergia, likely due to bradykinesia of the external urethral sphincter [27].

**DEEP BRAIN STIMULATION: MECHANISM OF ACTION**

DBS is a surgical procedure used to elicit chemical and electrical changes in the brain without destroying neural tissue [28]. Although the physiologic mechanisms remain elusive, it is postulated that DBS interrupts pathological oscillations, releases neuroprotective growth factors, and promotes neurogenesis and synaptic plasticity in order to modulate components of neural activity, including micturition [29]. To perform DBS, electrodes are surgically implanted into specific structures of the brain. Electrical stimuli are delivered to those regions, disrupting signaling locally and in associated networks [30]. The efficacy or particular effect of DBS can vary depending on the targeted anatomy or the spatial relationship of the stimulated electrical field [1,31]. DBS has been associated with an overall adverse event rate of up to 60%, many of which are reversible. These adverse events include but not limited to speech and gait difficulties, depression, cognitive disabilities, weight gain, urinary incontinence, urinary retention, urinary tract infection, surgical site infection, hemorrhage, and rarely, death [17,18,32-35].

The use of DBS in Parkinson’s disease began in 2002 after its FDA approval as an adjunctive therapy in PD patients with symptoms uncontrolled by pharmacologic agents alone [36]. Bilateral DBS of the subthalamic nucleus (STN) [37] and globus pallidus internus (GPi), the two most common sites for DBS implantation, have been demonstrated to improve motor symptoms in PD patients [28]. In a randomized trial of 156 severe PD patients randomized to bilateral DBS of the STN (STN-DBS) and medical therapy or medical therapy alone, those who underwent STN-DBS had a greater improvement in motor symptoms than medication alone [35]. Moreover, the combination of medical therapy and DBS may lessen the number of levodopa equivalents needed [6].

**EFFECTS OF DBS ON LOWER URINARY TRACT FUNCTION IN PD**

Several groups have studied the impact of DBS on lower urinary tract symptoms and voiding dysfunction in PD patients, including increased urinary frequency, nocturia, urgency, urinary incontinence, incomplete emptying, and its effect on quality of life. These results are summarized in Table 1.

**Lower urinary tract symptoms and voiding dysfunction**

While DBS has proven effective for improving motor symptoms in many levodopa-responsive patients, subjective effects on urinary symptoms in patients with severe PD have had variable results. A survey of PD patients comparing those who underwent DBS (n = 220) with those who did not (n = 196) showed significant improvements in frequency, urgency, incontinence, and overactive bladder symptom score in the DBS groups. Interestingly, these improvements were more substantial in female patients when compared to males [21]. In the EuroInf study, a multi-center, open label prospective study of 60 patients with PD, after a mean follow-up of 6 months, STN-DBS was associated with decreased urinary urgency, frequency, and nocturia [9]. These findings were supported by the subsequent EuroInf 2 study which prospectively compared non-motor symptoms in PD patients who underwent STN-DBS (n = 101) with intraependal levodopa infusion (n = 33) and apomorphine (n = 39). After a follow-up of 6 months, significant improvements in urinary symptoms including urgency, frequency, nocturia (P = 0.001), and sexual function (P = 0.020) as measured by the Nonmotor symptom scale were only seen in the STN-DBS group [8].

Other studies have demonstrated less subjective clinical improvement in LUTS. In one small report on 30 PD patients, 24 of which had urinary urgency, 30% had symptomatic improvement while 70% had no change or worsening in their urgency after DBS. Of 26 subjects with nocturia, only 12% felt subjective improvement after DBS compared to 88% with no
change or worsening nocturia [38]. Winge et al. performed a prospective study of 16 PD patients who underwent STN-DBS where LUTS were assessed pre- and post-operatively using two validated questionnaires, the international prostate symptom score (IPSS) and the Danish prostate symptom score (DanPSS). While patients demonstrated improved motor symptoms after STN-DBS, there was no change in overall LUTS. However, when stratified by symptom type, patients reported decreased overactive bladder symptoms at both 3 and 6 months post-operatively. There was a significant improvement in bothersome daytime frequency, nocturia, and urgency (DanPSS questions 5–8) after 3 months, but these improvements diminished after 6 months. Interestingly, the number of patients with severe bladder symptoms as reported by DanPSS score > 10 initially increased after 3 months but then decreased after 6 months [39]. On a subsequent analysis, Winge et al., compared advanced PD patients who underwent either conventional medical treatment (CMT) with STN-DBS, CMT with an apomorphine pump, or CMT alone. The three treatment groups did not demonstrate any differences with respect to their total IPSS or DanPSS scores, but DBS patients reported less nocturia and less bother from nocturia. DanPSS scores also correlated with DBS duration, but not with age or disease duration [6]. These mixed results may be attributed to the fact that LUTS may become more apparent in patients after their motor symptoms improve with DBS. DBS may also alter coping strategies that patients use to manage their LUTS [39].

### Urinary incontinence

The development of urinary incontinence has been associated with DBS; some reports attribute incontinence to the surgical procedure [40] or to disease progression [41]. One small study of 30 PD patients reported that only 21% of patients had improved continence after DBS, whereas 79% worsened or had no change in symptoms [38]. Conversely, one study of advanced PD patients who underwent STN-DBS demonstrated that both male and female patients had significantly improved urinary incontinence and frequency after 12 months. Those who underwent DBS of the GPi (GPI-DBS) also shared these improvements but did not reach statistical significance. There was no difference in either group with respect to impaired mobility urinary incontinence stemming from Parkinsonian-related immobility [19].

### Table 1. Summary of effects of DBS on LUTS.

| Parameter of bladder function | Author               | Year | Study population                                      | Key findings                                                                 |
|-------------------------------|----------------------|------|-------------------------------------------------------|-----------------------------------------------------------------------------|
| LUTS, voiding dysfunction     | Zong et al. [21]     | 2019 | 307 males and 109 females with PD                     | DBS associated with improved OAB-SS, urinary frequency, incontinence, and urgency |
|                               |                      |      |                                                       | No changes in nocturia, feeling of incomplete emptying, or dysuria          |
|                               |                      |      |                                                       | Females demonstrated greater improvement in AUA-SS, OAB-SS and QoL scores than men |
| LUTS, QoL                     | Dafsari et al. [9]   | 2016 | 35 males and 25 females with PD undergoing STN-DBS   | STN-DBS associated with significantly improved urinary frequency, nocturia, and urgency as measured by the Non-Motor Symptom Scale |
|                               |                      |      |                                                       | STN-DBS associated with 47% improvement in QoL scores as measured by Parkinson's Disease Questionnaire |
| LUTS                           | Dafsari et al. [8]   | 2019 | 173 patients with PD with PD; STN-DBS (n = 101), intrajejunal levodopa infusion (n = 33), or apomorphine (n = 39) | STN-DBS group associated with significant improvement in urinary symptoms and sexual function, which was not demonstrated in the other groups |
| Urinary incontinence, LUTS    | Vishwajit et al. [38]| 2009 | 30 patients with PD, 15 patients with essential tremor with DBS | In PD patients, DBS associated with 21% improvement in incontinence, 30% improvement in urgency, and 12% nocturia, whereas 79%, 70%, and 88% reported worsening or no change in symptoms, respectively |
| LUTS, urinary incontinence    | Witte et al. [19]    | 2018 | 128 patients with PD; STN-DBS (n = 63), GPI-DBS (n = 65) | STN-DBS associated with significant improvement in frequency and incontinence |
|                               |                      |      |                                                       | GPI-DBS associated with non-significant improvement in frequency and incontinence |
|                               |                      |      |                                                       | No change in nocturia or incontinence due to lack of mobility from PD          |
| LUTS, QoL                     | Mock et al. [13]     | 2016 | 33 patients with PD; STN-DBS (n = 20), GPI-STN (n = 13) | QoL scores improved after DBS, but results only significant for STN-DBS |
|                               |                      |      |                                                       | STN-DBS associated with mild improvement in AUA-SS and OAB-q scores but worse SHIM score |
|                               |                      |      |                                                       | GPI-DBS associated with improved SHIM scores but non-significant worsening of AUA-SS and OAB-q scores |
Quality of life
Voiding dysfunction is associated with poor quality of life in PD patients [4]. In a prospective trial of 33 PD patients who underwent DBS of either the STN (n = 20) or GPi (n = 13), DBS significantly improved quality of life scores in the overall group. When stratified by DBS target location, a quality of life benefit was only demonstrated in STN-DBS patients [13]. Dafsari et al. also reported that patients undergoing STN-DBS exhibited a 47% increase in quality of life, as measured by the Parkinson’s disease questionnaire (PDQ-8) [9].

EFFECT OF DBS ON URODYNAMIC PARAMETERS

Several groups have examined the objective impact of DBS on various cerebral target regions by measuring urodynamic outcomes. These results are summarized in Table 2.

Basal ganglia: subthalamic nucleus and globus pallidus interna

The basal ganglia likely have a role in inhibiting the spino-bulbo-spi

nal micturition reflex [3]. The STN [37] is a component of the basal ganglia that is typically tonically inhibited by the globus pallidus externa (GPe). The STN modulates the downstream activity of the GPi and substantia nigra pars reticulata [35]. Those structures then communicate with the thalamic nuclei, frontal cortex, supplementary motor area and dorsolateral prefrontal cortex [11]. In PD, the tonic inhibition of the GPe is diminished, leading to the development of motor symptoms. When not taking dopaminergic medications, bilateral STN-DBS in PD patients has been shown to have a sustained improvement of symptoms in such as tremor, rigidity, and dyskinesia [42].

DBS of the basal ganglia has yielded interesting results with respect to its impact on micturition. An early model in cats showed that high frequency STN-DBS of 50 Hertz or higher inhibited the micturition reflex via bladder relaxation and sphincter contraction [3]. A subsequent model of unilateral STN-DBS in pigs chemically induced to have Parkinsonian features exhibited decreased bladder compliance and increased pressure at maximal cystometric capacity (MCC) when stimulators were turned to the OFF state [43]. These studies provided early evidence that DBS could effectively modify urinary function [3,43].

STN- and GPi-DBS effects on urodynamics in humans with PD and other movement disorders have been evaluated in small studies, many of which report promising findings. Finazzi-Agro et al. retrospectively examined 5 patients with PD between 9 and 12 months after STN-DBS. All patients had detrusor overactivity with DBS in both the ON and OFF states; however, the bladder volume triggering a detrusor contraction was increased in the ON state. Bladder capacity also significantly increased from a median of 130 to 320 ml when transitioning from the OFF to the ON state [2]. Seif et al. confirmed these findings in their study of 16 PD patients with STN-DBS that were examined 6 to 29 months after stimulator implantation. Overall, bladder capacity, compliance, and time to first desire to void decreased when the stimulator was turned OFF. When the stimulator was turned back ON, time to first desire to void and bladder capacity both increased while compliance normalized. Moreover, detrusor overactivity was only observed when the stimulator was turned on OFF [15]. Herzog et al. compared STN-DBS in the ON and OFF states in 11 PD patients using positron emission tomography (PET). During bladder filling, bladder volume at first desire to void was decreased in the OFF compared to the ON state. The filling phase in the OFF state was also associated with increased activity in the lateral frontal cortex, which may indicate the cortex’s attempt to suppress undesired voiding at low bladder volumes [11]. These results may be attributed to STN-DBS’s role in normalizing the perception and processing of afferent information from the bladder, such as bladder filling, by the PAG, insula, and thalamus [44].

Other groups have reported more equivocal or detrimental results. One prospective study of 16 PD patients with STN-DBS did not demonstrate any significant changes on urodynamic studies before and after implantation after a median follow up of 6 months [39]. Mordasini et al. reported on 11 patients with severe dystonia who prospectively underwent GPi-DBS implantation. Urodynamic evaluation when DBS was turned ON revealed decreased maximum flow rate and increased postvoid residual, although DO was absent in all patients, 4 of whom demonstrated DO preoperatively [14].

The small sample size of these studies highlights the need for larger randomized trials to fully understand the objective bladder improvements in PD patients who undergo DBS of the basal ganglia. Results from these studies will be critical in further elucidating the uncertain role of the basal ganglia in the regulation of micturition.

Thalamus

The thalamus is a collection of nuclei located between the cerebral cortex and brainstem. It primarily functions in processing and integrating sensory information. During micturition, it is suspected that the thalamus filters afferent information which is then relayed to the insula and anterior cingulate cortex for higher cortical processing [45,46]. Studies have demonstrated activation of the thalamus in both the storage and voiding phases of micturition [46]. DBS of the ventral intermediate nucleus of the thalamus has been successful in improving tremors in PD patients, but its clinical effects on voiding are largely unknown [47]. In a small study of 7 patients with essential tremor, DBS of the ventral intermediate nucleus of the thalamus in the ON state decreased bladder capacity at the first desire and strong desire to void as well as at MCC. These effects were more profound for urologically asymptomatic patients with bilateral rather than unilateral DBS [12].

Brainstem

DBS of brainstem structures in PD patients has been successful in improving motor symptoms. For example, the pedunculopontine nucleus (PPN) degenerates in PD, and DBS of the PPN (PPN-DBS) has been shown to improve gait dysfunction in PD patients [7,16]. Several structures of the brainstem, such as the PMC and PAG have well-established roles in micturition. Other brainstem components are also involved in both bladder storage and emptying, although the exact mechanisms are unclear. More specifically, the locus coeruleus (LC) is a key region of the PMC that plays a crucial role in relaying signals to the sacral spinal cord to initiate voiding [1]. Conversely, the rostral pontine reticular nucleus (PnO) serves in inhibiting the PMC [1]. Some of these structures may degenerate in PD [48], making them a suitable target for DBS to improve urinary function.

In a report of rats undergoing saline infusion to induce continuous filling and voiding cycles, Green et al. demonstrated that DBS of the PAG (PAG-DBS) prior to voiding inhibited detrusor contractions during which both external urethral sphincter tonic contraction and continence were maintained. Voiding was suppressed for the duration of the stimu-
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The stimulation period (approximately 7 min) but resumed once stimulation was turned OFF. PAG-DBS also improved MCC [10]. These findings were corroborated in two other rat studies. Stone et al. reported that electrical stimulation of the ventrolateral PAG and tegmentum ventral and lateral to the PAG in rats reversibly inhibited normal voiding.

Table 2. Summary of effects of DBS on urodynamic parameters.

| Location of DBS placement | Author             | Year | Study population                          | Key findings                                                                                                                                 |
|---------------------------|--------------------|------|-------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Thalamus                  | Dalmose et al.     | 2004 | 5 Göttingen minipigs with Parkinsonian     | • When DBS was turned off during the storage phase, bladder capacity minimally decreased, and bladder compliance significantly decreased        |
|                           |                    |      | features induced by MPTP                   |                                                                                                                                             |
|                           | Finazzi-Agro et al.| 2003 | 3 males and 2 females with PD              | • DBS associated with increased bladder capacity and volume triggering bladder contraction                                                  |
|                           |                    |      |                                           | • Minimal decrease in amplitude of DO contractions                                                                                          |
|                           | Seif et al.        | 2004 | 7 males and 9 females with idiopathic PD   | • DBS associated with increased bladder capacity, increased time to first desire to void, and normalization of bladder capacity               |
|                           |                    |      |                                           | • No detrusor activity seen after DBS                                                                                                       |
|                           |                    |      |                                           | • When DBS was turned OFF, bladder capacity, compliance, and time to first desire to void decreased                                          |
|                           | Herzog et al.      | 2006 | 5 males and 5 females with idiopathic PD   | • DBS associated with increased bladder capacity at first urge to void                                                                       |
|                           |                    |      |                                           | • Increased regional cerebral blood flow in lateral frontal cortex and decreased bladder volume at first desire/urge to void when DBS was turned OFF |
|                           |                    |      |                                           | • Having a full bladder was associated with increased regional cerebral blood flow in the anterior cingulate cortex, which was more pronounced when DBS was turned OFF |
|                           | Winge et al.       | 2007 | 21 patients with idiopathic PD             | • No significant changes in urodynamic parameters after DBS after 6-month follow-up                                                         |
|                           | Mordasini et al.   | 2014 | 6 males and 5 females with severe         | • No detrusor activity seen with DBS ON                                                                                                      |
|                           |                    |      | therapy-refractory dystonia               | • DBS associated with decreased maximum urinary flow rate and increased postvoid residual                                                   |
| Basal ganglia              | Kessler et al.     | 2008 | 5 males and 2 females with essential       | • DBS associated with reduced bladder volume at first desire to void, strong desire to void, and MCC                                          |
|                           |                    |      | tremor                                    |                                                                                                                                             |
| Brainstem                 | Green et al.       | 2012 | Urethrane-anesthetized rats; 6 patients    | • In rats, DBS reversibly inhibited bladder contractions, and external urethral sphincter remained tonically contracted, preserving continence |
|                           |                    |      | with chronic neuropathic pain             | • In humans, patients tended to have a higher MCC after DBS, but no change in subjective pain scores                                         |
|                           | Stone et al.       | 2015 | 39 urethrane-anesthetized rats             | • PAG-DBS and tegmentum lateral/ventral to the PAG reversibly inhibited voiding                                                           |
|                           |                    |      |                                           | • Increased MCC without any changes in bladder compliance or respiratory function                                                           |
|                           | Chen et al.        | 2017 | 54 urethrane-anesthetized rats             | • PPN-DBS inhibited bladder contractions, the strength of which increased with increasing voltage                                            |
|                           |                    |      |                                           | • PnO and PAG-DBS inhibited bladder contractions, but less profoundly than PPN-DBS                                                              |
|                           |                    |      |                                           | • LC-DBS augmented bladder contractions                                                                                                      |
|                           | Jensen et al.      | 2009 | 4 Göttingen minipigs                      | • DBS of the structure homologous to the PMC increased detrusor pressure, which led to visible voiding in some subjects                   |
|                           |                    |      |                                           | • DBS did not affect consciousness or general thriving even after several weeks of implantation and stimulator use                           |
|                           | Roy et al.         | 2017 | 5 males with PD                           | • Increase in MCC after DBS                                                                                                               |

MCC significantly increased in the ON compared to the OFF state ($0.69 \pm 0.06$ ml vs. $0.41 \pm 0.04$ ml, respectively $P < 0.05$) without changing bladder compliance [5]. Chen et al. used rats to evaluate bipolar DBS of the PPN, PAG, LC, and PnO. PPN-DBS potently inhibited
reflexive bladder contractions; the amount of bladder contraction area inhibited increased with rising voltage. DBS of the PAG and PnO also inhibited reflexive bladder contractions, but less effectively than PPN-DBS. Conversely, DBS of the LC (LC-DBS) between 1.75 and 2 V enhanced reflexive bladder contractions [1]. Moreover, unilateral DBS of the supra-pontine region homologous to the PMC in minipigs demonstrated increased detrusor pressure and promoted voiding. The authors suggest that inhibition of this region may have a therapeutic role in controlling unwanted micturition [49].

Currently, the use of brainstem-targeted DBS for improving voiding dysfunction in humans is limited to two studies. Green et al. performed urodynamics in 6 patients who initially underwent PAG-DBS for the treatment of chronic neuropathic pain. When turned ON, PAG-DBS significantly increased MCC, possibly by diminishing discomfort associated with having a full bladder. PAG-DBS did not change first sensation of filling, or first/strong desire to void [10]. Similar findings were reported by Roy et al. who looked at 5 PD patients with deep brain stimulators previously placed in the PPN. MCC increased slightly with stimulation in the ON versus the OFF state (199 ml vs. 131 ml, Ρ < 0.05), but the response magnitude varied between subjects [7]. Taken together, these studies show promise for brainstem structures as plausible DBS targets to alter and improve voiding function in patients with PD and other neurologic diseases. Future research will not only aid in developing therapeutic strategies but may also elucidate the precise mechanisms of individual brainstem structures in micturition.

**FUTURE DIRECTIONS**

While DBS appears to be a promising therapy for modulating LUTS in PD patients, the current research is mostly limited to small cohorts. Larger clinical trials are needed to truly delineate how DBS affects voiding function with respect to urodynamics and subjective parameters.

NCT03202251 is a prospective cohort study enrolling patients with an American Urological Association symptom score (AUA-SS) > 8 and neurologic symptoms who are deemed candidates for DBS. Study participants will undergo subjective and objective assessment of their LUTS using validated questionnaires and urodynamics, respectively. Primary outcomes include change in AUA-SS and Incontinence Quality of Life score from pre-DBS to > 60 d after DBS [50]. Although this trial does not specify the placement of stimulators in a particular location, investigating the effects of DBS to different brain structures on voiding dysfunction would also be beneficial.

Furthermore, no studies exist comparing DBS with other common surgical interventions used in advanced PD patients with LUTS and voiding dysfunction, such as intravesical onabotulinum toxin A, sacral neuromodulation, or peripheral tibial nerve stimulation. While DBS is a more invasive procedure, it may be beneficial in patients who have PD-related motor and urinary symptoms. Such a study would be useful in counseling patients on therapy options and would enhance the interdisciplinary collaboration that is essential in the care of these patients.

The use of DBS may help alleviate urinary symptoms and improve voiding function in other neurological diseases. One study in rats with traumatic brain injury reported significant improvements in voiding efficiency after DBS of the PnO, the effect of which increased as stimulation voltage increased [51]. DBS-SCI (NCT03053791) is a phase I/II multi-center open-label trial assessing the effects of DBS targeting the mesencephalic locomotor region in spinal cord injury patients. The trial is mostly aimed at evaluating effects on motor function but important secondary outcomes include changes in sexual and urinary function, measured by validated questionnaires, bladder diary, urodynamics, and renal bladder ultrasound [52].

**CONCLUSION**

Many PD patients experience bothersome LUTS and voiding dysfunction, adversely affecting quality of life. For those who undergo DBS for motor symptoms, some may experience subjective and objective changes in their urinary habits, which may be principally dependent on the target of the stimulator. The physiology underlying DBS’s effects on voiding dysfunction and LUTS is not well elucidated; further work is needed to determine if these improvements are attributable to better control of motor symptoms or another mechanism. Larger, long-term randomized studies are warranted to fully delineate the benefits and other outcomes of DBS for LUTS and voiding dysfunction in patients with PD and other neurologic diseases.

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