CLINICS

CLINICAL SCIENCE

Neurological status predicts response to alpha-blockers in men with voiding dysfunction and Parkinson's disease

Cristiano M. Gomes,[I] Zein M. Sammour,[I] Jose de Bessa Junior,[I*] Egberto R. Barbosa,[II] Roberto I. Lopes,[I] Flávio S. Sallem,[II] Flavio E. Trigo-Rocha,[I] Homero Bruschini,[I] Victor W. Nitti,[III] Miguel Srougi[I]

[I]Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Division of Urology, São Paulo/SP, Brazil. [II]Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Department of Neurology, São Paulo/SP, Brazil. [III]New York University, Department of Urology, New York/, USA.

OBJECTIVES: To evaluate predictors of the response to doxazosin, a selective alpha-adrenoceptor antagonist, when used for the treatment of lower urinary tract symptoms in men with Parkinson's disease.

METHODS: In a prospective study, 33 consecutive men (mean age 59.2±7.0 years) with Parkinson's disease and lower urinary tract symptoms were evaluated. Neurological dysfunction was assessed with the Unified Parkinson's Disease Rating Scale. Urological assessment was performed at baseline and after 12 weeks of treatment with 4 mg/day of extended-release doxazosin, including symptom evaluation with the International Continence Society male short-form questionnaire, an assessment of the impact of lower urinary tract symptoms on quality of life and urodynamics. Clinical and urodynamic predictors of response were specifically evaluated.

RESULTS: Compared with the score at baseline, the total International Continence Society male short-form score was reduced after doxazosin administration, from 17.4±7.5 to 11.1±6.9 ($p<0.001$). The impact of lower urinary tract symptoms on quality of life was also significantly reduced, from 1.8±1.1 to 1.0±1.0 ($p<0.001$) and the maximum urinary flow varied from 9.3±4.4 to 11.2±4.6 ml/s ($p=0.025$). The severity of neurological impairment was the only predictor of the clinical response. Additionally, patients with a Unified Parkinson's Disease Rating Scale score lower than 70 had a significantly higher chance of clinical improvement with doxazosin treatment than those with higher Unified Parkinson's Disease Rating Scale scores did (RR = 3.10, 95% CI = [1.15 to 5.37], $p=0.011$).

CONCLUSIONS: Doxazosin resulted in the improvement of lower urinary tract symptoms and the maximum flow rate and was well tolerated in men with Parkinson's disease. The response to treatment is dependent on the severity of neurological disability.

KEYWORDS: Lower Urinary Tract Symptoms; Parkinson's Disease; Urodynamics; Doxazosin.

Gomes CM, Sammour ZM, Bessa Jr J, Barbosa ER, Lopes RI, Sallem FS, et al. Neurological status predicts response to alpha-blockers in men with voiding dysfunction and Parkinson's disease. Clinics. 2014;69(12):817-822.

Received for publication on May 2, 2014; **First review completed on** July 2, 2014; **Accepted for publication on** September 12, 2014

E-mail: josedebessa@gmail.com

*corresponding author

Tel.: 55 11 2661-8080

INTRODUCTION

Parkinson's disease (PD) is a progressive neurological disorder characterized by the degeneration of nigrostriatal dopaminergic neurons (1,2). Clinically, PD is characterized by rigidity, a resting tremor, bradykinesia and autonomic failure. Lower urinary tract symptoms (LUTS) are frequent in patients with PD and it is estimated that 27% to 60% of PD patients present with LUTS during the course of their disease (3-5). The most common urinary complaints are nocturia, an intermittent flow pattern, incomplete emptying and urgency/frequency, symptoms that have a significant negative effect on patients' quality of life (QOL) (4). Furthermore, urodynamic evaluation demonstrates abnormalities in most patients, which may include detrusor overactivity, detrusor underactivity and bladder outlet obstruction (BOO) (6,7).

Several factors account for the high prevalence of LUTS among patients with PD, including vesicosphincteric abnormalities secondary to the neurological disease, such as detrusor overactivity and inappropriate urethral sphincter

Copyright © 2014 **CLINICS** – This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

No potential conflict of interest was reported.

DOI: 10.6061/clinics/2014(12)05

relaxation. In addition, urinary tract comorbidities, such as benign prostatic hyperplasia (BPH) and degenerative alterations of the urinary tract associated with aging, may coexist. Thus, it is difficult to establish the role played by each one of these factors in the genesis of LUTS.

Men with PD who are bothered by their LUTS usually receive pharmacological treatment, which may include α-adrenoceptor antagonists and/or antimuscarinic agents, according to their symptoms and urodynamic findings. Although α-adrenoceptor antagonists are widely used for the treatment of LUTS in men, including PD patients, no studies have evaluated effects in this population (8,9). Because benign prostatic obstruction is a highly prevalent condition in older men, a group that commonly develops PD, it is important to evaluate the effect of an α-blocker for the treatment of LUTS in this population. Furthermore, it would be beneficial to be able to identify clinical prognostic factors associated with successful medical treatment of voiding dysfunction. Because several studies have shown that the severity of neurological impairment is associated with an increased risk of LUTS (3,4,10), we postulated that this parameter might also be a predictor of the pharmacological response.

MATERIALS AND METHODS

This was a prospective, open, non-controlled clinical study (trial number ISRCTN46238855 - www.controlled-trial.com/ISRCTN46238855) that assessed the possible clinical and urodynamic predictors of the response to alpha-blocker therapy in men with PD.

Over a period of two years, a total of 48 men with an established diagnosis of PD were referred from our Neurology Department Clinic for the treatment of LUTS. The inclusion criteria were idiopathic PD and an age above 40 years. Patients with multi-system atrophy and other neurological conditions were excluded. We also excluded subjects who used any bladder or prostate medications, including alpha-blockers, 5-alpha-reductase inhibitors, antimuscarinics or phosphodiesterase-5 inhibitors, over the past six months as well as those with a history of pelvic or prostate surgery and/or radiotherapy.

This study was approved by the institutional review board of our hospital. The patients agreed to participate in the study after full disclosure of its purpose and written informed consent was obtained from all.

The severity of neurological impairment was assessed with the Unified Parkinson's Disease Rating Scale (UPDRS). The assessment of this scale was performed by the referring neurologist and all patients on anti-parkinsonian medication were assessed in the ''on'' condition. The drug regimen of each patient was also registered.

LUTS were evaluated with the International Continence Society (ICS) male short-form questionnaire (ICSmSF), which consists of 14 questions regarding voiding symptoms (ICSV), incontinence (ICSI), frequency and nocturia (ICSFN) and an additional question concerning QOL related to urinary symptoms (11). Two questions about the duration of PD and LUTS were also included.

Patients were included irrespective of their ICSmSF score if they were bothered by their LUTS. They were specifically questioned about whether they wanted to receive medications for their symptoms and all were willing to undergo pharmacological treatment for them. All patients underwent further evaluation before medical treatment, including urinalysis; serum creatinine and prostate-specific antigen (PSA) testing; transabdominal prostate and urinary tract sonography; and full urodynamic analyses consisting of free uroflowmetry, post-void residual (PVR) volume measurement, filling cystometry and pressure-flow assessment.

BOO and detrusor contractility were assessed with the Schafer nomogram (12). Patients with mild obstruction (areas I and II of the nomogram) were included in the unobstructed group. Only patients whose detrusor contractility was considered very weak (VW) in the nomogram were classified as having detrusor underactivity. The methods, definitions and units used conformed to the standards recommended by the ICS. Based on the urodynamic analyses, only patients with an abnormal voiding pattern in the pressure-flow assessment were included. The patients should also have had BOO, detrusor underactivity or an equivocal obstruction grade (Schafer zone II) associated with a PVR volume>150 mL.

Fifteen patients were excluded because they did not complete the urological workup (5 patients), did not meet the urodynamic criteria (5 patients) or chose not to participate in the study because they refused to repeat the urological work-up after treatment (5 patients).

A total of 33 men were prospectively enrolled in the 12-week open-label study. Each patient received 4 mg/day of extended-release doxazosin at bedtime. The men were reevaluated at 12 weeks and efficacy was assessed by analyzing treatment-related changes in the ICSmSF score, QOL, the peak flow rate (Qmax), the PVR and urodynamic parameters from baseline to week 12. Adverse events reported by the patients or observed by the investigator during the study duration were recorded.

To evaluate the utility of different clinical parameters as predictors of the response to alpha-blockers, we assessed the associations between age, the severity of neurological impairment, the duration of PD, use of levodopa, ICSmSF, LUTS duration, prostate volume and urodynamic parameters and the response to the pharmacological treatment. Treatment success (a responder) was defined as an improvement in the LUTS of ≥50%, as measured by the ICSmSF questionnaire.

Statistical analysis

The data are expressed as the mean ± standard deviation (SD) or as absolute values and fractions. Student's t test or a paired t test was used to compare continuous variables, whereas categorical variables were compared using Fisher's exact test. The significance of clinical parameters for predicting the clinical response and the best threshold to distinguish responders were assessed based on receiver-operating characteristic (ROC) curves. All tests were 2-sided, with $p<0.05$ considered to be statistically significant. The data were processed using commercially available statistical software (GraphPad Prism, version 5.03 for Windows, San Diego, CA, USA).

RESULTS

The mean age of the patients was 59.2±7.0 years (range 44 to 73 years). The neurological evaluation demonstrated a mean UPDRS score of 70.5±20.6 (range 49 to 112). The mean duration of PD was 13.8±7.5 years (range 4 to 30 years) and the mean duration of LUTS was 3.9±2.9 years.

Table 1 - Anti-parkinsonian drug regimen taken by the patients.

Prescribed medications (number of patients)
Levodopa (8)
Levodopa + ED dopamine agonists (7)
Levodopa + Anticholinergics* (6)
Levodopa + NED dopamine agonists + Anticholinergics (3)
Levodopa + NED dopamine agonists (3)
Anticholinergics* (2)
Levodopa + ED dopamine agonists + NED dopamine agonists + Anticholinergics (1)
Levodopa + ED dopamine agonists + Anticholinergics (1)
NED dopamine agonists (1)
ED dopamine agonists + Anticholinergics (1)

*Anticholinergic agents for Parkinson's disease (biperiden hydrochloride and trihexyphenidyl).
Legend: ED - ergot-derived; NED - non-ergot-derived.

All patients were taking a variety of anti-parkinsonian drugs (Table 1). Levodopa alone or in combination with other agents was used by most (29, 87.9%) of the patients.

The mean ICSmSF score was 17.4±7.5 (range 3.0 to 36). The most common urinary complaints were nocturia, in 31/33 (93.9%) patients; intermittency, in 24 (72.7%); incomplete emptying, in 21 (63.6%); urgency, in 19 (57.5%); hesitation, in 18 (54.5%); a weak stream, in 17 (51.5%); increased urinary frequency, in 17 (51.5%); and urge incontinence, in 12 (36.3%). Two patients (6.1%) had a positive urine culture at the time of the evaluation and were treated accordingly. Serum creatinine was normal in all patients and the mean PSA value was 1.7±1.1 ng/mL (range 0.2 to 3.9 ng/mL). Additionally, the mean ultrasound-estimated prostate volume was 28.1±7.6 mL (range 18.9 to 44.0 mL) and the mean PVR volume was 43.9±44.0 mL (range 0 to 121 mL). Urinary tract sonography was normal in 32 patients, whereas one (3.0%) patient had bladder diverticula.

The baseline urodynamics revealed BOO in 25 (75.7%) patients, detrusor overactivity in 16 (48.4%) patients and detrusor underactivity in 6 (18.2%) patients.

Doxazosin was well tolerated by most patients. Adverse events and most frequently dizziness, were usually mild and transient and led to a discontinuation of doxazosin therapy in only one patient. No clinically significant changes in neurological symptoms were observed during the study.

Effects of 12-week doxazosin treatment on LUTS: Changes from baseline

The changes in the total ICSmSF score and the subscores of voiding symptoms are summarized in Table 2. A favorable response, defined as an improvement of ≥50% according to the ICSmSF questionnaire, was observed in 15 (45.4%) patients.

Table 2 - Changes in symptoms, peak urinary flow and post-void residual urine after doxazosin treatment.

	Baseline	12 weeks	*p*-value
ICSmSF score	17.4±7.5	11.1±6.9	<0.001
ICSV score	7.5±4.5	4.1±3.7	0.003
ICSI score	4.5±2.8	2.9±2.2	<0.001
ICSFN score	5.8±2.6	4.0±2.1	<0.001
QOL	1.8±1.1	1.0±1.0	<0.001
Peak flow rate (mL/s)*	9.3±4.4	11.2±4.6	0.025
Post-void residual (mL)	60±103.8	48.3±96.9	0.239

*Peak flow rate during free uroflowmetry.
Legend: ICSmSF - International Continence Society male short-form questionnaire; ICSV - voiding symptoms on the ICSmSF; ICSI - incontinence symptoms on the ICSmSF; ICSFN - frequency and nocturia on the ICSmSF; QOL - quality of life.

Effects of 12-week doxazosin treatment on urodynamic parameters: Changes from baseline

The observed changes in urodynamic parameters after doxazosin treatment are summarized in Table 3. The peak urinary flow was the only parameter that significantly improved in response to doxazosin, varying from 9.3±4.4 to 11.2±4.6 ($p=0.025$).

The average UPDRS score of the responders was 60.2±12.3, as opposed to 82.8±22.3 for the non-responders ($p=0.001$). The severity of neurological impairment was a good predictor of the clinical response and the UPDRS score that best discriminated responders from non-responders was 70. Patients with a UPDRS score lower than 70 had a significantly higher chance of clinical improvement with doxazosin treatment than those with higher UPDRS scores did (RR = 3.10, 95% CI = [1.15 to 5.37], $p=0.011$).

Other clinical parameters, such as age, the duration of PD, use of levodopa, the severity and duration of LUTS, prostate volume and urodynamic parameters such as the presence of detrusor overactivity and BOO, did not have a significant effect on the response to the pharmacological treatment (Table 4).

DISCUSSION

We are the first to show that alpha-adrenoceptor antagonist treatment is safe and effective in PD patients with LUTS. Although many clinicians have used alpha-blocking agents for the treatment of LUTS in this population, the effects of these medications have not been studied in a prospective and structured manner.

The non-motor symptoms of PD may represent the most disturbing symptoms experienced as the disease progresses and particularly voiding dysfunction, as it is well known that LUTS have a major impact on QOL (10). Indeed, studies using validated questionnaires have shown that over 50% of men with PD are affected by LUTS. Several factors account for the high prevalence of LUTS in this population. Neurogenic causes include detrusor overactivity, with an incidence ranging from 40 to 93% (6,7,13); impaired relaxation or bradykinesia of the urethral sphincter (13-16); and detrusor underactivity (6,7). Because BPH is a very common condition in the aged population and because pharmacological treatment is the first-line treatment (9), it is

Table 3 - Changes in urodynamic parameters after doxazosin treatment.

Parameter	Baseline	12 weeks	*p*-value
First desire to void (mL)	158.7±54.7	152.8±58.0	0.596
Maximum cystometric capacity (mL)	348.5±119.3	337.1±121.9	0.550
Bladder compliance (mL/cmH_2O)	53.3±51.3	51.6±30.8	0.873
Detrusor overactivity (n (%))	16 (48.4%)	13 (39.3%)	0.125
Peak flow rate (mL/s)*	7.4±4.4	8.4±3.7	0.176
Detrusor pressure at Q_{max} (cmH_2O)	62.8±30.2	57.6±14.5	0.262
Schafer obstruction class	3.2±1.6	3.1±0.9	0.351

*Peak flow rate during pressure-flow study.

important to evaluate the outcomes of medical therapy for LUTS in PD patients. Published reports have shown the efficacy of α-adrenoceptor antagonists in producing symptomatic improvement in patients with BPH (9,17,18). However, although widely used in men with PD, the efficacy of these agents in this population is not known. In fact, there are few studies regarding the treatment of PD patients with BOO. As BOO may be secondary to sphincteric disorders as well as BPH, surgical treatment has been considered to be a risky procedure in this population. For example, Staskin et al. reported a *de novo* urinary incontinence rate of 20% after TURP (19). Recently, however, in a retrospective series of 23 patients who underwent TURP, Roth et al. reported a successful outcome in 70% and no cases of *de novo* urinary incontinence (20).

We evaluated patients for 12 weeks based on previous data indicating that the effects of α-blockers on LUTS develop fully within this time frame (17) and a significant improvement in LUTS, including voiding, incontinence, frequency and nocturia, was observed. QOL was also significantly improved after treatment. Moreover, nearly 50% of our patients had an improvement of symptoms and QOL of at least 50%. We arbitrarily chose 50% improvement because it represents a sound improvement of symptoms and has been used as a success marker, even for the indication of invasive treatments such as the implantation of a sacral neuromodulator. A significant increase in the peak flow rates was also observed. Doxazosin was well tolerated and only one patient discontinued treatment due to dizziness.

An important aspect of our study, the evaluation of parameters that might be associated with successful medical treatment. We have shown that the severity of neurological impairment was a good predictor of the clinical response and that a UPDRS score of 70 was the best discriminator of responders from non-responders. In particular, patients with a UPDRS score lower than 70 had a 3.1-fold higher chance of clinical improvement with doxazosin treatment than those with higher UPDRS scores did. Other clinical parameters, such as age, the duration of PD, use of levodopa, LUTS duration and severity, prostate volume and urodynamic parameters, did not have a significant effect on the response to doxazosin.

Previous studies have shown a correlation between parkinsonian symptoms and LUTS (4,5). A possible reason for this, is the role of striatal dopaminergic stimulation in bladder control, which has been shown in animal studies (21). The worse outcomes with doxazosin treatment observed in patients with more severe neurological impairment are probably explained by the fact that in these patients, the role of neurological dysfunction is overwhelming and less likely to respond to alpha-blocking therapy.

Despite the impressive clinical improvement observed, the only obstruction-related urodynamic parameter that was significantly changed by doxazosin treatment was the maximum free flow rate. This is in accordance with the results of studies on BPH patients who failed to consistently show reductions in other parameters related to BOO upon treatment with α-blockers (18,22). It has been assumed that the improvement of LUTS associated with the use of α-blockers is mediated by the relaxation of prostatic and/or bladder-neck smooth muscle. However, the weak association between symptom improvement and obstruction relief has led authors to suggest other mechanisms for the beneficial effects of α-blockers in elderly males, including action on α-adrenoceptors in the spinal cord (23) and bladder (24). However, whether the effects of doxazosin are consequent to peripheral mechanisms, actions in the central nervous system or both remains speculative (9).

In our study, an absence of obstruction was not an exclusion criterion. However, we did not include patients with detrusor overactivity and a normal voiding phase because these patients usually receive antimuscarinic agents, so their inclusion could have confounded our results. We did include patients who would usually receive an α-blocking agent as the first-line medical treatment, including those with overt BOO as well as those with equivocal obstruction and an associated increased PVR,

Table 4 - Impact of clinical and urodynamic parameters on the response to doxazosin treatment.

	Responders (n = 15)	Non-responders (n = 18)	*p*-value
Age (years)	57.7±8.1	60.5±6.0	0.264
UPDRS score	60.2±12.3	82.8±22.2	0.001
PD duration (years)	13.0±7.4	15.1±7.6	0.478
Levodopa	13/15 (86.6%)	16/18 (88.8%)	0.840
ICSmSF	16.0±8.6	18.6±6.3	0.341
LUTS duration (years)	3.8±2.7	4.1±3.1	0.777
Prostate volume (mL)	24.9±5.5	31.0±8.3	0.176
Detrusor overactivity	6 (40%)	9 (53%)	0.502
Schafer obstruction class	3.0±1.3	3.3±1.7	0.639

which we arbitrarily considered to be over 150 mL. We also included patients with detrusor underactivity because, in our practice, we would offer them an alpha-blocker. It is important to emphasize that only 5/43 (11.6%) patients were excluded from the study due to urodynamic criteria, indicating that our study population is not a highly selected one and probably represents the average population of a tertiary-care center. In addition, as discussed previously, urodynamic parameters did not predict treatment outcomes. Based on these facts, routine use of urodynamic studies in PD patients who are being considered for pharmacological therapy does not appear to add information relevant to treatment decisions and evaluation of neurological impairment using the UPDRS appears to be the only predictor of outcomes. These recommendations, however, should be further investigated in future studies designed to examine the predictors of the response to pharmacological treatment in PD patients.

Although not an objective of our study, we regret that we were not able to adequately evaluate the sphincteric function of our patients. Because we could not offer video-urodynamics to most patients and considering the limited quality of our electromyographic recordings, we did not have the opportunity to evaluate urethral sphincter function and to possibly improve understanding of the pathophysiology of LUTS in PD patients. However, one important aspect of our study was the evaluation of prostate volume. In our series, the mean prostate volume was 28.1 mL, which is consistent with or even lower than the volume in the general population of the same age (25). This finding indicates that in our sample, prostate enlargement did not contribute significantly to LUTS. The heterogeneity of anti-parkinsonian drugs is a problem in most studies evaluating bladder dysfunction and even those designed to evaluate the effect of anti-parkinsonian drugs on bladder function have struggled with the effects of polypharmacy(26). During our study, no patient changed his anti-parkinsonian drug regimen. We registered all medications used by the patients to evaluate the possible effects of anti-parkinsonian agents on LUTS; as observed in most patients followed at a neurology clinic, many were on several medications pertaining to different classes of anti-parkinsonian drugs. We attempted to compare the patients based on the use of levodopa because there is certain evidence that this drug may have a degree of impact on LUTS (26). In the present study, 29 (87.9%) patients used levodopa and 13 (39.3%) were considered as good responders, a success rate similar to the overall response rate to doxazosin. However, we acknowledge that these findings have very limited significance because the overwhelming majority of our patients received levodopa.

The lack of a control group is certainly a weakness of the study because part of the clinical improvement observed in our patients could have been secondary to a placebo effect. However, the main objective of this study was to assess the possible predictors of the response to alpha-blocker therapy in men with PD. For such a study, the inclusion of a control group is not necessary.

CONCLUSIONS

Our study is the first to demonstrate the efficacy and safety of alpha-adrenoceptor antagonist treatment in men with PD. Doxazosin resulted in a significant improvement in LUTS within 12 weeks of therapy. An increase in the peak urinary flow rates was also observed, although no improvement in other urodynamic parameters was achieved. The severity of neurological impairment was a good predictor of the clinical response, with patients with a UPDRS score lower than 70 having a three-fold higher chance of clinical improvement than those patients with higher UPDRS scores. In contrast, urodynamic parameters did not predict treatment outcomes.

ACKNOWLEDGMENTS

The authors would like to express their wholehearted gratitude to Prof. Clare Fowler for her continuous support and valuable advice in the preparation of this manuscript.

AUTHOR CONTRIBUTIONS

Gomes CM, Buschini H were responsible for the study conception and design. Sammour ZM, Bessa Jr J, Lopes RI and Sallem FS were responsible for the data acquisition. Gomes CM, Bessa Jr J and Trigo-Rocha F were responsible for data analysis and interpretation. Gomes CM, Sammour ZM were responsible for the manuscript drafting. Bruschini H, Nitti VW, Barbosa E and Srougi M were responsible for the critical revision of the manuscript for important intellectual content. Bessa Jr J was responsible for the statistical analysis. Barbosa E and Srougi M provided administrative, technical and material support. Bruschini H, Srougi M were also responsible for the study supervision.

REFERENCES

1. Samii A, Nutt JG, Ransom BR. Parkinson's disease. Lancet. 2004;363 (9423):1783-93, http://dx.doi.org/10.1016/S0140-6736(04)16305-8.
2. Schapira AH. Disease modification in Parkinson's disease. Lancet Neurol. 2004;3(6):362-8, http://dx.doi.org/10.1016/S1474-4422(04)00769-0.
3. 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, http://dx.doi.org/10.1136/jnnp.68.4.429.
4. Sammour ZM, Gomes CM, Barbosa ER, Lopes RI, Sallem FS, Trigo-Rocha FE, et al. Voiding dysfunction in patients with Parkinson's disease: impact of neurological impairment and clinical parameters. Neurourol Urodyn. 2009;28(6):510-5, http://dx.doi.org/10.1002/nau.20681.
5. Winge K, Skau AM, Stimpel H, Nielsen KK, Werdelin L. Prevalence of bladder dysfunction in Parkinsons disease. Neurourol Urodyn. 2006;25(2):116-22, http://dx.doi.org/10.1002/nau.20193.
6. 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.
7. Sakakibara R, Hattori T, Uchiyama T, Yamanishi T. Videourodynamic and sphincter motor unit potential analyses in Parkinson's disease and multiple system atrophy. J Neurol Neurosurg Psychiatry. 2001;71(5):600-6, http://dx.doi.org/10.1136/jnnp.71.5.600.
8. Stohrer M, Blok B, Castro-Diaz D, Chartier-Kastler E, Del PG, Kramer G, et al. EAU guidelines on neurogenic lower urinary tract dysfunction. Eur Urol. 2009;56(1):81-8, http://dx.doi.org/10.1016/j.eururo.2009.04.028.
9. Oelke M, Bachmann A, Descazeaud A, Emberton M, Gravas S, Michel MC, et al. EAU Guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. Eur Urol. 2013;64(1):118-40, http://dx.doi.org/10.1016/j.eururo.2013.03.004.
10. Sakakibara R, Shinotoh H, Uchiyama T, Sakuma M, Kashiwado M, Yoshiyama M, et al. Questionnaire-based assessment of pelvic organ dysfunction in Parkinson's disease. Auton Neurosci. 2001;92(1-2):76-85, http://dx.doi.org/10.1016/S1566-0702(01)00295-8.
11. Donovan JL, Peters TJ, Abrams P, Brookes ST, aa Rosette JJ, Schafer W. Scoring the short form ICSmaleSF questionnaire. International Continence Society. J Urol. 2000;164(6):1948-55.
12. Schafer W. Principles and clinical application of advanced urodynamic analysis of voiding function. Urol Clin North Am. 1990;17(3):553-66.
13. Pavlakis AJ, Siroky MB, Goldstein I, Krane RJ. Neurourologic findings in Parkinson's disease. J Urol 1983;129(1):80-3.
14. Christmas TJ, Kempster PA, Chapple CR, Frankel JP, Lees AJ, Stern GM, et al. Role of subcutaneous apomorphine in parkinsonian voiding dysfunction. Lancet. 1988;2(8626-8627):1451-3, http://dx.doi.org/10.1016/S0140-6736(88)90932-4.
15. Fowler CJ. Urinary disorders in Parkinson's disease and multiple system atrophy. Funct Neurol. 2001;16(3):277-82.
16. Galloway NT. Urethral sphincter abnormalities in Parkinsonism. Br J Urol. 1983;55(6):691-3.

17. Narayan P, Evans CP, Moon T. Long-term safety and efficacy of tamsulosin for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia. J Urol. 2003;170(2 Pt 1):498-502.
18. Rossi C, Kortmann BB, Sonke GS, Floratos DL, Kiemeney LA, Wijkstra H, et al. alpha-Blockade improves symptoms suggestive of bladder outlet obstruction but fails to relieve it. J Urol. 2001;165(1):38-41.
19. Staskin DS, Vardi Y, Siroky MB. Post-prostatectomy continence in the parkinsonian patient: the significance of poor voluntary sphincter control. J Urol. 1988;140(1):117-8.
20. Roth B, Studer UE, Fowler CJ, Kessler TM. Benign prostatic obstruction and parkinson's disease–should transurethral resection of the prostate be avoided? J Urol. 2009;181(5):2209-13.
21. Seki S, Igawa Y, Kaidoh K, Ishizuka O, Nishizawa O, Andersson KE. Role of dopamine D1 and D2 receptors in the micturition reflex in conscious rats. Neurourol Urodyn. 2001;20(1):105-13, http://dx.doi.org/10.1002/1520-6777(2001)20:1<105::AID-NAU12>3.0.CO;2-9.
22. Kortmann BB, Floratos DL, Kiemeney LA, Wijkstra H, de la Rosette JJ. Urodynamic effects of alpha-adrenoceptor blockers: a review of clinical trials. Urology. 2003;62(1):1-9, http://dx.doi.org/10.1016/S0090-4295(02)02113-1.
23. Yoshiyama M, de Groat WC. Role of spinal alpha1-adrenoceptor subtypes in the bladder reflex in anesthetized rats. Am J Physiol Regul Integr Comp Physiol. 2001;280(5):R1414-9.
24. Hampel C, Dolber PC, Smith MP, Savic SL, Th rJ, Thor KB, et al. Modulation of bladder alpha1-adrenergic receptor subtype expression by bladder outlet obstruction. J Urol. 2002;167(3):1513-21.
25. Roehrborn CG, McConnell JD. Etiology, pathophysiology, epidemiology and natural history of benign prostatic hyperplasia. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ, editors. Campbell's Urology. 8 ed. Philadelphia: W. B. Saunders Co.; 2002. p. 1297-330.
26. Winge K, Werdelin LM, Nielsen KK, Stimpel H. Effects of dopaminergic treatment on bladder function in Parkinson's disease. Neurourol Urodyn. 2004;23(7):689-96, http://dx.doi.org/10.1002/nau.20054.