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REVIEW ARTICLE

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Management of neurogenic bladder in patients with Parkinson's disease: A systematic review

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Aims: To assess the different treatment methods in management of neurogenic bladder (NGB) in patients with Parkinson's disease (PD).

Methods: A systematic search was performed in Cochrane library, EMBASE, Proquest, Clinicaltrial.gov, WHO, Google Scholar, MEDLINE via PubMed, Ovid, ongoing trials registers, and conference proceedings in November 11, 2017. All randomized controlled trials (RCTs) or quasi-RCTs comparing any treatment method for management of NGB in patients with PD were included. The titles and abstracts of all identified studies were evaluated independently by two investigators. Once all of the potential related articles were retrieved, each author separately evaluated the full text of each article and the quality of the methodology of the selected studies using the Cochrane appraisal risk of bias checklist and then the data about the patient's outcomes was extracted. We registered the title in Joanna Briggs Institute (JBI) that is available in http://joannabriggs.org/research/registered_titles.aspx.

Results: We included 41 RCTs or quasi-RCTs or three observational study with a total of 1063 patients that evaluated pharmacological, neurosurgical, botulinum toxin, electrical neuromodulation, and behavioral therapy effects on NGB. Among the included studies only solifenacin succinate double-blind, randomized, placebo-controlled study was assessed as low risk of bias, and treatment led to an improvement in urinary incontinence.

Conclusions: Although several interventions are available for treatment NGB in patients with PD, at present there is little or no evidence that treatment improves patient outcomes in this population. Additional large, well designed, randomized studies with improved methodology and reporting focused on patient-centered outcomes are needed.

KEYWORDS
neurogenic bladder, Parkinson's disease, systematic review

1 | INTRODUCTION

Neurogenic bladder (NGB) is a non-specific term covering both underactivity and overactivity of bladder.[1] Overactive

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bladder (OAB) is a symptom-based diagnosis defined by the International Continence Society (ICS) as "urgency (with or without urge incontinence) usually with daytime frequency and nocturia, and when there is a relevant neurological condition it is called neurogenic OAB." The symptoms of OAB usually stem from detrusor muscle overactivity (detrusor overactivity, DO) but may also be caused by other forms of urethrovesical dysfunction. DO is investigated by urodynamic observation. In this condition, involuntary detrusor contractions occur during the filling phase of cystometry.[2] Urinary dysfunction especially neurogenic OAB as a manifestation of autonomic failure is the most common complication of patients with multiple sclerosis (MS), spinal cord injury (SCI), Parkinson's disease (PD), cerebrovascular accident/stroke, and spina bifida.[3–8]

Idiopathic Parkinson's disease (IPD) is an extrapyramidal progressive neurodegenerative neurologic disease, most commonly associated with prominent motor and non-motor symptoms. Urinary symptoms are frequently present in these patients[9] and usually occur after motor symptoms.[10] According to epidemiological studies, the urinary symptoms are seen in 37-70% of PD patients.[11]

Usually in PD patients, the primary urinary complaints of urinary dysfunction due to IPD include urgency, frequency, urinary incontinence (UI) (with a multifactorial origin: bladder dysfunction and functional problems influencing the patient's ability to perform appropriate toileting), and nocturia (maybe due to sleep disturbances and nocturnal polyuria). Frequency, urgency, urge UI (urinary storage symptoms) is prevalent complaints of 57-83% PD patients. However poor force of stream, hesitancy, incomplete emptying (as voiding symptoms) are seen in 17-27%.[9]

Three voiding centers that control bladder function are the sacral micturition center (at the spinal sacral S2 to S4 levels controlling bladder contraction), the pontine micturition center (in the brain stem, coordinating relaxation of the external sphincter synchronized with bladder contractions), and the cerebral cortex (exerting the final control of voluntary micturition at an appropriate time and place). The micturition reflex comes under basal ganglia control.[3,12]

In PD, the bladder hyperactivity mechanism may result from removal of the inhibitory mechanism of dopamine exertion via the pars compacta of the substantia nigra mediated by D1 receptors (through the inability to activate D1 mediated tonic inhibition)[3,12] on the urinary reflex.[13,14] It seems that the other mechanisms may include preferential damage to the inhibitory dopaminergic neurons.[3]

NGB often has a significant impact on quality of life with limitation of activities,[15] and incontinence has an additional negative impact on quality of life because of embarrassment, depression, and social isolation.[13] Without treatment, NGB leads to sepsis and renal failure that imposes the high burden on each health care system of communities.[16,17]

1.1 | Description of the intervention

There are different management strategies for treatment the symptoms and improvement the quality of life[10] based on the ICS standardization report.[2]

These interventions include conservative treatment[18] (as an alternative modalities to drugs in patients with motivation, or ineffectiveness of drugs or the present of drug side effects in long time users[19] such as pelvic floor muscle training,[2] biofeedback,[20] bladder training,[21] however, the evidences about its effect are poor[22]), behavioral modification, bladder reflex triggering and bladder expression[2]; medical management (anticholinergic[23–26] and L-dopa[27]); clean intermittent (in/out) catheterization (CIC)[2] and the indwelling catheters[28–35]; electrical stimulation[36]; sacral nerve roots stimulation[37–39]; dorsal penile and clitoral nerves electrical stimulation[40]; tibial nerve stimulation[2,41–45]; neuromodulation[46–48]; magnetic stimulation[49]; deep brain stimulation (DBS)[50]; intravesical application of several neurotoxic agents (including capsaicin, resiniferatoxin, and botulinum toxin [BTX])[51–54]; sacral roots stimulation by dorsal rhizotomy[37,55–57]; antiparkinsonian therapy[58]; surgery (TURP)[59]; and augmentation cystoplasty.[60,61]

1.2 | Why it is important to do this review

To improve the quality of life and alleviate the disability encompassing LUTS in PD patients, there are different management options with various efficacies. Several clinical trials on treatment methods for NGB in patients with PD (and other background information about it) have been done in different parts of the world; however, there are few reviews comparing the results of the treatment methods. Despite the importance of bladder-related issues in patients with PD, evidence to support management options for NGB are limited, indicating the importance of conducting a systematic review to sum up the best available evidence, and to design a stepwise algorithm for utilization by clinicians managing LUTS in PD patients.

2 | METHODS

2.1 | Criteria for considering studies for this review

2.1.1 | Study design

A systematic review was conducted according to predefined guidelines provided by the Cochrane Collaboration (2008).

2.1.2 | Types of studies

We included all randomized controlled trials (RCTs) and quasi-RCTs in which PD patients bothersome and were seeking

treatment because of experiencing lower urinary tract symptoms (LUTS) or voiding dysfunction, and who were clinically diagnosed by at least one validated questionnaire such as the American Urology Association Symptom Score, International Prostate Symptom Score (I-PSS), Overactive Bladder Symptom Score (OABSS), and the International Conference of Incontinence Questionnaire Short-form (ICIQ-SF).

2.2 | Types of participants

2.2.1 | Inclusion criteria

All relevant research articles involving PD patients with LUTS or voiding dysfunction (difficulty voiding), who were finding their symptoms bothersome and were seeking treatment, and who were clinically diagnosed by at least one validated questionnaire such as mentioned in above paragraph.

2.2.2 | Exclusion criteria

- Articles that did not have enough PD patients (fewer than 7 patients);
- all retrospective studies;
- studies without any access to full-text;
- withdrawn trials.

2.3 | Types of interventions

- Conservative management including pelvic floor muscle training (PFMT) (with or without biofeedback), bladder training, behavioral modification, bladder reflex triggering, and bladder expression.
- Medical treatment including anticholinergic drugs, Alpha and/or Beta-adrenergic, Antiparkinsonian therapy including: (Levodopa and carbidopa combined (Sinemet), Apomorphine, Dopamine Agonists, MAO-B Inhibitors, COMT (Catechol-O-methyl transferase) Inhibitors, Exelon Patch (rivastigimine transdermal system) donepezil, galantamine, NMDA receptor inhibitor.
- Catheterization (if compared with another non-drug intervention).
- Neurosurgical techniques including: selective sacral rhizotomy, artificial somatic-autonomic reflex pathway construction, Subthalamic deep brain stimulation (STN-DBS).
- Electrical or magnetic stimulation, sacral nerve neuromodulation (stimulation includes both non-invasive and implanted devices), anogenital ES, transcutaneous electrical nerve stimulation (TENS), percutaneous posterior tibial nerve stimulation (PTNS), Intravesical electrical stimulation (IVES), pudendal nerve electrical stimulation.
- Chemical denervation including intravesical application of several neurotoxic agents (vanilloids: capsaicin, resiniferatoxin) and botulinum toxin A.

2.4 | Types of outcome measures

2.4.1 | Primary outcomes

The number of people with PD experiencing symptoms of lower urinary tract who treated with measurable criteria (scores of valid questionnaires/evaluation Urodynamic).

2.4.2 | Secondary outcomes

A. Participant's observations
- General expression of PD patients with improving LUTS symptoms
- Satisfaction with treatment methods

B. Quantification of symptoms
- Flow rates;
- Post-void residual volume (PVR), incomplete bladder emptying, and retention;
- Changes in voided volumes and number of urination (urinary diaries);
- Changes in self-reported valid questionnaire scores.

C. Clinician's observations
- Objective measurements of voiding dysfunction (valid questionnaire scores or urodynamics).

D. Quality of life
General health status measures—Short Form-36 or other valid questionnaires including: OAB questionnaire Short Form (OAB-Q SF), Health Utilities Index Mark 3 (HUI3), OAB HRQL questionnaire, EuroQol five-dimensional (EQ-5D) questionnaire, the Qualiveen questionnaire, QoL-BM, the FICQoL Condition-specific health measures (specific instruments designed to assess impact of voiding dysfunction on quality of life).

E. Adverse effect.

2.5 | Search methods for identification of studies

2.5.1 | Electronic searches

A systematic search was performed in Cochrane library, EMBASE, Proquest, Clinicaltrial.gov, WHO, Google Scholar, MEDLINE via PubMed and Ovid databases in November 2017, using the following key words: lower urinary tract dysfunction, neurogenic bladder, lower urinary tract symptom, incontinence, urinary retention, overactive bladder, Parkinson disease, Parkinsonism, antimuscarnics,

Tolterodine ER, solifenacin succinate, trospium chloride, high dose of oxybutynin; apomorphine or L-Dopa, Desmopresin, Bromocriptine, Rasagiline, amantadine, Neurosurgical techniques, Thalamotomy, intravesical application of several neurotoxic agents, botulinum toxin, Electrical neuromodulation, Behavioral therapy. Also we looked for unpublished trial data and ongoing trials in ClinicalTrials.gov. We did not consider any limitation of date and language for this systematic review. Full details of the search strategies are reported in Appendix S1.

2.5.2 | Searching other resources

We screened reference lists of included trials and review articles, and contacted authors of included trials for further data. Also we hand-searched international congress abstracts. In addition, we searched unpublished or incomplete studies via investigators known to be involved in previous studies and other experts in the field.

2.6 | Data collection and analysis

2.6.1 | Selection of studies

Two authors independently read the titles and abstracts of all studies identified by the search strategy. Once we had retrieved all potentially relevant articles, each review author independently assessed the full text of each article for inclusion and then assessed the methodological quality of selected studies using the Cochrane appraisal risk of bias checklist.

2.6.2 | Data extraction and management

Two review authors independently recorded the following information using a data extraction form:

1. Participants: inclusion and exclusion criteria, number of participants in each group.
2. Methods: trial design, randomization method, allocation concealment, blinding of participants, investigators, and outcome assessors.
3. Interventions: including conservative and medical management; neurosurgical techniques; electrical or magnetic stimulation; chemical denervation, and botulinum toxin A.
4. Outcomes: primary and secondary outcomes, adverse events.
5. Others: country and setting, publication year, sources of funding.

Non-English language journals articles were translated before assessment. If a study was published more than once, the reports were summarized and the publication with the most complete information was entered into the study. And if the results were only published in older versions, this data was used. Any differences between published versions would be marked. Any information required by the original author has been written through correspondence and related information obtained through this review. Disagreement resolved in consultation with the third author.

2.7 | Assessment of risk of bias in included studies

Two independent reviewers evaluated the methodological quality of the selected trials. Assessing the risk of bias was performed through six-criterion appraisal checklist containing sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting and other bias. Each parameter includes one or more specific items. In all cases, an evaluation of "low risk" indicates a low risk of bias, an evaluation of "high risk" indicates high risk of bias, and an evaluation of "unclear risk" indicates uncertain risk of bias.

3 | RESULTS

3.1 | Description of studies

3.1.1 | Results of the search

We identified a total of 4325 potentially relevant reports of studies from our literature searches. After reviewing the titles and abstracts, we excluded 630 references as they were duplicate publications. Of the remaining 3695 references, we excluded 3687 references after screening based on title and abstract. One hundred and fifty-three full text records assessed for eligibility. Eighty-nine full text records were excluded as they had not included PD patients or did not have enough PD patients (fewer than seven patients), or were retrospective studies, or were studies without access to full-text, or were withdrawn trials. The remaining 59 records were appraised using tools and finally we included 41 studies in the quality synthesis in this review (Figure 1).

3.1.2 | Included studies

We included 41 RCTs or quasi-RCTs (and three observational) studies with a total of 1055 patients with PD. Most were published between 2004 and 2017.

3.1.3 | Excluded studies

We excluded 89 articles:

- NGB articles that had not included PD patients;
- articles that did not have enough PD patients (fewer than 7 patients);

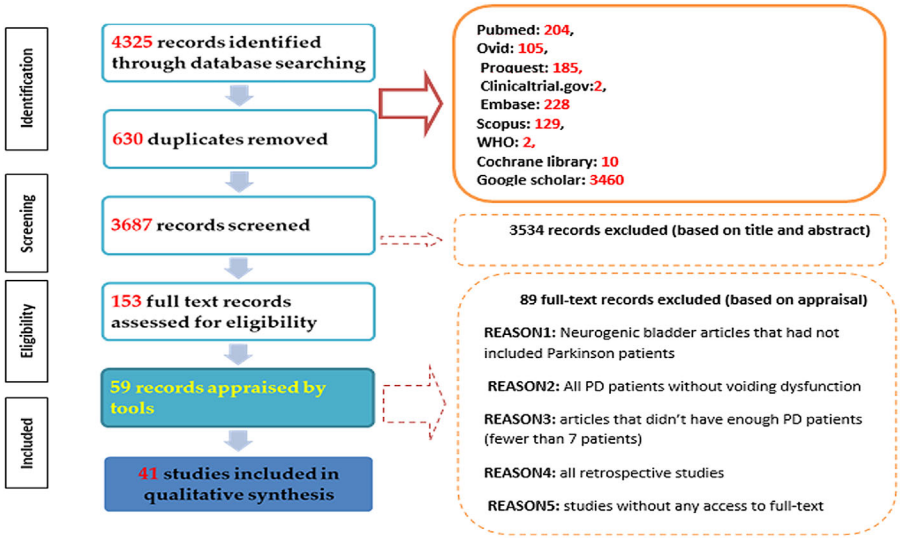

FIGURE 1 Study flow diagram

- all retrospective studies;
- studies without any access to full-text;
- withdrawn trials.

Characteristics of included studies: Of the included studies, two studies in the field of conservative behavioral therapy by Vaughan[62] were pilot studies. One of the Botox injection studies was open label,[63] three of them were prospective (Giannantoni,[64] Conte,[65] Kulaksizoglu[66]: Giannantoni's group republished their data in EU Journal of Neurology in Sep 2011 and previously they published in 2009), two of them were single before/after,[67,68] and the study by Jiang[69] was retrospective. Three transcutaneous tibial nerve stimulation related studies were prospective before/after,[70–72] one was single prospective before/after[73] and one study by Perissinotto[74] was a RCT. The studies by Krivoborodov[75] and Peters[76] were prospective before/after and there was an observational study in the field of neuromodulation. The studies by Herzog[77] and Seif[78] in relation to subthalamic stimulation were prospective before/after and Porter[79] conducted a clinical trial in the field of thalamotomy. Mock[80], Roy,[81] and Witte[82] conducted a studies in the field of Deep Brain Stimulation (DBS). The first was prospective before-after, the second was prospective non-blinded clinical trial and the third was randomized clinical trial. The prospective before-after studies by Brusa,[83] Kitta,[84] and Gubbiotti[85] were in the field of medications. Crescenze[86] and Brandi[87] in a single prospective before-after study evaluated the effect of SNM and parasacral electrostimulation, respectively.

Risk of bias in included studies: See Figures 2 and 3.

3.2 | Allocation

3.2.1 | Random sequence generation and allocation concealment

All medical therapy studies except Zesiewicz,[88] Perissinotto,[74] and Chen[89] was reported as high risk of allocation bias with no randomization and allocation consequence. In these studies, they used a computer generated randomization schedule. The other clinical trials in the included studies were unclear in randomization.[80,82]

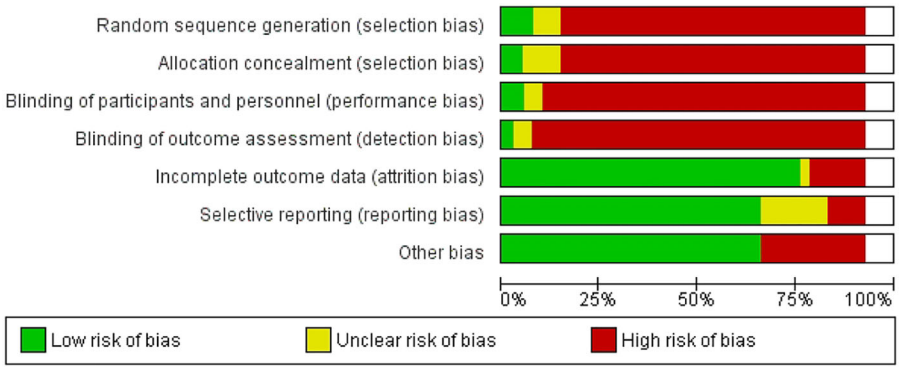

FIGURE 2 Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies

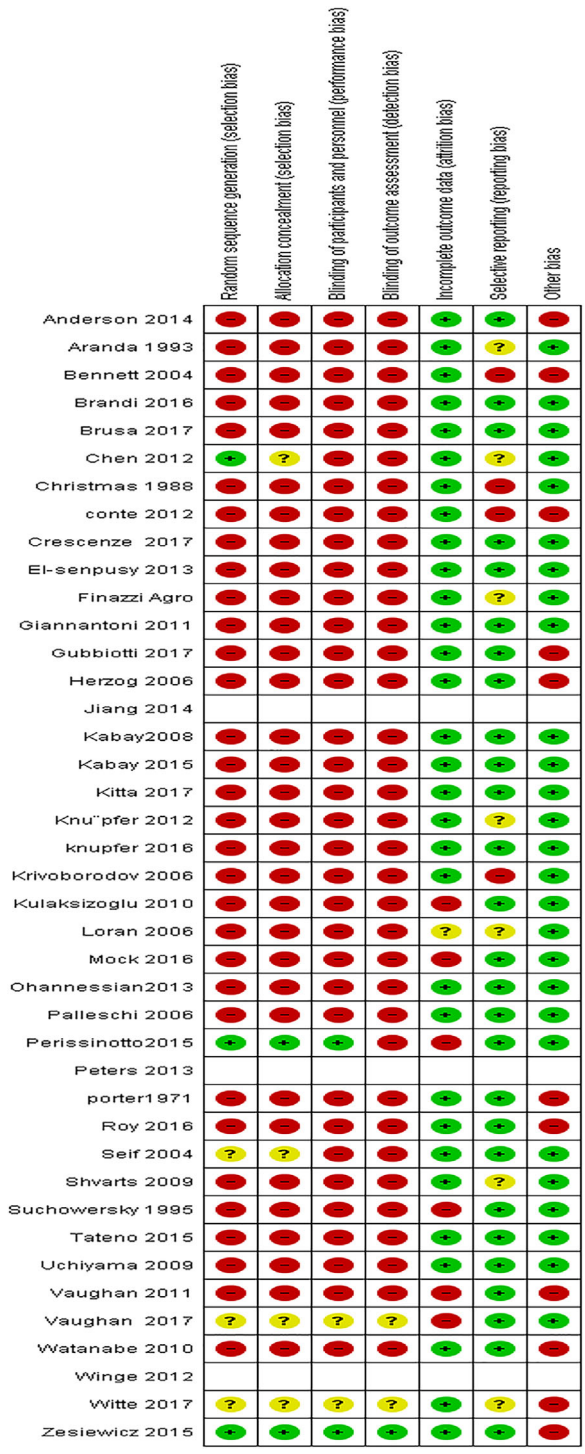

FIGURE 3 Risk of bias summary: review authors' judgments about each risk of bias item for each included study

3.2.2 | Blinding

The controlled trials of Zesiewicz[88] and Perissinotto[74] were double-blind. They carefully described the method of blinding and this was judged adequate. In the other trials blinding was not reported adequately and was considered as unclear risk of bias[82,90] and the prospective, non-blinded clinical trial study of Mock was assessed as high risk of bias.[80]

3.2.3 | Incomplete outcome data

In Loran study,[91] outcome data were incomplete and unclear. In Suchowersky,[92] only five patients completed the trial. In Perissinotto,[74] almost half ($n = 10$) of the included cases did not complete the study, so they had a large amount of incomplete follow up that could influence the result of trial. In other studies, incomplete outcome data were reported. Witte[82] reported that missing data points were only 2.3% of total data points.

3.2.4 | Selective reporting

Watanabe,[93] Zesiewicz,[88] and Vaughan[62] were at low risk of selective reporting bias. We could not confirm whether all pre-specified outcomes were reported in Loran,[91] Aranda, Chen, Finazzi Agro, Shvarts, and Knupfer[67,89,94–96] and therefore these were at an unclear risk of selective reporting bias. The others were at high risk of bias. In Shvarts,[96] 36 patients out of 253 had PD, but the result of the intervention was not reported separately in the abstract. In Bennett study,[97] only 7 out of 39 enrolled patients had PD but the outcome was only reported in total. In Okafor[98] Study's, only 6 patients (7.5%) out of 80 (19.4%) NLUTD cases (out of 412 total patients) had PD and the results were not reported separately.

3.2.5 | Other potential sources of bias

We did not identify any other potential sources of bias in the included studies.

3.2.6 | Effects of interventions

See: summary of findings for the main comparison Table 1.

4 | DISCUSSION

4.1 | Summary of main results

NGB and UI are common and embarrassing conditions in many neurological diseases such as PD, with a high impact on quality of life. In this systematic review, we assessed the effects of different treatment methods for LUTS in PD patients. According to our results, although several interventions are available for treating overactive NGB in PD patients, at present there is little or no evidence that current treatment improves patient outcomes in this population. Additional large, well-designed, randomized controlled studies with improved methodology and reporting focused on patient-centered outcomes are needed.

TABLE 1 Summary of findings for the main comparison

Reference	Type of intervention	Participant's and clinician's observations of alleviation LUTS symptoms and quantification of symptoms	Treated PD patients with measurable criteria	Quality of life	Adverse effect	Urodynamic evaluation			Comment
						Urodynamic variables	Baseline	Intervention	
Conservative management									
Vaughan et al[62]	Behavioral therapy	Urinary incontinence (weekly frequency) episodes decreased 83.3% from 9 (4-11) to 1 (0-3) after intervention, $P < 0.0001$. Nocturia (nightly) decreased from 1.9 (0.7-2.3) to 1.1 (0.4-1.9), $P = 0.07$. Urgency UI (weekly frequency) at Baseline, was 8 (4-10) before and 0 (0-2) in Week 8 after treatment, $P < 0.0001$. Nocturia (nightly) decreased from 1.9 (0.7-2.3) before to 1.1 (0.4-1.9) after treatment, $P = 0.07$		QOL scores on the ICIQ-OAB improved from 71.1 $\pm$ 23.9 to 54.7 $\pm$ 15.4 ($P = 0.002$). Symptom score decreased from 8.8 $\pm$ 2.7 to 6.1 $\pm$ 1.9 after treatment, $P = 0.008$. Bother scored decreased from 24.7 $\pm$ 7.8 to 15.9 $\pm$ 10.3, $P = 0.02$					
Vaughan et al[90]	(Pelvic floor muscle-exercise based behavioral therapy (BET)	BET reported greater reduction in OAB symptoms compared to CON ([−3.162.8] vs [1.762.2], $P = 0.04$). Weekly UI reduction was similar between BET (5.768.9) and CON (−6.2612.7) ($P = 0.4$). BET improved OAB symptoms in PD. Bladder diary self-monitoring was associated with UI reduction in both groups.		QOL and bother from OAB were significantly improved in BET ($P < 0.0001$ for both) compared to baseline.					It was a congress paper
Medical management									
Watanabe et al[93]	Antimuscarinic drugs (Tolterodine)		After treatment all these items were decreased significantly: Overactive bladder symptom score, International Consultation on incontinence Questionnaire-Short Form score, number of voids (per 24 h and night-time), number of urgency episodes in 24 h, number and amount of leaks in 24 h and amount of mean and maximum voided volumes.		Adverse events were noted in four patients (9%); the most frequent side-effects were dry mouth in three patients, followed by constipation in one patient. However, these patients could continue treatment because their side-effects were mild	Bladder capacity at first sensation and maximum cystometric capacity increased significantly, by an average of 36.8 mL ($P = 0.0402$) and 82.3 mL ($P < 0.0001$), respectively. Maximum cystometric capacity increased by more than 50 mL in 19 patients (49%) following treatment. Detrusor overactivity disappeared in three of 32 patients (9%), bladder capacity at first involuntary contraction increased significantly ($P = 0.0009$), and amplitude of detrusor overactivity decreased significantly ($P = 0.0025$). In patients with low-compliance bladder, bladder compliance increased significantly		Only five patients out of 39 had PD, and the result of intervention was not reported separately.

(Continues)

TABLE 1 (Continued)

Reference	Type of intervention	Participant's and clinician's observations of alleviation LUTS symptoms and quantification of symptoms	Treated PD patients with measurable criteria	Quality of life	Adverse effect	Urodynamic evaluation			
						Urodynamic variables	Baseline	Intervention	Comment
						($P = 0.0156$).			
Palleschi et al[99]			Mean micturition interval (minutes) was increased from 129 (±29) to 211 (±41) after treatment, $P = 0.05$. The episodes of mean daily micturition, mean number of urinary incontinence, was significantly decreased from 12.1 (±1.8) to 6.8 (±0.4), $P = 0.05$ and from 4 (±2.3) to 2.1 (±0.8) after treatment, $P = 0.024$ respectively. Urinary leakage was seen in 16 of 40 (40%) patients before and only seen in 6 cases (15%) after treatment.	24 patients from 32 (75%) had a negative OAB-q score with a significant reduction of urinary urgency rate (46%) and nocturnal micturition episodes. OAB-q parameters were improved after antimuscarinic treatment ($P < 0.001$). Three-days voiding diary results showed a decrease of daily micturition and urinary urgency episodes, after treatment. Mean voiding volume 179 (±38) mL vs 271 (±22) mL before and after treatment, $P < 0.05$.		Thirty-two out of forty (80%) patients concluded the protocol and 8/40 (20%) abandoned it because of the following events: 2/40 (5%) due to constipation; 3/40 (7.5%) dizziness/headache; 3/40 (7.5%) no clinical improvement. Dry mouth was the most frequent side effect reported by patients (11/32 = 34.3%) and defined moderate by 9 (28%) and severe by 2 (6.2%). No severe adverse events were reported.	Volumes of first detrusor involuntary contractions (mL), $P = 0.01$	77 ± 19	148 ± 27
						Volume of first desire to void (mL) $P = 0.024$	120 ± 27	153 ± 34 mL	
						Cystometric volume of leakage (mL) $P = 0.05$	176 ± 13	263 ± 31	
						Cystometric capacity (mL) $P = 0.05$	227 ± 20	339 ± 47	
						Amplitude (cm H_2O)	59 ± 17	46 ± 12	
						Mean post-voiding residual (mL)	78 ± 21	78 ± 42	
						Maximum flow rate (mL/s)	Male	14.8-18	13.9-18.3
							Female	16.3-21.6	15.9-21.1
						Pdet max flow (cm H_2O)	Male	62 ± 6	63 ± 8
							Female	22 ± 4	21 ± 6
						Detrusor overactivity (DO) was seen in 40/40 (100%) of patients before and 38/40 (95%) of cases after treatment.			

(Continues)

TABLE 1 (Continued)

Reference	Type of intervention	Participant's and clinician's observations of alleviation LUTS symptoms and quantification of symptoms	Treated PD patients with measurable criteria	Quality of life	Adverse effect	Urodynamic evaluation			
						Urodynamic variables	Baseline	Intervention	Comment
Loran et al[91]	Tolterodin, oxibutinin, trospium chloride and antiparkinsonian therapy	Voiding disorders reduced in 10 patients and no further treatment was needed. Voiding disorders reduced in all 3 groups of patients given the drugs.		Quality of life in the examinees improved considerably.		Cystometric capacity of the bladder increased in all 4 groups from 155 (86-450) mL to 220 (105-530) mL, on the average, and unstable contractions of the urinary bladder decreased from 3.1 (1-8) to 1.6 (0-5).			
Bennett et al[97]	Oxybutynin	The mean number of voids per 24 h was significantly decreased from 9.8 ± 0.8 at baseline to 6.6 ± 0.7 at week 12 ($P = 0.001$). The number of micturition episodes per night decreased from 1.8 ± 0.3 at baseline to 1.2 ± 0.2 at 12 weeks, ($P = 0.006$). The number of urge incontinence episodes per week significantly decreased from 4.3 ± 1.5 at baseline to 1.7 ± 0.7 week after 12 weeks ($P = 0.004$). Post-void residual urine (mL) was 33.9 ± 7.6 before and 51.3 ± 10.4 ($P = 0.17$) after treatment.		Improvements in sleep based on the decrease in nocturia	No serious adverse events: Dry mouth, Constipation, No new subjective central system side effects.				Only 7 patients out of 39 had Parkinson Disease but results are not shown separately.
Zesiewicz et al[88]	Solifenacin succinate	The mean of micturition and leaks were similar before and after treatment of solifenacine (9.03 ± 2.21) in treatment group vs 9.23 ± 3.31 in placebo group, ($P = 0.87$) and 1.33 ± 2.45 vs 1.72 ± 1.23, $P = 0.66$), respectively. Also the nocturia episodes's mean and mean number of micturitions per 24 h period did not differ significantly (2.23 ± 1.69 vs 1.90 ± 1.09 in solifenacine and placebo group, respectively, $P = 0.57$) and (8.78 ± 2.1 to 8 8.00 ± 3.36) compared to placebo (9.19 ± 3.46 to 8.94 ± 3.06, $P = 0.53$), respectively. The number of urinary incontinence episodes average per 24 h period		There were no significant changes in the Patient Perception of Intensity of Urgency Scale (PPIUS) or measures of quality of life (PD QOL: 125.00 ± 20.95 to 116.00 ± 26.42 in solifenacine group and 114.50 ± 10.73 to 112.92 ± 17.19 in placebo, $P = 0.47$, Mean (SD) of IQOL total in solifenacine group was 78.00 ± 20.03 and in placebo was 75.92 ± 18.87, $P = 0.80$.	Constipation was reported in 1 case out of 9 cases of active treatment in Solifenacin succinate group, xerostomia (2 patients out of 9 in active treatment), and urinary retention (in 1/9 participants on active treatment), which all resolved upon treatment discontinuation.			

(Continues)

TABLE 1 (Continued)

Reference	Type of intervention	Participant's and clinician's observations of alleviation LUTS symptoms and quantification of symptoms	Treated PD patients with measurable criteria	Quality of life	Adverse effect	Urodynamic evaluation			
						Urodynamic variables	Baseline	Intervention	Comment
		decreased significantly in the solifenacin group (1.48 ± 2.56 to 0.30 ± 0.31) compared to placebo (1.78 ± 1.27 to 1.61 ± 1.40, $P = 0.01$). Significant improvements were seen from baseline to endpoint in the mean daily number of urinary incontinence episodes (baseline = 1.33 ± 1.54 to 0.52 ± 1.01; $P = 0.03$) and the number of nocturia episodes (from 2.67 ± 1.08 to 1.64 ± 1.09; $P = 0.01$) as secondary outcomes. Patient Perception of Bladder Condition (PPBC) was improved in patients who received solifenacin succinate in open label phase ($P = 0.01$).							
Shvarts et al[96]	Trospium chloride	15 to 45 mg/day trospium chloride in 2-36 month courses; The response with minimal side effects was achieved in 94% patients.						This article was in Russian and the result of intervention was not reported separately in abstract (36 patient out of 253 had PD)	
95	MAO-inhibitors	IPSS filling score was 12.3 ± 2.5 before and 9.7 ± 1.1 after treatment $P < 0.01$. IPSS voiding score was 5.3 ± 2.1 before and 4.2 ± 1.2 after treatment $P < 0.01$				First sensation, mL	118 + 53	158 + 42*	$P < 0.001$* Ameliorated bladder volume measurements increase of bladder capacity (of about 16%) and of first desire to void (of about 34%). while significantly decreased residual volume (−53%). (abstract congress)
						NDOC threshold, mL	170 + 86	188 + 83*	
						Bladder capacity, mL	290 + 98	337 + 115*	
						NDOC amplitude, cmH_2O	55 ± 40	51 ± 42*	
						P det at Qmax, cmH_2O	30 + 16	32 + 12*	
						Qmax, mL/s	15 ± 4	13 ± 3*	

(Continues)

TABLE 1 (Continued)

Reference	Type of intervention	Participant's and clinician's observations of alleviation LUTS symptoms and quantification of symptoms	Treated PD patients with measurable criteria	Quality of life	Adverse effect	Urodynamic evaluation			Comment
						Urodynamic variables	Baseline	Intervention	
Aranda, et al[94]	Dopamine agonists				Adverse effects were mild: nausea, drowsiness, and yawning.	PMR increased in 3 cases and was stable in the others. The test was negative in the 3 hyporeflexic patients (mean BC change was 513-563 mL). The mean BC increase was 30% in hyperreflexic patients when no variation was observed in hyporeflexic subjects. The mean BC increase with apomorphine was 87% (132-247 mL), although uninhibited contractions persisted in all but one patient. The mean urethral pressure increase was 22% with apomorphine (50 to 61 cmH_20; $n = 5$) and 27% with L dopa (50-65 cmH_20; $n = 6$).			
Christmas et al		Post micturition volume decreased after apomorphine in 7 patients with off state residual urine (mean 185.7 mL). Increased maximum flow rate (mean increase 16.9 mL/s) and mean flow rate (mean increase 6.5 mL/s).			3 patients were unable to void during the off state	Reduction of bladder outflow resistance rate in all patients (the mean change (0.217 cm water s^2/mL^2) in 7 patients. Detrusor function during filling and voiding was not altered (Detrusor hyperreflexia was improved in some cases but was exacerbated in others).			
Uchiyama et al		Urinary urgency aggravated in 4 patients (50%), unchanged in 3 (37.5%), and alleviated in 1 (12.5%). After the bromocriptine trial, urinary urgency aggravated in 2 patients (25%) and remained unchanged in 6 (75%). Post-void residual (mL) in Bromocriptine group was 20.0 (21.4) before and 3.75 (5.2) after treatment, and for levodopa it was 1.9 (5.3), ($P < 0.05$). Maximum flow rate (mL/s) was 9.5 (4.0) before, and 10.0 (4.4) for Bromocriptine and 9.3 (2.2) for Levodopa after treatment ($P > 0.05$).				First sensation (mL)	Bromocriptine ($P < 0.05$)	107.5 (41.3)	83.8 (37.4)
							Levodopa $P < 0.01$		68.8 (16.4)
						Bladder capacity	Bromocriptine ($P > 0.05$)	213.8 (137.1)	191.8 (125.7)
							Levodopa ($P < 0.05$)		135.0 (51.8)

(Continues)

TABLE 1 (Continued)

Reference	Type of intervention	Participant's and clinician's observations of alleviation LUTS symptoms and quantification of symptoms	Treated PD patients with measurable criteria	Quality of life	Adverse effect	Urodynamic evaluation			
						Urodynamic variables	Baseline	Intervention	Comment
						Maximum detrusor pressure (mmH2O)	Bromocriptine ($P > 0.05$)	52.3 (10.1)	51.0 (12.2)
							Levodopa		60.8 (9.1)
Brusa et al[83]		LUT symptoms in the base condition were mild to moderate in all patients, according to IPSS scores. Total IPSS scores changed significantly during rotigotine treatment compared with baseline scores (from 11.3 ± 2.0 to 6.2 ± 3.2, $P < 0.0005$); in particular, filling (irritative) symptoms were significantly decreased by rotigotine administration, whereas obstructive (voiding) symptoms were unchanged. The UPDRS Part III score obtained on rotigotine, as expected, was significantly lower, indicating a significant enhancement after drug administration compared with the baseline condition (29.0 ± 8.1 vs 17.0 ± 4.0).				Bladder volume measurements ameliorated compared with baseline. bladder capacity increased 50 mL ($P < 0.001$), mean first desire to void increment (50 mL), and NDOC threshold increase (60 mL). No effect was observed for residual urine volume.			
						Bladder capacity	330 ± 126	390 ± 120*	
						Residual urine	32 ± 34	14 ± 27	
						NDOC amplitude	24.0 ± 31.0	27.0 ± 27.0	
						Pdet at Qmax	15.0 ± 8.0	21.0 ± 11.0	
						Qmax, mL/s	36.0 ± 14.0	36.0 ± 14.0	
Tateno et al[100]	N-methyl-D-aspartate (NMDA) antagonist	Mean (SE) daytime urinary frequency was 9.07 (0.64) before and 6.9 (0.42) after 150 mg amantadine administration and 6.90 (0.33) after daily 300 mg amantadine administration. These amounts were 2.89 (0.24), 1.97(0.21), 1.69 (0.10) for nighttime urinary frequency, 24.2 (6.69), 13.0 (3.58), 5.88 (1.61) for			In dose of 150 mg amantadine no patient had side effects. One patient developed hallucination, and two patients developed flashing sensation in dose of 300 mg.				

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TABLE 1 (Continued)

Reference	Type of intervention	Participant's and clinician's observations of alleviation LUTS symptoms and quantification of symptoms	Treated PD patients with measurable criteria	Quality of life	Adverse effect	Urodynamic evaluation			Comment
						Urodynamic variables	Baseline	Intervention	
		urinary urgency per week, 15.1 (9.94), 14.2 (10.2), and 2.31 (0.61) for urge incontinence per month, 145.6 (12.6) mL, 174.1 (11.3), and 180.2 (15.0) for urine volume per void. One month after daily administration of 150 mg amantadine, RU volume was 6.84 (SE, 3.63) and tended to decrease but not significantly. One month after daily administration of 300 mg amantadine, RU volume was 15.0 (SE, 3.60) and tended to decrease, but this change was not significant.							
Kitta et al[84]	Adenosine A2A receptor antagonist	Significant improvements were observed in the answers provided on urinary questionnaires after 1 year treatment (IPSS: 14.4 ± 7.6 vs 8.5 ± 6.8, OABSS: 6.9 $\pm$ 2.8 vs 5.5 ± 3.7; $P < 0.05$). 3-day voiding diary and nighttime urinary frequency significantly improved after 1-year treatment (3.0 ± 1.6 vs 2.4 ± 0.7; $P < 0.05$). However, no significant changes were observed in the urinary flow rate (Qmax) or post-voiding residual urine volume (RU) between before and after 1-year administration of istradefylline (Qmax (mL/s): 10.7 ± 3.9 vs 8.0 ± 2.8, RU (mL): 51.0 ± 60.0 vs 40.5 $\pm$ 30.8).		Data from the KHQ revealed that the domain of impact on life had significantly improved after 1 year treatment	No adverse urological effects were observed in any patient.				Istradefylline is a novel non-dopaminergic selective adenosine A2A receptor antagonist. It was a congress paper
Suchowersky et al[92]	Desmopressin	Mean number of nocturnal voids at Baseline was 2.67 $\pm$ 0.14 and after DDAVPl 2.12 ± 0.17 and after DDAVP2 was 1.51 ± 0.14 ($P = 0.0796$).			Mild epistaxis, confusion and hyponatremia were reported. Two patients failed to complete the trial due to problems of compliance and failure to keep the diaries.				Of the eight patients initially recruited, five completed the trial.
Gubbiotti et al[85]	Adrenergic agonists	At 3 months follow up, 6 (30%) patients stopped		The satisfaction rate was high with this kind of	No substantial side effects were reported.				It was a congress paper

(Continues)

TABLE 1 (Continued)

Reference	Type of intervention	Participant's and clinician's observations of alleviation LUTS symptoms and quantification of symptoms	Treated PD patients with measurable criteria	Quality of life	Adverse effect	Urodynamic evaluation			Comment
						Urodynamic variables	Baseline	Intervention	
		Mirabegron, due to: poor efficacy ($n = 4$) and the cost of the drug ($n = 2$). In the remaining 13 patients, VAS score changed from 3.8 ± 0.9 at baseline to 6.6 ± 1.7, urgency urinary incontinence decreased from 4.2 ± 2.1 to 3.1 ± 1.3, and the mean daily frequency of urgency decreased from 9.7 ± 3.6 to 6.2 ± 2.9. At the 6 months' follow-up these favorable results persisted in 13 patients. In this study, about 70% of PD patients continued to assume Mirabegron at the 6 month follow- up, showing a persistent improvement in their OAB symptoms.		treatment in the short-term follow-up.					
Botox injection									
Anderson et al[63]		Ten of 17 patients (59%) reported symptomatic changes of "moderately" to "markedly improved" on the global response assessment questionnaire by 3 months and a 50% incontinence decrease over 6 months relative to pretreatment was reported in 59% patients ($P = 0.02$); The mean voided urine volume was observed to be increased significantly only at month 3 after treatment ($P = 0.028$).	The part III (bladder problems) of KHQ score significantly at months 1 and 3 post-treatment ($P = 0.02$). The AUA mean symptom score of 18 ± 1.3 (SEM) at screening was significantly improved at all follow-up visits after onabotA; decreased to 12 ± 1.9 (SEM) at month 6 ($P = 0.006$). The significant improvements in the 3-day diary reports of leaks per day and AUA symptom scores over 6 months ($P < 0.05$) for all patients and the profile of responses separately for men and women.		2 men were given an alpha-blocking agent (tamsulosin 0.4 mg) for near-term management. Two episodes of UTI occurred in 2 women both of whom had a history of recurrent UTI. No other adverse events related to the treatment. Notably, minimal procedure discomfort occurred and no significant bleeding occurred after the injection procedures.	First desire to void (cc): in men 98 (20-216) and 79 (20-182) in women. In uroflowmetry decrease in peak flow and increase in PVR (average - 310 mL) during months 1 and 3 follow up was shown but returned to similar baseline levels by month 6. Median bladder contraction volume, 115 mL; maximum bladder pressure, 62 cm; and post-void volume, 9 mL. Moderate to marked symptom relief at 3 months.		5 patients out of 17 failed to complete the 6-month endpoint.	
Conte et al[65]		Daytime urinary frequency (baseline: 9.12 ± 0.3 vs 5 ± 0 at 6 months, $P = 0.002$) and nighttime baseline: 3.37 ± 1 vs 1.7 ± 0.4 at 6 months, $P = 0.04$) and daily episodes of urinary incontinence (baseline: 5.0 ± 0.5 vs 1.2 ± 0.4 at 6 months, $P = 0.001$) decreased significantly after the BoNT/		Significant improvement was seen in the I-QoL (baseline: 26.5 ± 2 vs 66.7 ± 6 at 6 months) and VAS scores (baseline: 3.6 ± 0 vs 7.12 ± 0 at 6 months) after BoNT/A (IQoL: $P = 0.0015$; VAS: $P = 0.0016$).	None	Maximum cystometric capacity. $P = 0.002$	270 ± 21 mL	467 ± 43 mL	8 patients out of 16 had PD and the others had SCI.

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TABLE 1 (Continued)

Reference	Type of intervention	Participant's and clinician's observations of alleviation LUTS symptoms and quantification of symptoms	Treated PD patients with measurable criteria	Quality of life	Adverse effect	Urodynamic evaluation			Comment
						Urodynamic variables	Baseline	Intervention	
		A injection.							
Jiang et al[69]		Urgency severity score in 9 PD patients was (3.71 ± 0.76) in baseline and 2.43 ± 1.27 after 3 months ($P = 0.022$); Urgency: 56.0 ± 26.4 vs 43.0 ± 16.3, $P = 0.329$; urgency urinary incontinence/3 days: 10.8 ± 16.8 vs 9.67 ± 15.0, $P = 0.749$			Acute urinary retention in 1 (11.1%); PVR > 150 mL in 3 (33.3%); Straining to void in 1 (11.3%); Hematuria in 1 (11.1%); UTI in 2 (22.2%); General weakness in 1 (11.1%)	Bladder capacity (mL) $P = 0.780$	266 ± 121	283 ± 181	They compare CNS lesion including 9 PD with control but retrospectively
						Pdet Q max (cmH2O) $P = 0.409$	26.3 ± 13.6	21.1 ± 7.34	
						Qmax (mL/s) $P = 0.872$	12.1 ± 4.81	11.6 ± 7.83	
						PVR (mL) $P = 0.048$	36.7 ± 32.4	114 ± 109	
Knuüpfer et al[67]		Post void residual bladder volume was 7 mL on average (0-35 mL).	After the treatment, all patients were able to void spontaneously.		No systemic side effects were obvious during treatment.	Maximum bladder capacity	168 mL	276 mL	
						First urge to void	109 mL	193 mL	
						Detrusor compliance	19 cm/H_20	28 cm/H_20	
Knüpfer et al[101]		All patients voided spontaneously, only 1 of 10 patients had a PVR greater than 150 mL. Bladder diary variables decreased significantly ($P \leq 0.011$) after OnabotA injection compared to variables prior injection. ICIQ scores changed from 16.63 ± 3.40 to.8.75 ± 3.99 points after treatment ($P = 0.005$). Day time frequency was decreased from 12.0 ± 3.39 times per day to 5.50 ± 3.4 and Night time frequency was decreased from 4.3 ± 2.32 times per night to 1.6 ± 0.97 ($P = 0.005$). The high pad consumption due to urinary incontinence episode (mean: 2.8 ± 2.35 per day) was decreased to 1 ± 0.94.			No urinary retention or side effects have been observed during/after treatment.	PVR (mL) ($P = 0.57$)	61.28 ± 75.91	77.0 ± 119.78	4 patients requested repeated injection after a mean period of 10 months between first and second injection.

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TABLE 1 (Continued)

Reference	Type of intervention	Participant's and clinician's observations of alleviation LUTS symptoms and quantification of symptoms	Treated PD patients with measurable criteria	Quality of life	Adverse effect	Urodynamic evaluation			Comment
						Urodynamic variables	Baseline	Intervention	
		Detrusor overactivity was observed on urodynamic in 9 patients before and in 2 patients after OnabotA-injection.							
						Maximum cystometric capacity (MCC) mL ($P = 0.005$)	196.2 ± 88.29	332.6 ± 135.45	
						Mean bladder volume (mL) in first desire to void ($P = 0.005$)	100 ± 51.51	202.38 ± 105.82	
						Mean bladder volume (mL) at strong desire to void ($P \leq 0.05$)	151.3 ± 61.41 mL to mL	271.5 ± 94.07	
						Maximum detrusor pressure in the contraction period of micturition cmH_2O ($P = 0.018$)	57.9 ± 33.1	18 ± 16.55	
						Bladder compliance [mL/ cmH_20] ($P = 0.123$)	18.65 ± 6.19	29.75 ± 28.79	
						No significant differences was found between the maximum flow rate (Qmax) before and after OnabotA injection ($P = 0.212$).			
Giannantoni et al[64]		(Daytime urinary frequency: baseline: 9.12 ± 0.3 vs 5 ± 0 at 6 months after injection, $P = 0.002$). Nighttime urinary frequency: baseline: 3.37 ± 1 vs 1.7 ± 0.4 at 6 months, $P = 0.04$; daily urinary incontinence episodes: baseline: 5.0 ± 0.5 vs 1.2 ± 0.4 at 6 months, $P = 0.001$). One and 3 months after botulinum toxin type A injection all patients reported that daytime and nighttime urinary frequency No patients had further episodes of urgency and urge urinary		Quality of life scores was improved in all patients after BTX-A injection one and 3 months (baseline: 26 ± 2 vs 66.7 ± 6 at 6 months) and VAS scores (baseline: 3.6 ± 0 vs 7.12 ± 0 at 6 months) after BoNT/A (IQoL: $P = 0.0015$; VAS: $P = 0.0016$).	None of the patients complained of systemic adverse events during or after the BoNT/A treatment.	UDC-first volume	246 ± 37 mL	?	

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TABLE 1 (Continued)

Reference	Type of intervention	Participant's and clinician's observations of alleviation LUTS symptoms and quantification of symptoms	Treated PD patients with measurable criteria	Quality of life	Adverse effect	Urodynamic evaluation			Comment
						Urodynamic variables	Baseline	Intervention	
		incontinence during the 5-month follow-up. In all patients post-void urinary residual volume increased and intermittent catheterization was required only in those with multiple system atrophy.							
						UDC-p max (cm H_2O)	21.5 ± 2	?	
						Maximum cystometric capacity mL ($P = 0.002$)	270 ± 21	467 ± 43	
						Urodynamics showed improvement in all urinary function variables tested.			
Kulaksizoglu and Parman[66]		Initial mean functional bladder capacity for the group was 198.6 ± 33.7 mL. In the third month control the mean bladder capacity increased to 319 ± 41.1 mL. The use of pads per day due to incontinence was dropped from 8-10 (mean:8.7) to 1-2 (mean: 1.6) per day at the 6 months. However, these amounts were increased to 6.6 per day for 6 patients at 12 months. On the caregivers' burden scale the baseline, the group mean was 8.75. At the 3rd and 6th months the mean value had dropped to 3.5 and 3.25, respectively. At month 9 there was a slight increase in the VAS scores to 5.2. At month 12 the mean score (8.5) reached almost the initial level.	The mean number of voiding per day was 16±8 at baseline. However 6 patients were completely incontinent and were used pad and thus the voiding frequency was missleading.	The quality of life assessment of primary caregiver as well as the patients also statistically improved after the injections ($P < 0.05$ for both).	No neurological detoriation, confusion or disorientation were noted. At the 9th month control 6 patients experienced some urgency which they could suppress and were continent, 4 patients reported occasional incontinence (once in 2–3 days) and 6 patients reported once daily or more incontinence episodes.	Mean pressure of uncontrolled bladder contraction that caused urinary leakage cmH2O	68 ± 23 (male)	40 ± 12	Medical therapy was prescribed for 12 patients and 4 asked for repeat injections.
							41 ± 19 (female)	29 ± 9	
						Mean functional bladder capacity	218.7 ± 32.1	355.1 ± 23.3 at 3 months; 399 ± 31.1 at 6	

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TABLE 1 (Continued)

Reference	Type of intervention	Participant's and clinician's observations of alleviation LUTS symptoms and quantification of symptoms	Treated PD patients with measurable criteria	Quality of life	Adverse effect	Urodynamic evaluation			Comment
						Urodynamic variables	Baseline	Intervention	
						(mL)		months; 401.4 ± 34.3 at 9 months; 295.2 ± 51.2 at 12 months	
Electrical stimulation									
El-Senousy et al[72]	PTNS	Frequency and leakage episodes have significantly decreased from a mean of 10.5 ± 2.1 and 3.5 ± 1.0 to a mean of 7.8 ± 1.2 and 2.2 ± 0.7 respectively ($P < 0.01$). Nocturia decreased from 3.4 ± 0.8 to 2.1 ± 0.8 ($P = 0.06$). Urge Incontinence was (3.52 ± 1.09) in pre- and (2.24 ± 0.7 0.04) in post-PTNS ($P = 0.04$) Nocturia decrease from (3.4 ± 0.8) in Pre-PTNS to (2.1 ± 0.8 0.06) in Post PTNS ($P = 0.06$)		IPSS and QOL were significantly better after PTNS	No serious adverse events or side effects were observed during or after treatment.	Mean 1st IDCV	150.6 ± 46.6	271.3 ± 67.3	
						MCC ($P < 0.01$)	232.9 ± 63.1	329.1 ± 65.7	
						Pdetmax, $P = 0.03$	32.03 ± 8.6	28.15 ± 5.5	
						PdetQmax and, $P = 0.06$	40.58 ± 7.9	37.39 ± 5.3	
						Qmax, $P = 0.06$	12.09 ± 2.6	13.21 ± 2.12	
Kabay et al[71]		Daytime frequency decreased by 5.6 voids daily ($P < 0.001$) urge incontinence decreased by 3.1 episodes daily ($P < 0.001$), urgency episodes decreased by 6.3 episodes daily ($P < 0.001$), nocturia decreased by 2.7 voids ($P < 0.001$), voided volume improved by a mean of 92.6 mL ($P < 0.001$). The change from baseline on the ICIQ-SF, OABv8, and OAB-q at 12-week PTNS treatment demonstrated statistically significant improvements in symptom severity Post-void residual volume (mL) was 73.7 ± 46.3 (0-213) before and 43.4 ± 22.8 (0-97) after		Significant improvements in symptom severity and health-related QoL was seen ($P < 0.001$).	No treatment-related adverse events were reported in the patients through 12 weeks.	Mean 1st IDCV on standard cystometry (mL) ($P < 0.001$)	133.2 ± 48.1 (24-265)	237.3 ± 43.1 (145-390)	

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TABLE 1 (Continued)

Reference	Type of intervention	Participant's and clinician's observations of alleviation LUTS symptoms and quantification of symptoms	Treated PD patients with measurable criteria	Quality of life	Adverse effect	Urodynamic evaluation			Comment
						Urodynamic variables	Baseline	Intervention	
		treatment, $P < 0.001$.							
						Mean MCC (mL) ($P < 0.001$)	202.2 ± 36.5 (115-320)	292.1 ± 50.6 (195-395)	
						First involuntary detrusor contraction At volume (mL) at baseline to $P < 0.001$	133.2 ± 48.1 (24-265)	237.3 ± 43.1 (145-390)	
						Pdetmax (cmH2O) $P < 0.001$	42.7 ± 19.6 (12-98)	26.8 ± 10.1 (9-51)	
						Maximum cytometric capacity At volume (mL) $P < 0.001$	202.2 ± 36.5 (115-320)	292.1 ± 50.6 (195-395)	
						Pdetmax (cmH2O) $P < 0.001$	49.7 ± 21.8 (18-95)	34.7 ± 11.5 (13-66)	
						PdetQmax $P < 0.001$	36.8 ± 11.1 (16-67)	25.9 ± 7.5 (9-43)	
						Qmax (mL/s) $P < 0.001$	2.2 ± 11.2 (5-16)	14.4 ± 4.8 (6-32)	
Kabay et al[73]						Mean 1st IDCV on standard cystometry at volume (mL) $P = 0.001$	145.2 ± 41.1 (55-265)	244.7 ± 51.7 (145-390)	
						Mean MCC at volume (mL) ($P < 0.001$)	204.8 ± 40.5 (115-320)	301.2 ± 51.5 (230-395)	
						Pdetmax (cmH2O) $P = 0.003$	40.2 ± 18.9	28.4 ± 9.7	
STN-DBS									
Herzog et al[77]						First desire to void (mL) while it decreased to in STNDBS OFF ($P < 0.01$)	In STN-DBS OFF 78.9 ± 36.6	In STN-DBS ON 140 ± 65.1	
						Bladder capacity at urge to void was mL in and increased mL ($P < 0.016$)	135.5 ± 64.6	199.5 mL ± 72.1	
Roy et al[81]						Five subjects (subjects 3-7) had increased bladder capacity with PPN DBS ON vs PPN DBS OFF, and		7 subjects with PPN DBS electrodes inserted for the control of	

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TABLE 1 (Continued)

Reference	Type of intervention	Participant's and clinician's observations of alleviation LUTS symptoms and quantification of symptoms	Treated PD patients with measurable criteria	Quality of life	Adverse effect	Urodynamic evaluation			Comment
						Urodynamic variables	Baseline	Intervention	
						statistical analysis showed that DBS significantly increased bladder capacity in this group (OFF DBS: 131 mL (range 39-230); ON DBS: 199 mL (range 103-440), $P < 0.05$, Wilcoxon test). Two subjects (subject 1 and 2) had a reduced bladder capacity with PPN DBS turned ON (OFF DBS: 137 mL (range 39-254), ON DBS: 188 mL (range 40-441), however, this change was not statistically significant due to the small group size (Figure 1). There was no effect of PPN DBS on detrusor overactivity in either group.		movement disorder (Parkinson's disease) symptoms were recruited. The effect of PPN-DBS on bladder function may vary depending on the precise location of the electrodes.
Mock et al[80]		Mean AUA-SI and OAB-q scores demonstrated no significant change postoperatively. PGI-I score was in the "minimally improved" to "no change" range in the STN target while fully in the "no change" range in the GPi target. SHIM scores had no significant changes post-surgery in either target but data trended differently in the two targets		The urologic QOL score significantly improved post DBS (3.24 ± 1.77 vs 2.52 ± 1.30; $P = 0.03$). Analyzed by target, only the STN showed significant change in QOL (vs 2.25 ± 1.33; $P = 0.04$).		There were no other significant differences in urologic scores post DBS noted in either target.		A total of 45 patients enrolled in the study but only 33 were included in the final analysis.	
Seif et al[78]						Initial desire to void (mL)	135 ± 43	199 ± 57	
						Maximal bladder capacity ($P < 0.005$)	174 ± 52	302 ± 101	
						Mean of Pdet	23 ± 10	32 ± 12 cmH_2O	
						Mean of Qmax	11 ± 5 mL/s	13 ± 5 mL/s	
						Residual Urine	114 ± 37 mL	71 ± 33 mL	
						Compliance of the bladder (cm H2O) was decreased			
Witte et al[82]		Urinary incontinence and frequency improved after both GPi DBS and STN DBS at 12 months, postoperatively, but this was only statistically significant for the STN DBS group ($P = 0.004$). The		Within group differences for gender indicated significant improvement of PDQL-28 scores 12 months after surgery in both men ($P = 0.01$) and women ($P = 0.05$).		Nocturia and urinary incontinence did not improve significantly after any type of DBS, irrespective of sex.			

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TABLE 1 (Continued)

Reference	Type of intervention	Participant's and clinician's observations of alleviation LUTS symptoms and quantification of symptoms	Treated PD patients with measurable criteria	Quality of life	Adverse effect	Urodynamic evaluation			Comment
						Urodynamic variables	Baseline	Intervention	
		improvements after DBS were present in both men ($P = 0.01$) and women ($P = 0.05$). Within group differences for nocturia (PDSS-8) and urinary incontinence due to parkinsonism (PDSS-9) did not improve significantly after 12 months for any type of DBS.No statistically significant differences were found between GPi DBS and STN DBS and between men and women.At 12 months, none of the patients had a Foley-catheter.							
Brandi et al[87]		The results present a significant improvement in urinary symptoms after the treatment with EP, with 71% of bowel continence and 86% of patients presenting type III Bristol stool Score.				Urodynamic parameters had an increase of maximum cystometric capacity at 57% of patients and reduce the residue in 60%.		A total of 7 patients participated in the study. It was a congress	
Peters et al[76]		Urinary frequency was improved 1 time/d in NDs patients (11.6 ± 4.1 pre-implantation vs 10.6 ± 2.8 for 24 months later $P = 0.0154$). Voiding diary variables (except for incontinence episodes (6.7 ± 5.3 vs 5.5 ± 4.8, $P = 0.0657$) and severity (4.1 ± 2.3 vs 5.0 ± 5.7, $P = 0.2165$) in the ND group), were improved significantly in patients with an implantable pulse generator: Urinary urgency (4.5 ± 2.9 (4.6); 35 pre-implantation vs 3.1 ± 1.9 for 24 months later $P = 0.0278$).	The ICSI-PI (23.2 ± 7.0 in pre implantation vs 14.4 ± 7.8 in 24 months later $P < 0.0001$) and OAB-q symptom severity (68 ± 24 vs 34 ± 16, $P < 0.0001$ pre implantation and 24 months later, respectively) over time were improved significantly. However, the SF-12 PCS (31 ± 11 vs 30 ± 12, $P = 0.4475$ pre implantation and 24 months later, respectively) and MCS scores (45 ± 11 vs 50 ± 13, $P = 0.6168$ pre-implantation and 24 months later, respectively) were not improved in patients with neurologic disease	HRQOL measures were 43 ± 23 vs 73 ± 21 $p \leq 0.0001$ pre implantation and 24 months later, respectively) over time improved significantly					This is an observational prospective and not trial. Only 10 patients out of 340 had PD and the results are not shown separately.
Krivoborodov et al[75]		Decrease in the average voiding frequency, number of leakage episodes after 12 sessions and 6 months							

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TABLE 1 (Continued)

Reference	Type of intervention	Participant's and clinician's observations of alleviation LUTS symptoms and quantification of symptoms	Treated PD patients with measurable criteria	Quality of life	Adverse effect	Urodynamic evaluation			Comment
						Urodynamic variables	Baseline	Intervention	
Ohannessian et al[70]						The maximum cystometric capacity (mL) ($P = 0.6$)	211 ± 106	260 mL ± 226	
Crescenze et al[86]		The mean number of voids decreased from 10.7 ± 2.7 to 8.0 ± 4.7 ($P = 0.259$) and number of pads from 4.1 ± 4.2 to 1.7 ± 2.3 ($P = 0.166$). The patient with retention reported decreased need for self-catheterization from five times per day to two. Three of the eight patients reported continued subjective benefits from the SNM therapy at 8-18 months after implantation.		Ten patients with PD who underwent a trial of SNM at a single center from 2009 to 2015–nine for refractory urgency and frequency or urgency incontinence and one for urinary retention and urgency.		Volumes at first desire to void (mL)	102.5 (47.0-150.0)	135.0 (70.0-180.0)	
						Volumes at strong desire and (mL) $P = 0.69$	150.0 (49.0-400.0)	185.0 (150.0-300.0)	
						Volumes at urgency (mL). $P = 0.96$	200.0 (85.0-500.0)	285.0 (200.0-650.0)	
						Maximum cystometric capacity $P = 0.86$	260.0 (88.0-500.0	235.0 (200.0-650.0)	
						Bladder compliance (mL/cmH_2O) $P = 0.94$	6.7 (−166.6 to 33.3)	8.3 (−55.0 to 66.6)	
						Detrusor overactivity amplitude (cmH_2O) $P = 0.43$	28.0 (5.0-109.0)	37.0 (7.0-61.0)	
						Maximum flow rate (mL/s) $P = 0.65$	8.0 (4.0-26.0)	8.5 (4.0-24.0)	
						Detrusor pressure at maximum flow rate (cmH_2O) $P = 0.87$	39.5 (4.0-78.0)	37.0 (7.0-110.0)	
						Postvoid residual volume $P = 0.6$	72.5 (56.0-120.0)	36.5 (7.0-161.0)	
Perissinotto et al[74]		Urge urinary incontinence was reported in 6 cases before and 4 cases after treatment in GroupI and 3 patients before and after treatment in GII. One patient	Cumulative OAB-V8 and ICIQ-SF Questionnaires Scores Before and After Treatment results showed that there are no significant differences in two group						Ten out of 23 patients in this randomized trial did not complete the study, due to difficulty in attending twice weekly that

(Continues)

TABLE 1 (Continued)

Reference	Type of intervention	Participant's and clinician's observations of alleviation LUTS symptoms and quantification of symptoms	Treated PD patients with measurable criteria	Quality of life	Adverse effect	Urodynamic evaluation			Comment
						Urodynamic variables	Baseline	Intervention	
		had Hesitancy before TTNS that disappear after treatment and 2 patients in sham group had this symptom without change after sham treatment. No statistically significant differences were found between two groups in the numbers of nocturia (4.0 (2.0-6.0) and 2.0 (0.0-12.0) before and after treatment in active TTNS group versus 4.4 (0.0-5.0) and 4.0 (0.0-5.0) in sham group), $P = 0.82$	before and after treatment (OAB-V8 score was 18.0 (6.0-27.0) before and 16.0 (6.0-25.0) after treatment in Group I, $P = 0.10$ and for ICIQ-SF these amounts were 70.0 (0.0-18) and 4.0 (0.0-16.0) for active TTNS group, $P = 0.09$). But when OAB-V8 and ICIQ-SF scores were compared at baseline and following treatment in TTNS group the differences was significant ($P < 0.03$ and $P < 0.01$, respectively), but in contrast, no differences were found in sham group when compared at baseline and following treatment ($P = 0.508$). 3-Day bladder diary assessment revealed that Frequency was seen in 6 and 2 patients, and urgency in 8 and 1 patients in Group I and 5 patients before and after treatment in Sham group respectively ($P < 0.04$).						may have influenced study findings
Porter and Bors[79]	Thalamotomy	From 17 cases with hyperactive dysfunction, in 13 cases residuum amounts decreased, in 3 cases unchanged and in 1 increased. From 13 cases with hypoactive dysfunction, in 11 cases residuum amounts decreased, and in 2 cases did not change. In a total of 10 patients with normal bladder function, residuum in 9 cases remained unchanged and increased in 1 patient. Bladder response improved in 5 cases of hyperactive bladder and in 6 patients with hypoactive bladder. However only in 1 patient with hyperactive bladder the bladder response aggravated.							

(Continues)

TABLE 1 (Continued)

Reference	Type of intervention	Participant's and clinician's observations of alleviation LUTS symptoms and quantification of symptoms	Treated PD patients with measurable criteria	Quality of life	Adverse effect	Urodynamic evaluation			Comment
						Urodynamic variables	Baseline	Intervention	
Combined therapy									
Chen et al[89]	Combined acupuncture and medication (Tolterodine)	Frequency of average urination of 24 h, frequency of incontinence of 24 h and average urine volume at a time were obviously improved (all $P < 0.01$), of which, the above items in group A (combined acupuncture and medication group) were superior to those in group B (medication group) (all $P < 0.05$)			The adverse reactions in group A were less than those in group B.				
Winge and Nielsen[102]	(Oral Medication with or without DBS or apomorphine pumps)	Bladder symptom severity correlated to the stage of disease (conventional treatment: $r = 0.364$, $P = 0.004$, apomorphine: $r = 0.73$, $P = 0.02$), there was an exception for patients who were treated with DBS. In these patient's symptom severity was correlated to DBS duration ($r = 0.34$, $P = 0.038$). In DBS treatment group, significant reduction in nocturia was reported in comparing to other groups (47% compared to 88% in conventional therapy and 66% in apomorphine pump-treated ($P = 0.007$). Symptom prevalence (DanPSS1-4 and individual symptoms assessed by either DanPSS or IPSS) was detectable among the treatment groups. Measurements of PMV revealed no differences between the treatment groups		All patients expressed satisfaction in quality of life. IPSS-QoL did not differ between the groups, but it correlated to age ($r = 0.32$, $P = 0.016$) and to disease stage ($r = 0.32$, $P = 0.013$) in the oral medication group. DBS patients significantly less bothered by nocturia ($P = 0.01$) compared to the other treatment groups, as assessed by DanPSS questionnaire.					

We described all studies results and conclusion in this part:

- Conservative management
  Only two pilot studies were conducted in the field of behavioral therapy. Pelvic floor muscle exercises using computer-assisted EMG biofeedback for 8 weeks, and bladder control strategies, significantly improved UI, nocturia, OAB symptoms, and QOL.[62,90] Uncontrolled pilot studies of behavioral intervention on older PD patients demonstrated statistically significant and clinically meaningful improvement of frequency of UI and QOL. The first study was assessed as high risk of bias and the second was unclear. Behavioral therapy is an effective management of PD-induced NGB without any side events. However, due to the lack of high quality evidences, conducting well-designed randomized controlled trials is recommended.
- Medical management
  1. Antimuscarinic drugs
     Pharmacologic interventions especially anticholinergic medications are the first-line option for treating NGB, reduces reflex (involuntary) detrusor contraction by blocking cholinergic transmission at muscarinic receptors. Nonselective anticholinergic agents include oxybutynin, tolterodine, and trospium chloride were the most antimuscarinic drugs that were prescribed for PD patients with LUTS. More selective for M2 and M3 receptors anticholinergic drug with fewer cognitive side effects than nonselective agent is solifenacin that showed an improvement in urinary incontinence, despite persistence in other OAB symptoms and some type of adverse events including constipation and xerostomia, which resolved after treatment discontinuation. The most anticholinergic drug that was evaluated on urinary function of PD patients was tolterodine. The dose of 4 mg/day of this anticholinergic agent with predominantly peripheral nonselective antimuscarinic activity[93] or in combination with dopamine regimen[99] leads to increment the bladder capacity, maximum cystometric capacity, and bladder compliance. Beside it amplitude of detrusor overactivity, overactive bladder symptom score, International Consultation on Incontinence Questionnaire–Short Form score, number of voids, urgency episodes and amount of leaks (per 24 h and nighttime), and amount of mean and maximum voided volumes all decreased significantly after treatment.[93] However, DIC amplitude, detrusor overactivity, mean post-voiding residue (PVR), maximum flow rate, and Pdetmax flow did not change in combination therapy method. Also 20% of PD patients abandon the protocol due to constipation, dizziness/headache and no clinical improvement.[99] The other antimuscarinic drugs, that is, oxybutynin (5 mg/day), trospium chloride (30 mg/day) and antiparkinsonian therapy for 2 months, beside tolterodine (4 mg/day), reduced voiding disorders and unstable contractions of the urinary bladder and increased cystometric capacity and QOL.[91] The high dose of oxybutynin like tolterodine had no serious adverse events in Bennett study[97] and improved episodes of frequency, nocturia, and incontinence. However, the residual urine remained unchanged after 12 weeks. Although we should have considered that only 7 patients out of 39 in this study had PD but results are not shown separately.
     Solifenacin succinate (5-10 mg daily) in 23 PD patients for 12 weeks had no significant improvement in the primary outcome measure in the double-blind phase, but there was an improvement in the number of micturition per 24 h period comparing to placebo at a mean dose of 6 mg/day ($P = 0.01$). In the open label phase, the mean number of UI episodes per 24 h period decreased ($P = 0.03$), as did the number of nocturia episodes per 24 h period ($P = 0.01$).[88]
     Tolterodine, oxybutynin, trospium chloride,[96] and Solifenacin succinate were the most antimuscarinic agents that were prescribed for PD patients with LUTS. Solifenacin succinate showed an improvement in urinary incontinence, despite persistence in other OAB symptoms and some type of adverse events including constipation and xerostomia, which resolved after treatment discontinuation. Tolterodine was the most effective management regimen with the less adverse events and well tolerated for the treatment of NDO in PD patients. Among the different anticholinergic agents as the first-line option for treating NGB, the only well designed randomized clinical trial belonged to solifenacin succinate with improvement of urinary incontinence, despite persistence in other OAB symptoms and some type of adverse events.
     However, the other well designed controlled clinical trial with a large sample size and longer follow up period is recommended for these agents.
  2. N-methyl-D-aspartate (NMDA) antagonist
     Daily 150 and 300 mg amantadine administration (by augmentation the effects of dopamine) for 1 month, decreased the urinary frequency, urgency, urge incontinence and mean feeling of incomplete emptying per week ($P = 0.049$). It ameliorated LUTS in PD patients and also storage as well as voiding symptom. PVR was decreased but not significantly in two different doses of it. No patient had side effects in 150 mg administration but hallucination, and flashing sensation developed in three patients with 300 mg daily dose.[100]
     Hence, dopamine agonists including amantadine, in a low dose of 150 mg without any systemic side events,

ameliorated LUTS and nocturnal polyuria in PD patients. Whereas, 300 mg of this agent had side effects.

3. Desmopressin
   Intranasal desmopressin (a synthetic analogue of 8-arginine vasopressin (ADH)) administration in five PD out of eight PD patients, that completed the trial decreased the nocturia. The side events include hyponatremia, confusion, and compliance problems.[92] It appears that desmopressin to be an effective medication for nocturnal polyuria in PD patients despite having some side events that lead to the cessation of three out of eight participants' consumption in the small trial.
4. Adrenergic agonists
   Mirabegron (agonist of β3-adrenoceptors) improved OAB symptoms, and increased the VAS score. Also urgency and urge urinary incontinence were decreased. But abandon by 30% of patients due to poor efficacy and cost of drug, while about 70% of PD patients continued to assume Mirabegron at the 6-month follow-up with no substantial side effects.[85] The first observation on the efficacy and tolerability of Mirabegron in PD patients with refractory OAB showed that, this drug due mainly to tolerability issues, can be considered the more relevant aspect of this kind of treatment in patients with PD and OAB.
   Among variety of medication side events, CNS effects is one of the important category of antimuscarinic adverse events. Patients with cognitive impairment are more susceptible to CNS events and to further cognitive decline. Palleschi reported 3 patients out of 40 (7.5%) developed dizziness/headache after tolterodine administration[100] and in Bennett study, the patients reported no new subjective CNS side effects after treatment with oxybutynin.[97] In the others, the authors did not mention any cognitive impairment in relation to this medication.
   Nausea, drowsiness, and yawning were reported mild in apomorphine and L-Dopa therapy.[94] And daily administration of 300 mg amantadine exacerbated the CNS symptoms of patients: one patient with mild cognitive dysfunction developed exacerbation of hallucination and two patients developed flashing sensation.[100] The other authors did not state the CNS side events in their studies.
   β3-adrenoceptors agonist (mirabegron) is a more expensive agent with more effectiveness, well tolerable and fewer side effects in improving the refractory OAB symptoms, despite the poor efficacy in some PD patients and cost of this agent. But, it can be considered the more relevant aspect of this kind of treatment in patients with PD and OAB.

- Botulinum toxin injection

Low-dose (100 U) of onabotulinumtoxinA (onabotA) with no systemic or CNS adverse events at the 6-month follow-up[65,102] decreased the mean incontinence (at least 50%),[63,65,69] daytime and nighttime urinary frequency episodes per day at 1 and 6 months, improved AUA symptom score and PVR.[63,65] In the third month, the mean voided volume according to 3-day voiding diaries ($P = 0.02$) was increased; a decrease in peak flow and increase in PVR during months 1 and 3 follow-up but returned to similar baseline levels by month 6[63]; urgency severity score was improved 3 months after treatment[69] and I-QoL at 6 months, VAS scores and MCC improved at 6 months after treatment.[65] However, urge UI per 3 days, cystometric bladder capacity, Pdet Qmax, and Qmax in PD patients did not change.[69]

No episodes of urinary retention requiring catheterization occurred[63,101]; although significantly increased PVR (partial retention) occurred in three men at the 1-month follow-up (310 mL average). No patient required intermittent catheterization; whereas, 2 men were given an alpha-blocking agent (tamsulosin 0.4 mg).[63]

The higher dose of OnabotA injection (200 IU) into detrusor muscle like the effect of low dose from this neurotoxin, improved quality of life scores, decreased daytime and nighttime urinary frequency[64] and improved the bladder diary variables ($P \leq 0.01$). Desire to void and maximum bladder capacity increased significantly in urodynamic ($P \leq 0.05$). Maximum detrusor pressure during voiding phase normalized. Detrusor over activity was less often detectable. Also ICIQ and pad consumption ($P \leq 0.05$) decreased significantly ($P = 0.005$). Mean MCC increased ($P = 0.005$), bladder compliance ($P = 0.123$), and maximum flow rate (0.212) did not change significantly.[68] No urinary retention or systemic side effects have been observed during/after treatment.[64,68] Although PVR increased postoperatively and intermittent catheterization was required only in those with multiple system atrophy.[64]

The highest dose of botulinum toxin-A (500 IU) decreased the mean pressure of uncontrolled bladder contraction at the third month in females and no leakage was noted even with uncontrolled contractions. Overall voiding frequency improved in all patients. Number of incontinence episodes in those who did not use diapers dropped at the third month and was found acceptable by their caregivers. At the sixth month, the number of incontinence episodes was similar to those at the third month. At month 12, the mean score reached almost the baseline level. The mean bladder capacity had increased at 3, 6, 9, and 12 months, respectively ($P < 0.05$ for all time points).[66]

Botulinum toxin by blocking the neuromuscular junction presynaptic vesicle fusion prevents acetylcholine release and blocks signal transmission across the neuromuscular junction. Moreover, it prevents the excitatory effects of

nerve growth factor (NGF) on bladder function. Injection of botulinum toxin A into the detrusor with different doses of 100, 200, or 500 IU weak it. One of the beneficial effects is its long-lasting nature and in low doses, it had no urinary retention or systemic side effects during/after treatment. Although, PVR increased postoperatively and intermittent catheterization was required only in those with multiple system atrophy.

These encouraging results in a small study sample should prompt further studies in a larger population. In general, the possibility of longstanding urinary retention and chronic catheterization need careful evaluation of these very vulnerable population before choosing intravesical onabotA treatment. However, all research in this field were assessed as high risk of bias due to the nature of these studies that had no control arm.

- Electrical stimulation
  1. PTNS

     Frequency and leakage episodes, meanwhile nocturia and urge incontinence[71,72,75] decreased and IPSS and QOL,[72] ICIQ-SF, OABv8, and OAB-q[75] were significantly improved after PTNS. Urodynamic parameters significantly improved. Mean first IDCV and MCC ($P = 0.001$),[72,73] significantly increased after PTNS and Pdetmax, Qmax, and PVR were decreased significantly.[72,73,75] No serious adverse events or side effects were observed during or after treatment.[72]
  2. STN-DBS

     DBS lead to increment of bladder capacity[77,78,81] and improvement of urological QOL. However, when analyzed by target, only the STN showed significant change in QOL ($P = 0.04$). There were no other significant differences in urologic scores post DBS noted in either target.[80] Significant changes in first desire to void and urge to void were occurred post STN-DBS,[77,78,87] whereas Pdet and Qmax were not found to differ significantly.[78] PVR decreased in 60% of patients in one,[87] but did not differ in the others.[78]

     UI and frequency improved after both GPi-DBS and STN-DBS at 12 months, postoperatively, but this was only statistically significant for the STN-DBS group ($P = 0.004$). The improvements after DBS were present in both men and women. Nocturia and UI did not improve significantly after any type of DBS, irrespective of sex. At 12 months, none of the patients had a Foley-catheter and PDQL-28 improved in STN group ($P = 0.004$).[82]
  3. Neuromodulation

     In a prospective study staged neuromodulation on neurogenic patients and among them on 10 PD patients, urinary frequency, urgency ($P = 0.0278$), voiding diary variables (except for incontinence episodes and severity, $P > 0.05$), before and after treatment in both neurogenic and non-neurologic patients were improved, however, the SF-12 MCS scores were approximately 8-10 points lower in the progressive neurologic group at baseline ($P = 0.018$) and at 3 months ($P = 0.033$). Over time, small, but statistically insignificant, improvements were seen in both groups for voiding frequency, daily incontinence episodes, incontinence severity, urgency, and SF-12 MCS scores.

     An insignificant decline in the SF-12 PCS scores was noted in the progressive group. However, in comparison of the non-neurogenic and neurogenic groups, both the progressive and the non- progressive groups demonstrated statistically and likely clinically significant improvements within 2 years on the ICSI-PI ($P = 0.0006$ and $P < 0.0001$), OAB-q symptom severity ($P = 0.0136$ and $P = 0.0006$), and HRQOL measures ($P = 0.0014$ and $P = 0.0024$), respectively. HRQOL measures were improved significantly after neuromodulation ($P < 0.0001$).[76]

     Tibial nerve stimulation (TNS), reduced the average voiding frequency, number of leakage episodes after 12 sessions and 6 months,[75] the number of urgency, and nocturia episodes when compared with the baseline ($P < 0.01$); however, there was no statistically significant differences were found when the number of episodes of nocturia was compared between the sham group and the active treatment group ($P = 0.88$). Also, OAB-V8 and ICIQ-SF scores were improved ($P < 0.01$). Intravesical volume at strong desire to void ($P < 0.05$) and volume at urgency ($P < 0.01$) were increased.[74] But in other study on six PD or MSA patients did not show significant difference in urodynamic parameters and symptoms of disease.[70] However, an over 50% symptomatic improvement was achieved in 26 of 29 patients including 6 patients who were refractory to anticholinergic agents and nine men with benign prostatic hyperplasia.[75] We should have considered that 10 out of 23 patients in this randomized trial did not complete the study, due to difficulty in attending twice weekly that may have influenced study findings.[74]

     At least a 50% improvement in the symptoms with stage I or PNE were seen. The mean number of voids ($P = 0.259$) and number of pads decreased ($P = 0.166$). The need for self-catheterization was decreased.[86]

     Although the majority of studies in the field of electrostimulation on management of urinary dysfunction in PD patients emphasizes on its positive effects, additional placebo controlled works enrolling more patients are required to ensure these preliminary results. The only randomized clinical trial with 128 patients in this field conducted without control group showed improvement in UI and frequency, without any change in nocturia and nighttime incontinence.

Only two of electrostimulation studies were randomized clinical trial and one study was non-blind clinical trial. The Witte study[82] was assessed as unclear risk except attrition low risk of bias. The randomized clinical trial study of Perissinotto[74] was assessed as low risk of bias in selection, performance and reporting bias and high in detection and attrition.

PTNS was the most effective intervention with no serious adverse events. And then, TNS and DBS were in the next ranks. Although the majority of studies in the field of electrostimulation on the management of urinary dysfunction in PD patients emphasizes on its positive effects, additional placebo-controlled works enrolling more patients are required to ensure these preliminary results.

- Combined therapy

Combined Baihui (GV 20), Sishengcong (EXHN1), and Yintang (EXHN3) were punctured with electro acupuncture, once a day and 1 mg, twice a day tolterodine in comparing only 2 mg/twice a day of tolterodine improved the frequency of average urination of 24 h, frequency of incontinence of 24 h, and average urine volume at a time urination (in all $P < 0.01$) and UPDRS III scores ($P < 0.05$). These results were investigated in both group. However, they were superior in combined therapy and also the adverse events were less reported in this group.[89]

Bladder symptom severity correlated to the stage of disease (conventional treatment $P = 0.004$, apomorphine $P = 0.02$), there was an exception for patients who were treated with DBS. In these patient's symptom severity was correlated to DBS duration ($P = 0.038$). In DBS treatment group, significant reduction in nocturia was reported in comparing to other groups ($P = 0.007$) and were significantly less bothered by nocturia ($P = 0.01$). IPSS and IPSSQoL scores did not significantly differ between treatment groups.[102] In the clinical study by Chen,[89] the patients were randomized assigned in two intervention group (combined acupuncture and medication group [group A] and a medication group [group B], 30 cases in each group). This study had no control arm, thus well designed RCT is recommended to evaluate the effect of combined therapy. And the other study by Winge was a cohort one.[102]

The other less common management methods are shown in Appendix S2.

4.2 | Overall completeness and applicability of evidence

The current evidence is very limited in terms of size and applicability.

4.3 | Quality of the evidence

The included studies had some limitations which require consideration. First, only two randomized control trials were detected. One of them was in the field of electrostimulation (TTNS)[74] and the other was about antimuscarinic therapy.[88] There were other two randomized clinical trial that had no control arm.[80,82] Only Zesiewicz and Perissinotto described the method used to generate the allocation sequence and whether the method of allocation was concealed or not. The study of Witte do not describe the method of randomization and their study's had not control arm and the study of Mock were non-blind randomized clinical trial. Second, in Perissinotto study,[74] almost 50% of the trial patients discontinued the trial, and the trial authors excluded all of them from the data analysis. All of the above mentioned limitations may affect the quality of the evidence.

Considering the low quality of evidences, we should have assumed that the majority of PD patients were elderly and one of the limitation of RCT conducting is that the old patients cannot include in this type of studies that responsible to the lack of enough RCTs. The other possible cause is the less common prevalence of PD comparing to other neurological conditions, for example, spinal cord injury that may be responsible to small sample size of included studies.

4.4 | Potential biases in the review process

We undertook an extensive and comprehensive literature search to minimize bias in the review process of RCT to meet our inclusion criteria. After that we searched via databases for other quasi-randomized trials or observational trials. In the preparation of this review, two review authors independently read and screened studies for inclusion, independently completed data extraction and assessed the quality of included trials to minimize potential biases. We will include any data we receive in an update of this review.

4.5 | Agreements and disagreements with other studies or reviews

To our knowledge, treatment methods for LUTS in patients with PD have not been systematically reviewed previously.

5 | CONCLUSIONS

In our systematic review, we find that non-pharmacologic interventions including behavioral therapy is an effective management method for PD induced NGB without any side events. Tolterodine was the most effective medications with the less adverse events and well tolerated for the treatment of NDO in PD patients. Also, among the different

anticholinergic agents as the first-line option for treating NGB, the only well designed randomized clinical trial belonged to solifenacin succinate with improvement of urinary incontinence, despite persistence in other OAB symptoms and some type of adverse events.

Dopamine agonists including amantadine, in a low dose of 150 mg without any systemic side events, ameliorated LUTS and nocturnal polyuria in PD patients. Whereas, 300 mg of this agent had side effects. Desmopressin was an effective medication for nocturnal polyuria in PD patients. despite having some side events that lead to the cessation of its consumption in 37% of patients in the small trial. β3-adrenoceptors agonist (mirabegron) is a more expensive agent with more effectiveness, well tolerable and fewer side effects in improving the refractory OAB symptoms, despite the poor efficacy in some PD patients and cost of this agent. But, it can be considered the more relevant aspect of this kind of treatment in patients with PD and OAB. Injection of botulinum toxin A into the bladder detrusor with different doses of 100, 200, or 500 IU weak the detrusor muscles. One of its beneficial effects, is long-lasting nature and in low doses, it had no urinary retention or systemic side effects during/after treatment. Although, PVR increased postoperatively and intermittent catheterization was required only in those with multiple system atrophy. These encouraging results in a small study sample should prompt further studies in a larger population. When non-pharmacologic and pharmacologic treatments fail to control NGB, surgical options including neuromodulation are appropriate treatment methods. PTNS was the most effective intervention with no serious adverse events. And then, TNS and DBS were in the next ranks. Although the majority of studies in the field of electrostimulation on the management of urinary dysfunction in PD patients emphasizes on its positive effects, additional placebo-controlled works enrolling more patients are required to ensure these preliminary results. Although several interventions are available for treatment NGB in patients with PD, at present there is little or no evidence that treatment improves patient outcomes in this population. The majority of the included studies in this field were assessed as high risk of bias with small sample size and had no control arm. Additional large, well designed, randomized controlled studies with improved methodology and reporting focused on patient-centered outcomes are needed.

5.1 | Implications for practice

The evidence base on the treatment methods for LUTS in patients with PD is limited by a risk of bias, small sample sizes, and lack of enough well-designed eligible trials.

5.2 | Implications for research

Future well-designed RCTs with larger sample sizes are needed to assess the effect of treatment methods for LUTS in PD.

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AUTHORS' CONTRIBUTIONS

CRC and SH aimed in hypothesis development and designed the search question. FP conducted the search strategy. HS extracted the data and wrote the first draft of the manuscript. SH and HS critical appraised the selected articles. CRC and SH critically reviewed and edited the manuscript and all authors approved the final version for submission.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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