Urological Dysfunction

12

Henry Moore and Carlos Singer

Abstract

Symptoms of urinary dysfunction occur frequently in patients with Parkinson's disease (PD), particularly men. Irritative symptoms, such as frequency, urgency, and urge incontinence, are reported in 57–83% of patients with PD. Obstructive symptoms, such as hesitancy and weak urinary stream, may be present in 17–36% of individuals. The appearance of urinary symptoms may follow the appearance of motor symptoms by a few years. Several mechanisms, such as detrusor hyperreflexia, detrusor areflexia, coexistent obstructive uropathies, and dysfunction of infravesical mechanisms, can be responsible for the urinary dysfunction in patients with PD. Detrusor hyperreflexia is the urodynamic correlate of irritative urinary symptoms. Detrusor areflexia is uncommon in PD and, when present, is usually secondary to the use of anticholinergic medications. Coexistent obstructive uropathies may complicate the clinical picture in patients with PD and produce both obstructive and irritative symptoms. Urinary dysfunction in PD also may be the result of dysfunctional infravesical mechanisms such as sphincter bradykinesia. In terms of pathogenesis, voiding dysfunction in PD is primarily due to the loss of the inhibitory effect that the basal ganglia exert on the pontine micturition center. This inhibitory effect likely is mediated by D1 dopamine receptors and results in a "quiet bladder" during the filling phase. In terms of treatment, the irritative symptoms often can be treated successfully with anticholinergic drugs; however, for refractory overactive bladder, intravesical botulinum toxin injections or deep brain stimulation surgery may be required. If the symptoms are obstructive in nature, bladder catheterization and sometimes urological surgery may be necessary.

H. Moore, M.D. • C. Singer, M.D. (✉)
Parkinson's Disease and Movement Disorder Center,
Department of Neurology, University of Miami – Miller
School of Medicine, 1501 NW 9th Ave., 2nd Floor,
Room # 2031A, Miami, FL 33136, USA
e-mail: CSInger@med.miami.edu

R.F. Pfeiffer and I. Bodis-Wollner (eds.), *Parkinson's Disease and Nonmotor Dysfunction*,
Current Clinical Neurology, DOI 10.1007/978-1-60761-429-6_12,

Keywords

Urinary dysfunction • Parkinson's disease • Irritative • Urgency • Urge incontinence • Detrusor hyperreflexia • Detrusor areflexia • Anticholinergics • Obstructive • Obstructive uropathy • Dysfunctional infravesical mechanisms • Sphincter bradykinesia • Voiding dysfunction • Basal ganglia • Pontine micturition center • Botulinum toxin • Deep brain stimulation • Urinary urgency • Lower urinary tract symptoms • Urge incontinence • Dopamine • Levodopa • Hoehn and Yahr • Multiple system atrophy • Myogenic areflexia • Pseudodyssynergia • Vesicosphincter dyssynergia • Sphincter tremor • Dopamine agonists • Erectile dysfunction • Transurethral prostatectomy • Sphincter EMG • Onuf's nucleus • Detrusor reflex • Pontine storage center • Positron emission tomography • Oxybutynin • Tolterodine • Solifenacin • Darifenacin • Trospium chloride • Propantheline bromide • Hyoscyamine • Flavoxate • Tolterodine LA • Oxybutynin LA • Trospium XR • Urodynamic studies • Intermittent catheterization • Biofeedback • Cystostomy • Cystometrogram • Thalamotomy • Neurogenic bladder • Postvoid residual volume • Subthalamic nucleus • Detrusor • Repetitive transcranial magnetic stimulation • Percutaneous posterior tibial nerve stimulation • Periaqueductal gray matter • Involuntary detrusor contraction • Mean maximum cystometric capacity

Introduction

Parkinson's disease (PD) is a synucleinopathy characterized by motor manifestations that include tremor, bradykinesia, rigidity, gait impairment, and postural instability. A variety of nonmotor manifestations also are associated with PD. Patients with PD frequently present with urinary dysfunction. The treating neurologist should have a basic knowledge of the most frequent patterns of presentation to provide advice on their significance and guide the patient regarding available treatments. This chapter has been organized in sections to summarize key issues of this subject.

Prevalence of Urological Symptoms

Urinary dysfunction affects between 27% and 39% of patients with PD [1, 2]. Urinary dysfunction may be the initial symptom of PD in 3.9% of the cases. The relative risk of bladder symptoms in persons with PD is twofold [3]. Two series have investigated the prevalence of specific urological symptoms in patients with PD and compared them with controls [4, 5]. Significantly higher prevalence figures in PD were found for urinary urgency [4, 5], sensation of incomplete bladder emptying [4], nocturia [5], daytime frequency, and urge incontinence. The estimates for obstructive symptoms (hesitancy and weak stream) exhibit the most discrepancy between men and women, perhaps reflecting overlap with prostatic disease (see Table 12.1).

Sammour et al. [6] prospectively evaluated lower urinary tract symptoms (LUTS), using the International Continence Society questionnaire, in 110 patients (84 men) with PD. Sixty-three patients (57.2%) were symptomatic. Quality of life was affected by the severity of LUTS; the symptoms with the worst impact were nocturia (80.9%) and intermittency (44.5%). Other symptoms of less impact were incomplete emptying in 40%, hesitancy in 37.3%, urgency in 36.3%,

Table 12.1 Prevalence of urological symptoms in two populations of patients with PD

Urinary symptoms	Singer et al. [4]	Sakakibara et al. [5]
Urinary urgency	46% (men)	54% (men) 42% (women)
Sensation of incomplete bladder emptying	42% (men)	
Nocturia		63% (men) 53% (women)
Daytime frequency		16% (men) 28% (women)
Urge incontinence		70% (men) 28% (women)

[a]Determined to be significantly higher than a control population

increased urinary frequency in 35.4%, and urge incontinence in 20.9%.

Irritative Versus Obstructive Symptoms

Urinary symptoms are usually grouped either as irritative (frequency, urgency, and urge incontinence) or obstructive (hesitancy and weak urinary stream). Irritative symptoms invariably predominate by a large margin. Proportions for irritative compared with obstructive symptomatology range from 73% versus 27% to 83% versus 17%, respectively [7–9]. Pavlakis et al. [10] reported a distribution of 57% irritative, 23% obstructive, and 20% mixed symptomatology in a group of 30 patients with PD.

Obstructive symptoms are not consistently reported, as illustrated by at least three reports [11–13]. Alternatively, more careful attention to nonmotor symptoms during the "off" state may uncover a higher prevalence of urinary symptomatology [14] and possibly a different proportion of irritative versus obstructive symptoms.

Appearance and Progression of Urological Symptoms

There is limited information regarding the time of appearance of urinary symptoms in PD in relation to the motor symptoms. Both the severity and duration of disease may be influential. Chandiramani et al. [13] reported an average lapse of 5.75 years between the onset of motor symptoms and the onset of urological symptoms. Araki et al. [15] studied 70 urologically symptomatic patients with PD and noted that the symptoms index scores of the patients increased with disease severity.

Sammour et al. [6] reported that voiding dysfunction increased with the neurological impairment, but not with the patient's age or disease duration. In their series, the use of levodopa, anticholinergics, and dopamine agonists had no impact in the lower urinary tract symptoms. The authors concluded that the severity of neurological disease is the only predictive factor for the occurrence of voiding dysfunction.

Sakakibara et al. [16] studied ^{123}I-β-CIT SPECT scans of seven PD patients with urinary dysfunction and compared them with four PD patients free of urinary symptoms. The uptake was significantly reduced in the former group, suggesting a link between severity of the nigrostriatal dopaminergic deficit and presence of urinary symptomatology.

Urodynamic Correlation of Detrusor Hyperreflexia

Detrusor hyperreflexia is a cystometric finding characterized by the presence of involuntary detrusor contractions in response to bladder filling that the patient is unable to inhibit. These contractions generate pressure values of 15 cm of water [10, 17, 18].

Some authors have reported a very close clinical correlation between irritative symptoms and detrusor hyperreflexia in PD [8, 15]. The prevalence of detrusor hyperreflexia found among urologically symptomatic patients with PD ranges from 45% to 100% [7–11, 15, 17, 19, 20]. This prevalence is similar to the one reported for irritative symptoms in PD (see section "Irritative Versus Obstructive Symptoms"). The information on factors predisposing to detrusor hyperreflexia in PD also seems to parallel the information on irritative symptoms (see section

"Appearance and Progression of Urological Symptoms"). Detrusor hyperreflexia may also be found in urologically asymptomatic PD patients [7].

There is limited information regarding conditions that predispose to the development of detrusor hyperreflexia. Stocchi et al. [21] reported that, of their 30 PD patients, those with a normal urodynamic pattern (36.6%) had significantly less severe disease and shorter duration of disease than those with abnormal patterns. Araki et al. [15] studied 70 PD patients who had been referred for urological evaluation and were free of obstructive etiologies. Sixty-seven percent (47/70) had pure detrusor hyperreflexia, with the majority (42/47) being Hoehn and Yahr stage 3 or higher.

Detrusor Areflexia

Detrusor areflexia is a cystometrographic finding with decreased sensation during filling and increased bladder capacity [8, 11] (>600 cc), along with a desire to void first experienced at a high-filling volume [22]. The postvoid residual volume is higher than 100 cc [22]. This results in hesitancy and weak urinary stream.

Detrusor areflexia is uncommon in PD. Incidence figures in series of urologically symptomatic patients have ranged from 0% to 27% [8, 15, 20]. Stocchi et al. [21] did not find detrusor areflexia in any of their 30 patients who had PD (symptomatic or asymptomatic) who were studied with urodynamics after anticholinergics had been withheld.

Medication Effects and Other Etiologies

Anticholinergic drugs are the most common cause of detrusor areflexia in patients with PD according to some authors [18]. In fact, the concurrent use of anticholinergics is frequently mentioned in reported findings of detrusor areflexia in PD [7, 9–11].

However, in some instances, detrusor areflexia may be found in patients with PD in the absence of anticholinergic medication. One example is the study by Raz of urologically symptomatic patients with PD, in which the confounding effect of anticholinergic drugs was eliminated by withdrawing them 1 week prior to the urodynamic investigations [8]. In those cases, the clinician must consider other alternative possibilities to the diagnosis of PD such as multiple system atrophy (see section "Diagnosis of Multiple System Atrophy"), coexistent obstructive uropathy (see section "Impact of Coexistent Obstructive Uropathies"), and "myogenic" areflexia.

Myogenic areflexia was originally described as the result of muscle fiber injury caused by an overdistended bladder secondary to obstruction [23]. Recently, a myopathic process of the bladder wall has been proposed to be present in the absence of obstruction. Araki et al. [15] have invoked this theory to explain the findings in 6 of their 70 patients referred for urological evaluation. These patients, all stage 4 in the Hoehn and Yahr scale, had detrusor hyperreflexia that was associated with impaired contractile function in the absence of obstructive etiologies. A similar process has been reported in the elderly [24].

Impact of Coexistent Obstructive Uropathies

Obstructive uropathies (i.e., benign prostatic hypertrophy in the man, stenosis of the bladder neck in the woman) have been recognized as causes in their own right of both irritative and obstructive symptoms in the general population [23]. Such irritative symptoms associated with obstructive uropathies are equally the product of a detrusor hyperreflexia and indistinguishable from the purely neurogenic type. Certain investigations have pointed to the presence of obstructive uropathies as contributing causes of urinary symptoms in some PD patients [9, 10, 20, 25]. The prevalence figures vary from 17% to 33%. However, correlation with specific obstructive symptoms is at times not outlined with sufficient clarity [9, 10, 20].

Dysfunction of Infravesical Mechanisms

PD also may course with dysfunctional infravesical mechanisms (DIVMs). A full urodynamic evaluation includes measurement of infravesical mechanisms, such as urethral pressure profile, urinary flow, and sphincter EMG recording during bladder filling and bladder emptying. DIVMs encompass dysfunction of the striated urethral sphincter and the pelvic floor, either occurring alone or in combination.

Although different kinds of DIVMs have been described in patients with PD (see Table 12.2), they have been inconsistently reported and in variable numbers [7, 10, 21, 25]; sometimes they are not found at all [20]. The descriptions are sometimes poorly characterized and may not be confirmed again in other reports. Correlation with clinical symptomatology is frequently inadequate or lacking [7, 10, 25]; therefore, the clinical significance of DIVMs is unclear.

Table 12.2 List of dysfunctional infravesical mechanisms reported in the literature

Dysfunction	References
Elevated urethral pressure profile	[7, 8]
Decreased urinary flow	[9, 26]
Sphincter bradykinesia	[10, 17, 19, 25]
Pseudodyssynergia	[10]
Sphincter "tremor"	[19]
Vesicosphincter dyssynergia	[15, 17, 25]
Involuntary asymptomatic sphincteric activity	[9, 26]

Sphincter Bradykinesia, Pseudodyssynergia, and Vesicosphincter Dyssynergia

The most frequent DIVM is known as sphincter bradykinesia, consisting of delayed relaxation of the striated urethral sphincter and pelvic floor musculature. There is a normal guarding reflex with an increase in striated muscle activity during bladder filling before the onset of detrusor contraction. Sphincter bradykinesia is an abnormality in which involuntary EMG activity persists through at least the initial part of the expulsive phase of the cystometrogram (CMG) [10].

In one series [10], 11% (3/28) of patients with PD had sphincter bradykinesia. In another study, Galloway [19] reported that 42% (5/12) of his urologically symptomatic patients were unable to relax the external urethral sphincter with voiding, which was associated with low flow rates. Andersen et al. [25] studied 24 urologically symptomatic patients with parkinsonism (the term "Parkinson's disease" is not used). The same authors revised their data in a subsequent article [17] and reported electromyographic findings in these 24 patients with PD. The authors did not specify whether all 24 patients were symptomatic. Of these patients, 21% (5/24) had impaired sphincter control, defined as poor ability to contract or relax the sphincter on command.

Pseudodyssynergia has been reported less frequently than sphincter bradykinesia. Pseudodyssynergia has been defined as "an attempt at continence by voluntary contraction of the pelvic musculature during an involuntary detrusor contraction" [23]. Pavlakis et al. [10] reported pseudodyssynergia in two patients, part of a group of ten in whom the maximum flow rate was decreased. The clinical role of this phenomenon could not be defined because of coexistent prostatic obstruction. Sphincter "tremor" was described in 11 of 12 patients in another series [19]. Neither pseudodyssynergia nor sphincter "tremor" has been confirmed in subsequent reports.

Vesicosphincter dyssynergia is a DIVM also reported less frequently than sphincter bradykinesia. Whereas Pavlakis et al. [10] called attention to the absence of vesicosphincter dyssynergia, Andersen et al. [17, 25] reported two patients with an abnormality they initially called "dyssynergia" [25] but later labeled "spasticity" [17]. In a series of 70 PD patients referred for urological evaluation who were free of obstructive etiologies, Araki et al. [15] found two patients (3%) who had both hyperreflexia and detrusor-sphincter dyssynergia (2/70).

Berger et al. [9, 26] studied 29 patients with PD (24 men and 5 women) who were urologically symptomatic. In 61% (14/23) of patients tested, they documented sporadic involuntary electromyographic activity of the external sphincter during *involuntary* detrusor contractions, but in none did this phenomenon cause obstruction. They labeled this phenomenon "involuntary sphincteric activity." Because this phenomenon was not associated with radiographic or manometric evidence of obstruction at the level of the membranous urethra, the authors concluded that it did not meet criteria for the definition of detrusor-sphincter dyssynergia. This activity is reminiscent of pseudodyssynergia in that both occur in response to involuntary detrusor contractions, but pseudodyssynergia is seen as a *voluntary* act.

Dopaminergic Medication

Dopaminergic medication likely improves voiding by facilitating relaxation of the striated sphincter and increasing bladder contractility. Raz [8] demonstrated a decrease in the urethral pressure profile (UPP) after treatment with levodopa in ten patients who had PD with urological symptoms. An increase in the UPP occurred in patients whose treatment with levodopa was interrupted for 1 week (number of patients not specified).

In a series of 30 patients with PD, 11 displayed delayed or incomplete perineal floor relaxation [21]. All experienced greatly improved perineal muscle control after subcutaneous injection of apomorphine (4 mg), a dopamine agonist. There was no effect on detrusor hyperactivity. In another series of ten patients who had PD with urinary symptoms [27], urodynamic studies were performed before and after the subcutaneous administration of apomorphine. Voiding efficiency improved after apomorphine injection with an overall decrease in bladder outflow obstruction. There was an increase in the mean and maximum flow rates in nine patients and reduction in postmicturition residual volume in six. This was accompanied by fluoroscopic evidence of widening of the urethra at the level of the distal sphincter mechanism. Three patients were unable to void during the "off" state as a consequence of decreased detrusor contractility, despite considerable discomfort and a feeling of bladder fullness [27]. After apomorphine injection, voiding detrusor pressure in these three patients increased and calculated bladder outflow resistance fell, resulting in considerable improvement in voiding. No information was provided whether these patients were on anticholinergic drugs. Because all of the patients were premedicated with domperidone, a peripheral dopamine antagonist, the investigators concluded that the effects of apomorphine on both smooth and striated musculature of the lower urinary tract must be mediated by changes in central dopaminergic transmission [27].

Uchiyama et al. [28] reported the effects of a single dose of 100 mg levodopa on urinary function in 18 patients who had PD with severe end-of-dose wearing off. Patients were on levodopa and dopamine agonists, but not on anticholinergics. There was an increase in detrusor contractility; alternatively, there was an increase in urethral obstruction. However, the net effect favored the increase in bladder contractility. The result was a decrease in residual volume, that is, an improvement in voiding efficiency.

Effects of Dopaminergic Medication on Detrusor Activity

Fitzmaurice et al. [20] reported on nine urologically symptomatic patients who had PD with detrusor hyperreflexia. The effects of levodopa were variable. Six patients had less severe detrusor hyperreflexia when "off" (including one patient whose hyperreflexia disappeared); three were better when on levodopa. A description of the impact of treatment on the actual symptoms was not provided. Detrusor function during the filling (storage) phase was not consistently altered by apomorphine in another study [27], in which detrusor hyperreflexia improved in some cases and deteriorated in others. In their study of 18 patients with PD who had severe wearing off, Uchiyama et al. [28] showed an unpredictable

effect on bladder function during filling. Urinary urgency (with or without detrusor hyperreflexia or low-compliance bladder) was aggravated in nine patients (50%), alleviated in three (17%), and unchanged in six (33%).

Diagnosis of Multiple System Atrophy

Early and prominent urinary symptoms and "obstructive" symptoms (in the absence of obstruction) are clues to the diagnosis of multiple system atrophy (MSA). Chandiramani et al. [13] performed a retrospective study of 52 patients with MSA and 41 patients with PD. Of MSA patients, 60% (31/52) had urinary symptoms preceding or coinciding with diagnosis of the disease. Sixteen patients reported frequency, urgency, or incontinence before the onset of parkinsonism; 15 patients developed urinary symptoms at the same time as parkinsonism. In contrast, in 94% of patients with PD, the urogenital symptoms clearly followed the neurological diagnosis by a few years. Two other series, identified in a review by Fowler [29], also confirm a 60% prevalence of *early* urinary symptoms in MSA. In one series [13], patients with MSA were more likely to suffer from troublesome incontinence (73%); elevated postvoid residuals were also more likely compared with PD patients (66% versus 16%, respectively). Among males with MSA, 93% had erectile dysfunction (ED), including 48% in whom ED preceded the MSA diagnosis. Although ED also may develop in PD, the proportion of early ED is less [30]. In the series of Chandiramani et al. [13], all 11 men with MSA who underwent transurethral prostatectomy (TURP) were incontinent postoperatively (see section "Urological Surgery for Prostate Obstruction").

Fowler [29] has proposed the following five urogenital criteria as implied in the diagnosis of MSA: (1) urinary symptoms preceding or presenting with parkinsonism, (2) ED preceding or presenting with parkinsonism, (3) urinary incontinence, (4) significant postmicturition residual (>100 mL), and (5) worsening bladder control after urological surgery. However, none of these criteria are specific, and the clinician has to view their presence in context with the remaining clinical features.

Sphincter EMG

Patients with MSA have cell loss in Onuf's nucleus, which has been associated with electromyographic changes that include denervation (fibrillations and positive sharp waves) and reinnervation (abnormal and prolonged polyphasic potentials). Such urethral sphincter abnormalities are also reflected in the anal sphincter, a more easily accessible structure [31].

Stocchi et al. [21] reported that EMG provides important differentiating data between MSA and PD. The main feature that differentiated 32 MSA patients from 30 patients with PD was abnormal sphincter EMG in 75% (24/32) of the MSA patients, compared with none of the PD patients. Vodusek conducted a comprehensive review of the subject [32]. He concluded that anal sphincter EMG abnormalities could distinguish MSA from PD during the first 5 years after the onset of symptoms and signs if other causes for sphincter denervation (e.g., surgery) had been ruled out. However, with such criteria, as Vodusek readily admits, sphincter EMG offers a low sensitivity.

Voiding Dysfunction in PD

Voiding is a function of the autonomic nervous system with a core segmental representation in the spinal cord. As the bladder fills, afferent stimuli are conducted to the S2–S4 segments. During bladder filling, the efferent sympathetic nervous system, via hypogastric nerves originating in the lumbar spinal cord, is active. This allows distension of the bladder to accommodate the urine, closure of the internal urethral sphincter [33], and inhibition of parasympathetic excitatory effect on the detrusor muscle [34]. During this phase, the external and internal urethral sphincters are tonically contracted, and there is increased tone in the striated musculature of the pelvic floor. At a certain level of bladder distention, a reflex efferent

response is triggered by activated motor neurons, which stimulate the detrusor muscle via the pelvic nerve (parasympathetic) and relax the internal urethral sphincter via parasympathetic inhibition of sympathetic terminals that innervate the bladder neck. At the same time, inhibition of Onuf's nucleus and pudendal motor nuclei causes relaxation of the striated urethral sphincter and the perineal floor, respectively.

This segmentally organized function is subject to facilitatory and inhibitory impulses from higher neurological centers that allow for voluntary control of the detrusor reflex. Specifically, impulses from the cortical micturition center in the mesial frontal lobes [21] connect to the pontine-mesencephalic reticular formation. Two micturition centers exist in the pons: the pontine micturition center and pontine storage center [35, 36]. The former is the most important and facilitates the urinary reflex. The pontine storage center is less well understood, but it has connections with the somatic nerves that cause closure of the external urethral sphincter [37]. This pathway is influenced further by the basal ganglia, the thalamic nuclei, and the anterior vermis of the cerebellum [10, 17]. Micturition is also influenced by the anterior cingulate gyrus, the locus ceruleus, the nucleus tegmento lateralis dorsalis [10, 17], and the periaqueductal gray area [35, 36, 38]. The periaqueductal gray area receives afferent information from the bladder regarding bladder fullness, as well as from the hypothalamus and other higher cortical centers. It may act as a relay center facilitating voiding through connections with the pontine micturition center [39]. Input from higher cortical centers ensures that voiding takes place at a time and place that is socially acceptable [40].

Based on a series of experiments and subsequent experience with basal ganglia surgery, the basal ganglia appear to exert an inhibitory effect on the pontomesencephalic micturition center. Lewin et al. performed pivotal experimental studies in cats that are still being cited as the backbone for current theory on pathophysiology [41, 42]. Lewin et al. stimulated the thalamus and different sites of the basal ganglia and found that the stimulation was inhibitory of detrusor contractions. Stimulation of the red nucleus, the subthalamic nucleus, and the substantia nigra was even more inhibitory than that of the thalamus. This may suggest that current deep brain stimulation procedures may be more effective in improving voiding dysfunction if STN rather than the thalamus is the target. Stereotaxic thalamotomy in parkinsonian patients, on the other hand, demonstrated an increase in detrusor activity [11].

Recent positron emission tomography (PET) studies in young, healthy individuals have demonstrated that specific sites in the brainstem and higher brain may play crucial roles in micturition control. Brain regions activated by bladder distention included the periaqueductal gray area, pons, anterior cingulate area, anterior insula, putamen, thalamus, and cerebellum [35, 36, 38, 43]. In comparison, brain PET of PD patients with detrusor overactivity showed bladder filling associated with activation of the periaqueductal gray area, supplementary motor area, insula, putamen, thalamus, and—most prominently—of the cerebellar vermis; the pons was not activated during detrusor overactivity. The authors concluded that these alterations in brain activation sites in response to bladder filling may be related to the pathophysiology of detrusor overactivity in PD [44].

In terms of stimulation of dopamine receptors, stimulation of D1 receptors is inhibitory; D2 stimulation is facilitatory. This combination of effects would result in a D_1 effect during bladder filling and a D_2 effect during bladder emptying.

Treatment of Irritative Symptoms

Irritative symptoms, a manifestation of detrusor hyperreflexia, are responsive to anticholinergic drugs. However, exclusion of obstructive uropathy prior to symptomatic treatment is advisable. Oxybutynin, tolterodine, solifenacin, darifenacin, and trospium are some of the most commonly used drugs [45]. Other agents include propantheline, hyoscyamine, and flavoxate. The oxybutynin dose ranges from 2.5 mg at bedtime to 5 mg TID.

Potential adverse effects include hesitancy, weak urinary stream, dry mouth, difficulty with visual accommodation, constipation, and aggravation of glaucoma.

Some experts have suggested using extended-release forms of anticholinergics to prevent high serum levels during therapy, with the notion that this may reduce the likelihood of cognitive dysfunction [46]. Examples include tolterodine LA at doses of 2–4 mg once daily and oxybutynin LA at doses of 5–30 mg once daily [47]. More recently, oxybutynin transdermal has been released [47]. This route avoids first-pass metabolism, resulting in a lower concentration of its active metabolite. Because this metabolite has a higher affinity in vitro for parotid cells than for bladder cells, it may explain the lower incidence of dry mouth reported with transdermal oxybutynin [47]. If therapy with a single anticholinergic agent proves to be suboptimal, the tricyclic antidepressant, imipramine, can be used in combination, since it has a different receptor site profile [23].

Solifenacin and darifenacin have emerged as alternatives to traditional anticholinergic drugs. They act specifically on the M3 receptors present on the bladder, avoiding stimulation of the muscarinic receptors present in the heart, CNS, and salivary glands, which is responsible for the adverse effects of these medications [40]. These drugs have the same efficacy as the older agents, but superior tolerability with fewer side effects [48].

If anticholinergic CNS side effects are of concern, one can choose trospium, which is a nonselective antimuscarinic agent that, due to its low lipid solubility, does not cross the blood-brain barrier. It also is not metabolized by cytochrome P450 and, thus, is less likely to produce drug interactions. It is excreted mainly unchanged in the urine, which accounts for its rapid onset of clinical effect and prolonged efficacy. Placebo-controlled trials document the efficacy of trospium in the treatment of overactive bladder, but comparative trials with other anticholinergics are scarce [49]. An extended-release formulation has been effective and well tolerated for the treatment of overactive bladder in two randomized phase III trials [50].

Botulinum toxin has emerged as a promising therapy for patients with refractory symptoms. Several studies have been performed using botulinum toxin type A in the treatment of idiopathic overactive bladder and neurogenic bladder secondary to spinal cord injuries; in these studies, the efficacy appears to be high in terms of clinical and urodynamic improvements and beneficial effects on quality of life. Information on the management of detrusor overactivity in PD has been scarce. Giannantoni et al. [51] investigated the effectiveness and safety of botulinum toxin type A injected into the detrusor muscle in four patients with PD and two with MSA. All the patients received 200 U botulinum toxin type A injected into the detrusor muscle at 20 sites under cystoscopic guidance at a single session on an inpatient basis. One and 3 months after botulinum toxin type A injection, all the patients reported a decrease in daytime and nighttime urinary frequency and improvement in quality of life scores. No patient had further episodes of urgency or urge incontinence during the 5-month follow-up. Urodynamic studies showed improvement in all urinary function variables tested. No systemic adverse effects were recorded during or after treatment. In all patients, postvoid urinary residual volume increased, but intermittent catheterization was required only in those with MSA. The authors of this small series concluded that botulinum toxin type A is a potentially effective alternative in the treatment of refractory overactive bladder. However, larger trials must be performed to confirm these promising findings [52].

Treatment of Obstructive Symptoms

The successful treatment of obstructive symptoms of hesitancy and weak urinary stream begins with a careful drug history, searching for medications with an anticholinergic effect. Urodynamic studies should follow that investigate for the presence of detrusor areflexia, DIVM, or an obstructive uropathy. The treatment of obstructive

symptoms is based on ruling out structural causes of obstruction first, followed by ensuring bladder emptying by either intermittent or permanent catheterization. Combination treatment with anticholinergic drugs and optimization of dopaminergic treatment are also recommended.

A frequent clinical setting for the development of detrusor areflexia in PD occurs when symptomatic detrusor instability (hyperreflexia) is treated with anticholinergic drugs. This may produce the urodynamic findings of involuntary bladder contractions associated with incomplete emptying, secondary to unsustained detrusor contractions [23]. In that case, management consists of combining anticholinergic drugs with clean, intermittent catheterization by oneself or others. Successful management also helps in preventing recurrent urinary tract infections.

Another possible cause of obstructive symptoms is DIVM. In cases of external urethral sphincter bradykinesia or pseudodyssynergia with high-voiding pressures (>90-cm H_2O), some investigators recommend both anticholinergic drugs and intermittent catheterization (similar to treatment employed for mixed detrusor hyperreflexia with incomplete bladder emptying) because persistent high pressures are certain to result in damage to the bladder and, ultimately, to the upper urinary tract [23]. Sphincter bradykinesia also is responsive to dopaminergic treatment [8, 21, 27], whereas pseudodyssynergia may be correctable with biofeedback [10].

Patients with MSA are also more likely to have poor bladder compliance and sphincter insufficiency [26]. This could result in episodes of incontinence, including both overflow and stress incontinence (in addition to hesitancy and weak stream). Intermittent catheterization, with or without anticholinergic drugs (e.g., oxybutynin), may be the initial treatment [13, 26]. In some cases, desmopressin spray may be used [13]. Because of motor dysfunction, treatment may evolve to permanent indwelling catheterization or suprapubic cystostomy [26, 46]. Stress incontinence in females can be treated with urethral suspension or a sling procedure, but if there is concurrent detrusor hyperreflexia, the consequence may be suboptimal [46].

Urological Surgery for Prostate Obstruction

Surgical relief of prostatic obstruction (or other obstructive uropathies) is advisable, but the resolution of urinary symptoms following surgery is unpredictable. Resolution of detrusor instability can be expected in 60–70% of patients postoperatively if the instability is the result of prostatic obstruction [23]. The patient should be advised that such operations (i.e., prostatectomy) are primarily indicated for relief of obstruction and to avoid the need of catheterization [9], but they may not eliminate the often coexistent irritative symptoms.

Berger et al. [9] reported persistence of urge incontinence in eight men with PD who had undergone prostatic surgery with evidence of detrusor hyperreflexia in seven patients. They could not find any urodynamic parameters that would predict preoperatively whether a hyperreflexic bladder will stabilize after successful relief of the obstruction [9]. If urge incontinence persists after surgery, anticholinergic therapy can be added. If it still persists, condom catheter drainage may be necessary. There are no urodynamic parameters capable of estimating preoperatively which hyperreflexic bladder will stabilize after successful obstruction relief.

Urologists should be aware of the necessity to rule out MSA prior to surgery. In the series of Chandiramani et al. [13], postoperative results were very different for PD and MSA patients. Three of the five PD patients who underwent transurethral prostatectomy (TURP) reported a good result. Despite oral oxybutynin, one patient with an adequate flow rate had persistent urgency but improved considerably after intravesical oxybutynin. Another patient had a large postvoid residual after TURP due to an atonic bladder of unknown etiology. All 11 men with MSA who underwent TURP were incontinent postoperatively. Nine (82%) had problems immediately, and two (18%) became incontinent within 1 year. Similarly, five anti-incontinence procedures in three women were unsuccessful.

Basal Ganglia Surgery

It is reasonable to expect improvement of urological symptoms in those patients undergoing deep brain stimulation surgery, but more studies are necessary. Murnaghan [7] reported results of basal ganglia surgery on urological symptoms and findings in 29 patients with PD. In the analysis, 8 patients complained of bladder disturbances, and 11 had abnormal CMGs. There were 11 patients who had CMGs performed pre- and postoperatively; only five were unchanged postoperatively. Normal bladder function was converted into hyperreflexic bladder in two of four patients examined before and after stereotaxic lesions of the thalamic nuclei, whereas stereotactic lesions of the posterior limb of the internal capsule normalized three of four uninhibited bladders. Murnaghan concluded that thalamotomy may be associated with increased bladder tonus and pallidotomy with decreased bladder tonus. Capsulotomy may reduce tonus, but bladder sensation may be affected [7].

In 1971, Porter and Bors [11] also reviewed the effects of thalamotomy on bladder function. They studied the impact of uni- and bilateral thalamotomy on 49 patients with PD (11 of whom had normal function). They found that neurogenic bladder dysfunction occurred more frequently in clinically bilateral cases. It was only after bilateral stereotaxic surgery that improvement of bladder function could be consistently documented. The same authors followed up on the status of 40 patients over a long term (4–8 months after their last operation, unilateral or bilateral). These patients had somatic manifestations that had been "significantly improved" after the surgery (no quantification provided). These results indicated that the neurogenic bladder of the parkinsonian patient was responsive to surgical therapy, although the response was not as prompt or successful as treatment of somatic manifestations. Furthermore, the subjective response of the individual was often more pronounced than the objective evidence of improvement. The authors postulated that thalamotomy improved the postvoid residual volume by relaxing the bladder floor and—especially in the "hypoactive bladder"—by increasing the activity of the detrusor muscle [11]. This analysis is consistent with the findings of Murnaghan [7]. It would have been of interest to learn if the use of anticholinergic drugs had decreased postoperatively as a possible alternative explanation to the decline in postvoid residual. Andersen et al. [25] examined 44 patients with parkinsonism, including eight who had undergone thalamotomy. None of the eight patients had normal bladder function. The authors concluded that stereotactic operations on the thalamus could produce uninhibited bladder contractions with a subsequent risk of urological disturbances.

To date, there are some reports of the beneficial effects of deep brain stimulation in the management of refractory irritative urological symptoms. One of the first reports regarding the beneficial effects of basal ganglia surgery on parkinsonian voiding dysfunction was by Finazzi-Agrò et al. [53]. The authors studied five patients who had undergone bilateral implantation of subthalamic nucleus (STN) electrodes. These patients had not been assessed urologically preoperatively. Instead, they were studied urodynamically 4–9 months after surgery with comparisons made between the stimulator-on and stimulator-off states (no mention made as to being on or off levodopa during the procedures). The authors found consistent improvement in bladder capacity and reflex volume (bladder volume at first hyperreflexic detrusor contraction). Seif et al. [54] reported a series of 16 patients with PD and detrusor hyperreflexia who underwent STN-DBS and demonstrated that STN-DBS has a significant and urodynamically recordable effect leading to normalization of pathologically increased bladder sensibility. Shimizu et al. [55] conducted an International Prostate Symptom Score (IPSS) analysis and pressure flow study (PFS) on six patients before and after a chronic stimulating electrode was placed in the STN and evaluated how subjective symptoms and bladder function changed. The IPSS total value, involuntary detrusor contraction threshold volume, and the maximum bladder capacity all improved ($p \leq 0.05$), which suggested that STN-DBS positively

contributes to improvement in urinary function. Winge et al. [56] performed a prospective study of 16 patients with PD investigating LUTS by questionnaires (ISPS, symptoms only) and Danish Prostate Symptom Score (DanPSS, symptoms, and bother of symptoms), and bladder control assessed by urodynamics, before and after the implantation of electrodes in the STN. Symptoms of overactive bladder (IPSS) decreased along with the troublesome symptoms of overactive bladder (DanPSS), $p \leq 0.01$ for both. Urodynamic parameters before and after implantation of electrodes in the STN, evaluated with and without the stimulation on, did not change significantly. Herzog et al. [57] studied 11 PD patients with bilateral STN-DBS during urodynamic bladder filling in STN-DBS ON and OFF condition. A filled bladder led to a significant increase in regional cerebral blood flow (rCBF) by brain PET in the anterior cingulate cortex, which was further enhanced during STN-DBS OFF. A significant interaction between bladder state and STN-DBS was observed in the lateral frontal cortex, with increased rCBF when the bladder was filled during STN-DBS OFF. The data suggest that STN-DBS ameliorates bladder dysfunction and this modulation may result from facilitated processing of afferent bladder information, normalizing the perception of urinary bladder filling in patients with PD.

Other Therapeutic Alternatives

Repetitive transcranial magnetic stimulation (rTMS) and percutaneous posterior tibial nerve stimulation (PTNS) are additional therapeutic alternatives for PD patients with detrusor overactivity.

The effects of inhibitory rTMS on several of the motor and nonmotor symptoms of PD are being studied [58]. Brusa et al. studied the effects of a 2-week course of low-frequency (1 Hz) inhibitory rTMS on bladder function of eight advanced PD patients [59]. The IPSS was used to measure the subjective LUTS, and a urodynamic evaluation was performed. rTMS was able to improve temporarily LUTS in PD patients, increasing bladder capacity and the first sensation of filling phase. Reduction of IPSS score also was noted, due to improvement in filling phase symptoms. The beneficial effects assessed with the IPSS lasted for up to 2 weeks after the end of stimulation. The mechanism of action of rTMS is unknown. It is possible that inhibitory rTMS induces an opposite modulation of the descending corticospinal tract output targeting the detrusor muscle, resulting in a reduced bladder overactivity. As an alternative mechanism, the authors proposed that rTMS may modulate the pontine micturition center, site of descending excitatory projections to parasympathetic sacral centers and/or periaqueductal gray (PAG), where afferent proprioceptive projections of the bladder terminate. Further studies directly measuring pelvic floor/detrusor muscle EMG activity before and after rTMS might improve our knowledge regarding the mechanism of action of this therapy.

Several different electrical stimulation techniques have been used to treat urinary disorders. Acute perineal nerve stimulation decreases detrusor overactivity in patients with spinal cord injury. Chronic nerve stimulation of perineal skin/sacral dermatomes has been used to manage urge incontinence. Sacral neuromodulation, with implantation of an S3 stimulator, has been proposed to treat refractory urge incontinence due to detrusor overactivity. The mechanism of action of these techniques is still unknown but may involve a rebalancing of inhibitory and excitatory impulses that control bladder function in the CNS [60]. PTNS inhibits bladder activity by depolarizing somatic sacral and lumbar afferent fibers [61]. Afferent stimulation provides central inhibition of the preganglionic bladder motor neurons through a direct route in the sacral cord [62]. Krivoborodov et al. [63] evaluated the effects of tibial neuromodulation in 29 patients with detrusor overactivity due to PD. They observed a decrease in the average voiding frequency and number of leakage episodes after 12 sessions and 6 months of tibial neuromodulation. Symptomatic improvement greater than 50% was achieved in 26 of 29 patients, including six patients who were refractory to anticholinergic agents and nine men

with benign prostatic hypertrophy. Kabay et al. [60] evaluated the effects of tibial neuromodulation in 32 patients with PD and detrusor overactivity associated with urodynamic findings. The urodynamic evaluations were performed before and during PTNS. The mean and first involuntary detrusor contraction (IDC) and the mean maximum cystometric capacity (MCC) were significantly improved during PTNS. The authors concluded that these results demonstrate the objective acute effect of PTNS on urodynamic parameters.

References

1. Araki I, Kuno S. Assessment of voiding dysfunction in Parkinson's disease by the international prostate symptom score. J Neurol Neurosurg Psychiatry. 2000;68(4):429–33.
2. Campos-Sousa RN, Quagliato E, da Silva BB, de Carvalho Jr RM, Ribeiro SC, de Carvalho DF. Urinary symptoms in Parkinson's disease: prevalence and associated factors. Arq Neuropsiquiatr. 2003;61(2B):359–63.
3. Hobson P, Islam W, Roberts S, Adhiyman V, Meara J. The risk of bladder and autonomic dysfunction in a community cohort of Parkinson's disease patients and normal controls. Parkinsonism Relat Disord. 2003;10(2):67–71.
4. Singer C, Weiner WJ, Sanchez-Ramos JR. Autonomic dysfunction in men with Parkinson's disease. Eur Neurol. 1992;32(3):134–40.
5. Sakakibara R, Shinotoh H, Uchiyama T, et al. Questionnaire-based assessment of pelvic organ dysfunction in Parkinson's disease. Auton Neurosci. 2001;92(1–2):76–85.
6. Sammour ZM, Gomes CM, Barbosa ER, et al. Voiding dysfunction in patients with Parkinson's disease: impact of neurological impairment and clinical parameters. Neurourol Urodyn. 2009;28(6):510–5.
7. Murnaghan GF. Neurogenic disorders of the bladder in Parkinsonism. Br J Urol. 1961;33:403–9.
8. Raz S. Parkinsonism and neurogenic bladder. Experimental and clinical observations. Urol Res. 1976;4(3):133–8.
9. Berger Y, Blaivas JG, DeLaRocha ER, Salinas JM. Urodynamic findings in Parkinson's disease. J Urol. 1987;138(4):836–8.
10. Pavlakis AJ, Siroky MB, Goldstein I, Krane RJ. Neurourologic findings in Parkinson's disease. J Urol. 1983;129(1):80–3.
11. Porter RW, Bors E. Neurogenic bladder in parkinsonism: effect of thalamotomy. J Neurosurg. 1971;34(1):27–32.
12. Niimi Y, Ieda T, Hirayama M, et al. Clinical and physiological characteristics of autonomic failure with Parkinson's disease. Clin Auton Res. 1999;9(3):139–44.
13. Chandiramani VA, Palace J, Fowler CJ. How to recognize patients with parkinsonism who should not have urological surgery. Br J Urol. 1997;80(1):100–4.
14. Raudino F. Non motor off in Parkinson's disease. Acta Neurol Scand. 2001;104(5):312–5.
15. Araki I, Kitahara M, Oida T, Kuno S. Voiding dysfunction and Parkinson's disease: urodynamic abnormalities and urinary symptoms. J Urol. 2000;164(5):1640–3.
16. Sakakibara R, Shinotoh H, Uchiyama T, Yoshiyama M, Hattori T, Yamanishi T. SPECT imaging of the dopamine transporter with [(123)I]-beta-CIT reveals marked decline of nigrostriatal dopaminergic function in Parkinson's disease with urinary dysfunction. J Neurol Sci. 2001;187(1–2):55–9.
17. Andersen JT. Disturbances of bladder and urethral function in Parkinson's disease. Int Urol Nephrol. 1985;17(1):35–41.
18. Martignoni E, Pacchetti C, Godi L, Micieli G, Nappi G. Autonomic disorders in Parkinson's disease. J Neural Transm Suppl. 1995;45:11–9.
19. Galloway NT. Urethral sphincter abnormalities in Parkinsonism. Br J Urol. 1983;55(6):691–3.
20. Fitzmaurice H, Fowler CJ, Rickards D, et al. Micturition disturbance in Parkinson's disease. Br J Urol. 1985;57(6):652–6.
21. Stocchi F, Carbone A, Inghilleri M, et al. Urodynamic and neurophysiological evaluation in Parkinson's disease and multiple system atrophy. J Neurol Neurosurg Psychiatry. 1997;62(5):507–11.
22. Andersen JT, Bradley WE. Cystometric, sphincter and electromyelographic abnormalities in Parkinson's disease. J Urol. 1976;116(1):75–8.
23. Sotolongo Jr JR. Voiding dysfunction in Parkinson's disease. Semin Neurol. 1988;8(2):166–9.
24. Resnick NM, Yalla SV. Detrusor hyperactivity with impaired contractile function. An unrecognized but common cause of incontinence in elderly patients. JAMA. 1987;257(22):3076–81.
25. Andersen JT, Hebjorn S, Frimodt-Moller C, Walter S, Worm-Petersen J. Disturbances of micturition in Parkinson's disease. Acta Neurol Scand. 1976;53(3):161–70.
26. Berger Y, Salinas JN, Blaivas JG. Urodynamic differentiation of Parkinson's disease and Shy Dragger syndrome. Neurourol Urodyn. 1990;9:117–21.
27. Christmas TJ, Kempster PA, Chapple CR, et al. Role of subcutaneous apomorphine in parkinsonian voiding dysfunction. Lancet. 1988;2(8626–8627):1451–3.
28. Uchiyama T, Sakakibara R, Hattori T, Yamanishi T. Short-term effect of a single levodopa dose on micturition disturbance in Parkinson's disease patients with the wearing-off phenomenon. Mov Disord. 2003;18(5):573–8.
29. Fowler CJ. Urinary disorders in Parkinson's disease and multiple system atrophy. Funct Neurol. 2001;16(3):277–82.

30. Singer C, Weiner WJ, Sanchez-Ramos J, Ackerman M. Sexual function in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry. 1991;54(10):942.
31. Eardley I, Quinn NP, Fowler CJ, et al. The value of urethral sphincter electromyography in the differential diagnosis of parkinsonism. Br J Urol. 1989;64(4):360–2.
32. Vodusek DB. Sphincter EMG and differential diagnosis of multiple system atrophy. Mov Disord. 2001;16(4):600–7.
33. Chancellor MB, Yoshimura N. Neurophysiology of stress urinary incontinence. Rev Urol. 2004;6 Suppl 3:S19–28.
34. Keane DP, O'Sullivan S. Urinary incontinence: anatomy, physiology and pathophysiology. Baillieres Best Pract Res Clin Obstet Gynaecol. 2000;14(2):207–26.
35. Blok BF, Willemsen AT, Holstege G. A PET study on brain control of micturition in humans. Brain. 1997;120(Pt 1):111–21.
36. Nour S, Svarer C, Kristensen JK, Paulson OB, Law I. Cerebral activation during micturition in normal men. Brain. 2000;123(Pt 4):781–9.
37. Griffiths DJ. The pontine micturition centres. Scand J Urol Nephrol Suppl. 2002;(210):21–6.
38. Matsuura S, Kakizaki H, Mitsui T, Shiga T, Tamaki N, Koyanagi T. Human brain region response to distention or cold stimulation of the bladder: a positron emission tomography study. J Urol. 2002;168(5):2035–9.
39. Kavia RB, Dasgupta R, Fowler CJ. Functional imaging and the central control of the bladder. J Comp Neurol. 2005;493(1):27–32.
40. Blackett H, Walker R, Wood B. Urinary dysfunction in Parkinson's disease: a review. Parkinsonism Relat Disord. 2009;15(2):81–7.
41. Lewin RJ, Dillard GV, Porter RW. Extrapyramidal inhibition of the urinary bladder. Brain Res. 1967;4(4):301–7.
42. Lewin RJ, Porter RW. Inhibition of spontaneous bladder activity by stimulation of the globus pallidus. Neurology. 1965;15(11):1049–52.
43. Athwal BS, Berkley KJ, Hussain I, et al. Brain responses to changes in bladder volume and urge to void in healthy men. Brain. 2001;124(Pt 2):369–77.
44. Kitta T, Kakizaki H, Furuno T, et al. Brain activation during detrusor overactivity in patients with Parkinson's disease: a positron emission tomography study. J Urol. 2006;175(3 Pt 1):994–8.
45. Abramovicz M. Tolterodine for overactive bladder. Med Lett. 1998;40:101–3.
46. Siroky MB. Neurological disorders cerebrovascular disease and parkinsonism. Urol Clin North Am. 2003;30(1):27–47, v.
47. Abramovicz M. Oxybutynin transdermal (Oxytrol) for overactive bladder. Med Lett. 2003;45(1156):38–9.
48. Appell RA. Pharmacotherapy for overactive bladder: an evidence-based approach to selecting an antimuscarinic agent. Drugs. 2006;66(10):1361–70.
49. Biastre K, Burnakis T. Trospium chloride treatment of overactive bladder. Ann Pharmacother. 2009;43(2):283–95.
50. Staskin DR, Rosenberg MT, Sand PK, Zinner NR, Dmochowski RR. Trospium chloride once-daily extended release is effective and well tolerated for the treatment of overactive bladder syndrome: an integrated analysis of two randomised, phase III trials. Int J Clin Pract. 2009;63(12):1715–23.
51. Giannantoni A, Mearini E, Del Zingaro M, Santaniello F, Porena M. Botulinum A toxin in the treatment of neurogenic detrusor overactivity: a consolidated field of application. BJU Int. 2008;102 Suppl 1:2–6.
52. Giannantoni A, Rossi A, Mearini E, Del Zingaro M, Porena M, Berardelli A. Botulinum toxin A for overactive bladder and detrusor muscle overactivity in patients with Parkinson's disease and multiple system atrophy. J Urol. 2009;182(4):1453–7.
53. Finazzi-Agro E, Peppe A, D'Amico A, et al. Effects of subthalamic nucleus stimulation on urodynamic findings in patients with Parkinson's disease. J Urol. 2003;169(4):1388–91.
54. Seif C, Herzog J, van der Horst C, et al. Effect of subthalamic deep brain stimulation on the function of the urinary bladder. Ann Neurol. 2004;55(1):118–20.
55. Shimizu N, Matsumoto S, Mori Y, et al. Effects of deep brain stimulation on urodynamic findings in patients with Parkinson's disease. Hinyokika Kiyo. 2007;53(9):609–12.
56. Winge K, Nielsen KK, Stimpel H, Lokkegaard A, Jensen SR, Werdelin L. Lower urinary tract symptoms and bladder control in advanced Parkinson's disease: effects of deep brain stimulation in the subthalamic nucleus. Mov Disord. 2007;22(2):220–5.
57. Herzog J, Weiss PH, Assmus A, et al. Subthalamic stimulation modulates cortical control of urinary bladder in Parkinson's disease. Brain. 2006;129(Pt 12):3366–75.
58. Edwards MJ, Talelli P, Rothwell JC. Clinical applications of transcranial magnetic stimulation in patients with movement disorders. Lancet Neurol. 2008;7(9):827–40.
59. Brusa L, Agro EF, Petta F, et al. Effects of inhibitory rTMS on bladder function in Parkinson's disease patients. Mov Disord. 2009;24(3):445–8.
60. Kabay SC, Kabay S, Yucel M, Ozden H. Acute urodynamic effects of percutaneous posterior tibial nerve stimulation on neurogenic detrusor overactivity in patients with Parkinson's disease. Neurourol Urodyn. 2009;28(1):62–7.
61. Vodusek DB, Light JK, Libby JM. Detrusor inhibition induced by stimulation of pudendal nerve afferents. Neurourol Urodyn. 1986;5:381–9.
62. Fall M, Lindstrom S. Electrical stimulation. A physiologic approach to the treatment of urinary incontinence. Urol Clin North Am. 1991;18(2):393–407.
63. Krivoborodov GG, Gekht AB, Korshunova ES. Tibial neuromodulation in the treatment of neurogenic detrusor hyperactivity in patients with Parkinson's disease. Urologiia. 2006;(4):3–6.