

SUPPLEMENTARY DIGITAL MATERIAL 1

Supplementary Table I.—Characteristics and outcomes of studies included in the systematic review.

Authors Years	Study design; Evidence levels	Characteristics of patients	Symptoms	Diagnostic tools	Therapeutic approaches	Duration of treatment	Follow up	Results	Risk of bias
Canbaz 2017	Retrospective study; Level 2	21 pt, 5 males and 16 female pt; 42.7±6.9 y	Urge incontinence, urgency, and frequency	Frequency, nocturia, urgency, urge incontinence, voided volume. OAB-q, OAB-V8, ICIQ-SF	Percutaneous Posterior Tibial Nerve Stimulation (PTNS)	12 consecutive weekly sessions	3-6-9 and 12 months	Frequency, incontinence, urgency episodes, and nocturia decreased daily. Voided volume improved	High risk
De Seze 2011	Prospective study; Level 2	70 patients, 51 women and 19 men 48.3±10.2 y	Symptoms of an overactive bladder	QOL, urgency, frequency, maximum cystometric capacity,	Transcutaneous posterior tibial nerve stimulation (PTNS)	Daily sessions of 20 min	3 months	Clinical improvement of symptoms of the patients	Low risk

				reflex volume					
Engeler 2015	Prospective study; Level 2	17 pt, 13 female pt, 4 male pt. 46.2 (range 16.9-74.6 y)	Refractory neurogenic lower urinary tract dysfunction	Voided volume, post void residual, frequency, incontinence	Sacral neuromodulation	Implantation of neuromodulator	Assessment after 6 months and then each year. 24 months, 6 years	Chronic sacral neuromodulation is effective and safe	Unclear risk
Ferreira 2019	Clinical trial; Level 1	Group A: 15 females pt, 38.6 ± 13.5 y Group B: 15 females pt, 49.8 ± 16.5 y	Urinary incontinence	EDSS, perineal sensitivity; OAB-q, Cutaneous anal reflex; Genital dystopia; voluntary contraction; Stress test with loss of urine,	Group A: Traditional exercises + intravaginal electrostimulation Group B: Traditional exercises	Twice a week for 6 months	6 months	Rehabilitation plus electrostimulation engendered better results than exercise alone	Low risk

				Qualiveen questionnaire ; PERFECT					
Fjorback 2007	Prospective study; Level 2	12 pt, 7 men, 5 females pt 46 y (range: 32–63 y)	Symptoms of Detrusor Overactivity	Bladder volume at first contraction and maximum detrusor pressure	Posterior Tibial Nerve Stimulation (PTNS)	Acute assessment	Acute assessment	Electrical stimulation of posterior tibial nerve has no acute effects.	Low risk
Gobbi 2011	Prospective study; Level 2	18 pt, 2 male, 16 female pt 46,6±13 y	Symptoms of detrusor overactivity , dyssynergia	EDSS, frequency, nocturia, urgency, voided volume, residual, QoL, VAS	Percutaneous posterior tibial nerve Stimulation (PTNS)	30 min, once a week for 12 sessions	3 months	PTNS is effective, safe and well-tolerated	Low risk
Kabay, 2008	Prospective study; Level 2	29 pt, 12 male, 17 female pt 46.5±8.5 y	Urge incontinence, urgency,	EDSS, cystometry capacity	Percutaneous posterior tibial nerve	-	-	PTNS is effective to suppress detrusor	Low risk

			and frequency		stimulation (PTNS)			overactivity in MS patients	
Kabay 2009	Prospective study; Levels 2	19 pt, 6 male, 13 female pt 44.9 ± 8,3 y	Symptoms of neurogenic detrusor overactivity	Voided volume, detrusor contraction, pressure and capacity, maximal flow rate	Percutaneous Posterior Tibial Nerve Stimulation (PTNS)	30 min once a week for 3 months	3 months	PTNS results in prominent improvements on the clinical and urodynamic outcome	Low risk
Khan 2010	Clinical trials; Levels 1	58 pt Group A: 24 pt Group B 34 Control 49.9 ± 8.6 y	Detrusor overactivity, sphincter dyssynergia, poor bladder compliance, urinary retention	EDSS, IIQ, QOL	Treatment group received personalized, multidisciplinary rehabilitation program. Control group maintenance program only	2-3 session/week for 6 weeks. Continue with maintenance program for 12 months	12 months	The treatment group compared with the control group showed improvement in IIQ	Low risk
Lucio 2010	Clinical trials; Levels 1	27 pt, Group A 13 pt	Frequency, urgency, urge	PERFECT, EDSS, capacity,	Pelvic Floor Muscle	Twice a week for 12 weeks	3 months	PFMT is an effective approach	Low risk

		Control group 14 pt 34.7±8.8 y	urinary incontinence, nocturnal enuresis, nocturia, hesitancy, slow stream, incomplete emptying	compliance, maximal flow rate, frequency, voided volume	Training (PFMT)				
Lucio 2011	Clinical trial; Levels 1	Group A: 18 female pt Group B: 17 female controls 35 y (range 20-49 y)	Overactive bladder symptoms	ICIQ-SF, QoL, EDSS, OAB-V8, PERFECT	Pelvic floor muscle training (PFMT) with home exercises, <i>versus</i> perineometer inside the vagina with no exercise.	Twice / week for 30 min for 12 weeks	3 months	There was improvement in the QoL and reduction of overactive bladder symptoms for women who did the PFMT.	Low risk
Lucio 2014	Clinical trial; Levels 1	30 pt Group A: 10 Group B: 10 Group C: 10	Lower urinary tract symptoms	PFM function, PFM tone, FSFI	Group A: PFMT+ EMG biofeedback Group B:	30 min of treatment sessions twice per week	3 months	PFMT alone or in combination with NMES or TTNS	Low risk

		45.5 y (range 27-54 y)		questionnaire , PERFECT; EDSS, VAS	PFMT+ EMG biofeedback and NMES Group C: PFMT+EMG biofeedback+ PTNS			contributes to the improvement of arousal, lubrication, satisfaction and improves the score of FSFI	
Lucio 2016	Clinical trial; Level 1	30 female pt Group A: 10 Group B: 10 Group C: 10 43.5 y (range 42-52 y)	Lower urinary tract symptoms	24-hour pad test, 3-day bladder diary, strength and muscle tone, urodynamic studies, EDSS, OAB-V8, ICIQ-SF, Qualiveen instrument	Group A: PFMT + EMG biofeedback + NMES Group B: PFMT + EMG biofeedback +NMES Group C: PFMT + EMG biofeedback + PTNS	50-minute treatment sessions twice per week	3 months	PFMT alone or in combination with NMES or TTNS is effective	Low risk
McClurg 2006	Clinical trial; Levels 2)	30 female pt 50,5 y (range 33-67 y)	Urinary symptoms	EMG, 3-day Voiding Diary, 24-	Group 1: PFTA	Stimulation at clinic	0, 9 weeks;	Group 3 demonstrated superior benefit	Low risk

				hour Pad-Test, Uroflowmetry, IIQ, UDI, KHQ, MSQoL54	Group 2: PFTA+EMG Biofeedback; Group 3: PFTA +EMG Biofeedback +NMES	(weekly) was initially for 5 min, increasing to a maximum of 30 min for 9 weeks	4, 6 months	in the number of leaks and pad test than Group 2, with Group 1 showing less improvement when compared to week 0	
McClurg, Ashe 2008	Clinical trial; Levels 1	74 pt, Group A 37 pt, 26 female, 11 male Group B 37 pt, 31 female, 6 male pt	Symptoms of lower urinary tract dysfunction	Incontinence Impact Questionnaire, Urinary distress inventory, he International Prostate Symptom Score, VAS, Multiple Sclerosis Impact Scale, Barthel index	Neuromuscular Electrical Stimulation	9 weeks	0, 9 weeks; 4, 6 months	Active Neuromuscular Electrical Stimulation, Pelvic Floor Muscle Training and EMG Biofeedback could alleviate symptoms of lower urinary tract Dysfunction in MS	Low risk

McClurg, Lowe-Stronge 2008	Clinical trial; Levels 1	37 pt, 11 male, 26 female pt 52.0±8.8 y	Lower urinary tract dysfunction	Bladder diary, pad test, uroflowmetry, International Prostate Symptom Score; VAS	PFMT and EMG biofeedback	9 weeks	9, 16, 24 weeks	9-week PFMT program improved the function of PFM, reduced the symptoms associated with lower urinary tract dysfunction and increased QoL in people with MS	Low risk
McClurg 2009	Clinical trial; Level 1	Group A: 37 pt Group B: 37 controls 11 male pt, 26 female pt >18 y	Symptoms associated with lower urinary tract dysfunction	Leakage of episode per day, symptoms questionnaire, pelvic floor muscle function using	Group A: PFMT + vaginal or anal electrical stimulation Group B: PFMT	EMG biofeedback at weekly clinic visit for 9 weeks	9,16, and 24 weeks	At 9 weeks, group A had significantly less incontinence, and lighter pads than group B. At 24 weeks, pad weights were the only	High risk



				Oxford, and EMG.				objective outcome that remained statistically significant.	
Rafii 2017	Clinical trial; Levels 1	50 pt, female pt 33 y (range 18-50 y)	Urinary incontinenc e	EDSS, ICIQ- SF, DASS- 21	Pelvic Floor Muscle Training (PFMT)	Exercises 3 times a day for 12 consecutive weeks at home.	1, 2, 3 months	PFMT reduces urinary incontinence, stress, anxiety and depression	Low risk
Vahtera 1997	Clinical trial; levels 1	80 pt, 50 female, 30 male pt 42.4± 9.5 y	Symptoms of lower urinary tract dysfunction	EMG, post voided residual volume, EDSS	Pelvic floor muscle exercises (PFMT)	3-5 times a week for at least 6 months	3 weeks, 2-6 months	PFMT combined with electrical stimulation of the pelvic floor constitute an effective treatment for lower urinary tract dysfunction in	Low risk

								male MS patients	
Zecca, Digesu, Robshaw, Puccini 2014	Prospective study; Level 2	83 pt, 21 male, 62 female pt 49 y (range 22-72 y)	Symptoms of detrusor overactivity, detrusor sphincter dyssynergia, detrusor underactivity	3-day bladder diary, PPBC, PPIUS, KHQ, OAB-q	Percutaneous tibial nerve stimulation (PTNS)	30 min once a week for 12 weeks	3 months	A sensory response, alone or in combination with a motor response, is better associated with a successful outcome of PTNS than motor response alone	High risk
Zecca, Digesu, Robshaw, Sing 2014	Prospective study; Level 2	83 pt, 21 male, 62 female pt 49 y (range 22-72 y)	Lower urinary tract symptoms	Bladder diary, post-micturition residual of voiding	Percutaneous tibial nerve stimulation (PTNS)	30 min once a week for 12 weeks	24 months	Prolonged PTNS improves lower urinary tract symptoms	High risk

Patients pt; Years old y; Multiple Sclerosis MS; PERFECT P power, E endurance, R repetitions, F fast contractions, ECT every contraction timed; Overactive Bladder OAB; Electromyography EMG; Pelvic floor muscle PFM; Pelvic floor muscle training PFMT; Neuromuscular electrical stimulation NMES; Transcutaneous posterior tibial nerve stimulation TPTNS; Overactive Bladder Questionnaire OAB-q, Over-Active Bladder

Awareness Tool - 8-item OAB-V8, Incontinence Questionnaire Short Form ICIQ-SF, Quality of Life Questionnaires QoL; Multiple Sclerosis Quality of Life-54 Instrument MSQoL54; Kings Health QoL questionnaire KHQ; Expanded Disability Status Scale EDSS; Incontinence Impact Questionnaire IIQ-7; Female Sexual Function Index FSFI; Urogenital Distress Inventory UDI; King's Health Questionnaire KHQ; Pelvic Floor Training Advice PFTA; Depression, Anxiety and Stress Scale - 21 Items DASS-21; Patient perception of bladder condition PPBC; patient perception of intensity of urgency scale PPIUS.

## References

1. European Multiple Sclerosis Platform: Recommendations on rehabilitation services for persons with multiple sclerosis in Europe. Brussels: EMSP; 2004.
2. Amarenco G, de Sèze M, Ruffion A, Sheikh I. Clinical and urodynamic evaluations of urinary disorders in multiple sclerosis. *Ann Phys Rehabil Med* 2014;57:277-87.
3. Al Dandan HB, Coote S, McClurg D. Prevalence of Lower Urinary Tract Symptoms in People with Multiple Sclerosis: A Systematic Review and Meta-analysis. *Int J MS Care*. 2020;22:91-99.
4. de Sèze M, Ruffion A, Denys P, Joseph PA, Perrouin-Verbe B. The neurogenic bladder in multiple sclerosis: review of the literature and proposal of management guidelines. *Mult Scler*. 2007;13:915-28.
5. Lúcio AC, Perissinoto MC, Natalin RA, Prudente A, Damasceno BP, D'ancona CA. A comparative study of pelvic floor muscle training in women with multiple sclerosis: its impact on lower urinary tract symptoms and quality of life. *Clinics (Sao Paulo)*. 2011;66:1563-8.
6. Gallien P, Gich J, Sánchez-Dalmau BF, Feneberg W. Multidisciplinary management of multiple sclerosis symptoms. *Eur Neurol*. 2014;72:20-5.
7. Di Benedetto P, Finazzi-Agrò E. Conservative management of adult neurogenic lower urinary tract dysfunction. *EJPRM* 2017;53:981-90.
8. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 2015;2;350:7647.
9. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, *et al*. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA*. 2000; 283:2008–12.
10. Methley AM, Campbell S, Chew-Graham C, McNally R, Cheraghi-Sohi S. PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. *BMC Health Serv Res*. 2014;14:579.
11. Higgins JPT, Green S. *Cochrane handbook for systematic reviews of interventions*. Oxford: Cochrane Collaboration; 2008.
12. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, *et al*. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64:383-94.

13. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, *et al.* GRADE guidelines 6. Rating the quality of evidence--imprecision. *J Clin Epidemiol.* 2011;64:1283-93.
14. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, *et al.* GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). *J Clin Epidemiol.* 2011;64:407-15.
15. Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, *et al.* GRADE guidelines: 5. Rating the quality of evidence--publication bias. *J Clin Epidemiol.* 2011;64:1277-82.
16. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, *et al.* GRADE Working Group. GRADE guidelines: 8. Rating the quality of evidence--indirectness. *J Clin Epidemiol.* 2011;64:1303-10.
17. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I<sup>2</sup> index? *Psychol Methods.* 2006;11:193-206.
18. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. *Contemp Clin Trials.* 2007;28:105-14.
19. Higgins JP, Altman DG, Gøtzsche PC, Jüni P. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Br. Med. J.* 2011; 343: 889–893.
20. Canbaz Kabay S, Kabay S, Mestan E, Cetiner M, Ayas S. Long term sustained therapeutic effects of percutaneous posterior tibial nerve overactive bladder in multiple sclerosis patients: 12-months results. *Neurourol Urodyn.* 2017;36:104-110.
21. Gobbi C, Digesu GA, Khullar V, El Neil S, Caccia G, Zecca C. Percutaneous posterior tibial nerve stimulation as an effective treatment of refractory lower urinary tract symptoms in patients with multiple sclerosis: preliminary data from a multicentre, prospective, open label trial. *Mult Scler* 2011;17:1514-9.
22. Kabay SC, Yucel M, Kabay S. Acute effect of posterior tibial nerve stimulation on neurogenic detrusor overactivity in patients with multiple sclerosis: urodynamic study. *Urology.* 2008; 71:641-5.
23. Kabay S, Kabay SC, Yucel M, Ozden H, Yilmaz Z, Aras O, *et al.* The clinical and urodynamic results of a 3-month percutaneous posterior tibial nerve stimulation treatment in patients with multiple sclerosis-related neurogenic bladder dysfunction. *Neurourol Urodyn.* 2009;28(8):964-8.

24. Zecca C, Digesu GA, Robshaw P, Puccini F, Khullar V, Tubaro A, *et al.* Motor and sensory responses after percutaneous tibial nerve stimulation in multiple sclerosis patients with lower urinary tract symptoms treated in daily practice. *Eur J Neurol.* 2014;21:506-11.
25. Lúcio AC, Campos RM, Perissinotto MC, Miyaoka R, Damasceno BP, D'ancona CA. Pelvic floor muscle training in the treatment of lower urinary tract dysfunction in women with multiple sclerosis. *Neurourol Urodyn.* 2010;29:1410-3.
26. Lúcio A, D'ancona CA, Perissinotto MC, McLean L, Damasceno BP, de Moraes Lopes MH. Pelvic Floor Muscle Training With and Without Electrical Stimulation in the Treatment of Lower Urinary Tract Symptoms in Women With Multiple Sclerosis. *J Wound Ostomy Continence Nurs.* 2016;43:414-9.
27. de Sèze M, Raibaut P, Gallien P, Even-Schneider A, Denys P, Bonniaud V, *et al.* Transcutaneous posterior tibial nerve stimulation for treatment of the overactive bladder syndrome in multiple sclerosis: results of a multicenter prospective study. *Neurourol Urodyn.* 2011;30:306-11.
28. Rafii F, Sajjadi M, Shareinia H, Sarraf P. Pelvic Floor Muscle Training Instruction to Control Urinary Incontinence and its Resulting Stress, Anxiety and Depression in Patients with Multiple Sclerosis. *Jundishapur J Chronic Dis Care.* 2017; 6:37333.
29. Fjorback MV, van Rey FS, van der Pal F, Rijkhoff NJ, Petersen T, Heesakkers JP. Acute urodynamic effects of posterior tibial nerve stimulation on neurogenic detrusor overactivity in patients with MS. *European Urol* 2006;51:464-70
30. Vahtera T, Haaranen M, Viramo-Koskela AL, Ruutiainen J. Pelvic floor rehabilitation is effective in patients with multiple sclerosis. *Clin Rehabil* 1997; 11: 211–219.
31. McClurg D, Ashe RG, Lowe-Strong AS. Neuromuscular electrical stimulation and the treatment of lower urinary tract dysfunction in multiple sclerosis--a double blind, placebo controlled, randomised clinical trial. *Neurourol Urodyn.* 2008;27:231-7.
32. McClurg D, Ashe RG, Marshall K, Lowe-Strong AS. Comparison of pelvic floor muscle training, electromyography biofeedback, and neuromuscular electrical stimulation for bladder dysfunction in people with multiple sclerosis: a randomized pilot study. *Neurourol Urodyn.* 2006;25:337-48.
33. McClurg D, Lowe-Strong A, Ashe RG. The benefits of pelvic floor muscle training in people with multiple sclerosis and lower urinary tract dysfunction. *Neurourology and Urodynamics* 2008;27:231–237 .

34. Ferreira AP, Pegorare AB, Salgado PR, Casafus FS. Impact of a pelvic floor training program among Women with Multiple Sclerosis: A Controlled Clinical Trial. *Am J Phys Med Rehabil.* 2016;95:1-8.
35. McClurg D, Lowe-Strong A, Ashe R. Pelvic floor training for lower urinary tract dysfunction in MS. *Nurs Times.* 2009;105:45-7.
36. Khan F, Pallant JF, Pallant JI, Brand C, Kilpatrick TJ. A randomised controlled trial: outcomes of bladder rehabilitation in persons with multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2010;81:1033-8.
37. Engeler DS, Meyer D, Abt D, Müller S, Schmid HP. Sacral neuromodulation for the treatment of neurogenic lower urinary tract dysfunction caused by multiple sclerosis: a single-centre prospective series. *BMC Urol.* 2015;23:15:105.
38. Zecca C, Digesu GA, Robshaw P, Singh A, Elneil S, Gobbi C. Maintenance percutaneous posterior nerve stimulation for refractory lower urinary tract symptoms in patients with multiple sclerosis: an open label, multicenter, prospective study. *J Urol.* 2014;191:697-702.
39. Pereira CMA, Castiglione M, Kasawara KT. Effects of physiotherapy treatment for urinary incontinence in patient with multiple sclerosis. *J Phys Ther Sci.* 2017;29:1259-1263.
40. Lúcio AC, D'Ancona CA, Lopes MH, Perissinotto MC, Damasceno BP. The effect of pelvic floor muscle training alone or in combination with electrostimulation in the treatment of sexual dysfunction in women with multiple sclerosis. *Mult Scler.* 2014;20:1761-8.
41. Roe B, Williams K, Palmer M. Bladder training for urinary incontinence in adults. *Cochrane Database Syst Rev* 2000;1308.
42. Subak LL, Quesenberry CP, Posner SF, Cattolica E, Soghikian K. The effect of behavioural therapy on urinary incontinence: a randomized controlled trial. *Obstet Gynecol* 2002; 100: 72–78.
43. Eustice S, Roe B, Paterson J. Prompted voiding for the management of urinary incontinence in adults (Cochrane Review). *Cochrane Database Syst Rev* 2000;(2):2113.
44. Shafik A, Shafik IA. Overactive bladder inhibition in response to pelvic floor muscle exercises. *World J Urol.* 2003;20:374-7.
45. Yamanishi T, Kaga K, Fuse M, Shibata C, Uchiyama T. Neuromodulation for the Treatment of Lower Urinary Tract. *Low Urin Tract Symptoms* 2015;7:121–32.

46. Tracey JM, Stoffel JT. Secondary and tertiary treatments for multiple sclerosis patients with urinary symptoms. *Investig Clin Urol*. 2016;57:377-383.
47. Silva Ferreira AP, de Souza Pegorare ABG, Miotto Junior A, Salgado PR, Medola FO, Christofolletti G. A Controlled Clinical Trial on the Effects of Exercise on Lower Urinary Tract Symptoms in Women With Multiple Sclerosis. *Am J Phys Med Rehabil*. 2019;98:777-782.
48. Andersson KE, Appel R, Cardozo L, Chapple C, Drutz H, Fourcroy J, *et al*. Pharmacological treatment of urinary incontinence. ICS; 2005 [Internet]. Available from: [https://www.ics.org/Publications/ICI\\_3/v2.pdf/chap14.pdf](https://www.ics.org/Publications/ICI_3/v2.pdf/chap14.pdf) [cited 2022, Jan 24].