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Review Article

Onabotulinumtoxin intra-detrusor injection for lower urinary tract symptoms (LUTS) in patients with multiple sclerosis (MS): A systematic review and meta-analysis

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Abstract

Background: Lower urinary tract symptoms (LUTS) are common complications in patients with multiple sclerosis (MS). Different studies evaluated the effects of Onabotulinumtoxin on urinary findings in patients with MS. We designed this systematic review and meta-analysis to estimate pooled efficacy of intra-detrusor injections of botox for urinary symptoms in patients with MS.

Methods: A comprehensive systematic search was conducted on five databases of PubMed, Scopus, EMBASE, Web of Science, and Google scholar on February 2022. . We extracted data regarding the total number of participants, first author, publication year, the country of origin, mean age, F/M ratio, duration of the disease, duration of the treatment, mean Expanded Disability Status Scale (EDSS), maximum cystometric capacity (MCC), and maximum detrusor pressure (MDP).

Results: Preliminary search of databases retrieved 1618 articles, after deduplication, 934 studies remained. Five studies were included for meta-analysis. The most frequent country of origin was the USA, and the mean EDSS ranged between 2.9 and 5.1. Urinary tract infection (UTI) and urinary retention were the most prevalent complications. The SMD of MDP ($MDP_{week\ 12}$-$MDP_{baseline}$) was -1.32(95%CI:-1.77, -0.37) (I^2=52.9%, P=0.1). The SMD of MCC ($MCC_{week\ 12}$-$MCC_{baseline}$) was 1.65 (95%CI: 0.44, 2.86) (I^2=92.4%, p<0.001). The SMD of MDP ($MDP_{week\ 4}$-$MDP_{baseline}$) was -3.6 (95%CI:-7.3, 0.16) (I^2=98.3%, p<0.001). The SMD of MCC ($MCC_{week\ 4}$-$MCC_{baseline}$) was 5.05 (95%CI: 0.14, 9.96) (I^2=98.8%, p<0.001).

Conclusions: This systematic review and meta-analysis demonstrated that injection of intra-detrusor Onabotulinumtoxin had a positive effect on improving urodynamic findings in patients with MS.

Keywords: Multiple sclerosis, Urinary, Systematic review.

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Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) that has a wide range of complications comprising physical and psychological disturbances urinary and bladder dysfunction affect the overall quality of life in these patients(1, 2). Between 50 and 90% of patients with MS suffer from lower urinary tract symptoms (LUTS) (3) including urgency, frequency, nocturia, and urge urinary incontinence (4). LUTS result in a physical functioning disturbance in addition to social activities (5). Current treatments focus on improving function as well as the quality of life (6). Pharmacotherapy, surgery, and intramuscular injections of botulinum toxin are frequently used in the treatment of LUTS (4). Onabotulinumtoxin (BOTOX®, Allergan, Inc., Irvine, CA), is a neurotoxin, that acts by blocking presynaptic acetylcholine release leading to temporary chemodenervation of the bladder (7).

Intra-detrusor injections of botox (a minimally invasive option) have been shown to be effective in improving urodynamic findings leading to a better quality of life (8, 9). Up to now, different studies evaluated the effects of botox on urinary findings in patients with MS while the results differ between studies. So, we designed this systematic review and meta-analysis to estimate pooled efficacy of intra-detrusor injections of botox for urinary symptoms in patients with MS.

Methods

A comprehensive systematic search was conducted on five databases of PubMed, Scopus, EMBASE, Web of Science, and Google scholar on February 2022. Also, gray literature including references of the reviews and included articles were investigated to find potentially relevant articles. We designed search strategy for mentioned databases based on following keywords: ((Multiple Sclerosis*) OR (Disseminated Sclerosis*) OR (Sclerosis* AND Multiple) OR (Sclerosis* AND Disseminated) OR ((Multiple Sclerosis*) AND (Acute Fulminating)) AND ((Botulinum*) OR (Toxins* AND Botulinum) OR (Botulinum* AND Neurotoxins*) OR (Toxins* AND (Clostridium botulinum Neurotoxins*)) OR ((Botulinum Toxin*)) OR ((Botulinum Neurotoxin*)) OR ((Clostridium botulinum Toxins*)) OR ((Botulin*)))

Inclusion criteria of study were defined as follows: 1) Clinical trials (before-after studies) 2) Retrospective/prospective cohorts. We had no language limitation.

Exclusion criteria were as follows: 1) case-control studies 2) cross sectional studies 2) Letters to the editor 3) case reports. We had no language limitation in this study.

Data extraction: After obtaining the search results from the different databases, we imported them to ENDNOTE. We deleted duplicates, and titles, and abstracts of potential studies were assessed.

Potential full texts were obtained, and two independent researchers extracted data from each study and entered in Excel file. We extracted data regarding total number of participants, first author, publication year, the country of origin, mean age, F/M ratio, duration of the disease, duration of the treatment, mean Expanded Disability Status Scale (EDSS), maximum cystometric capacity (MCC), and maximum detrusor pressure (MDP).

Risk of bias assessment: Two independent researchers evaluated the potential risk of bias using the Quality assessment of nan-randomized studies(ROBINS-I) and Quality assessment of randomized trials(ROB2) scales (10, 11). Only studies with full text were evaluated (not conference abstracts).

Statistical analysis: All statistical analyses were performed using STATA (Version 14.0; Stata Corp LP, College Station, TX, USA). We used random effects model (The variables were number with cognitive impairment and total number of included patients). To determine heterogeneity, inconsistency (I^2) was calculated. Standardized mean difference (SMD) was calculated as the effect size of the treatment.

Results

Preliminary search of databases retrieved 1618 articles, after deduplication 934 studies remained for Title/Abstract screening. Finally, eleven articles were included in the systematic review and of those, five studies were eligible for meta-analysis. Figure 1 shows the selection of relevant articles.

The included studies were from the USA, France, Russia, Portugal, Switzerland, UK, Egypt, and Germany. Totally, 970 participants (80.1% females) were included in the systematic review with mean ages ranged 12-131. The mean EDSS reported in the included studies were in range 2.9-5.1 and the most prevalent complications were urinary tract infection (UTI) and urinary retention. Main characteristics of included articles are summarized in table 1.

The SMD of MDP ($MDP_{week\ 12}$-$MDP_{baseline}$) was -1.32 (95%CI:-1.77, -0.37) (I^2=52.9%, P=0.1) (figure 2). The SMD of MCC ($MCC_{week\ 12}$-$MCC_{baseline}$) was 1.65 (95%CI: 0.44, 2.86) (I^2=92.4%, p<0.001) (figure 3). The SMD of MDP ($MDP_{week\ 4}$-$MDP_{baseline}$) was -3.6 (95%CI:-7.3, 0.16) (I^2=98.3%, p<0.001) (figure 4). The SMD of MCC ($MCC_{week\ 4}$-$MCC_{baseline}$) was 5.05 (95%CI: 0.14, 9.96) (I^2=98.8%, p<0.001) (figure 5). The quality assessment of included studies are summarized in tables 2 & 3.

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis showing the effects of intra-detrusor injections of botox for urinary symptoms in patients with MS. The results show that the effects of botox injection were higher after 4 weeks compared with the results of week 12. The SMD of MDP was -3.6 after 4 weeks and -1.3 after 12 weeks which indicates that maximum detrusor pressure decreases more after 4 weeks of injection. We also found that botox injection was more effective in increasing MCC after 4 weeks than after 3 months.

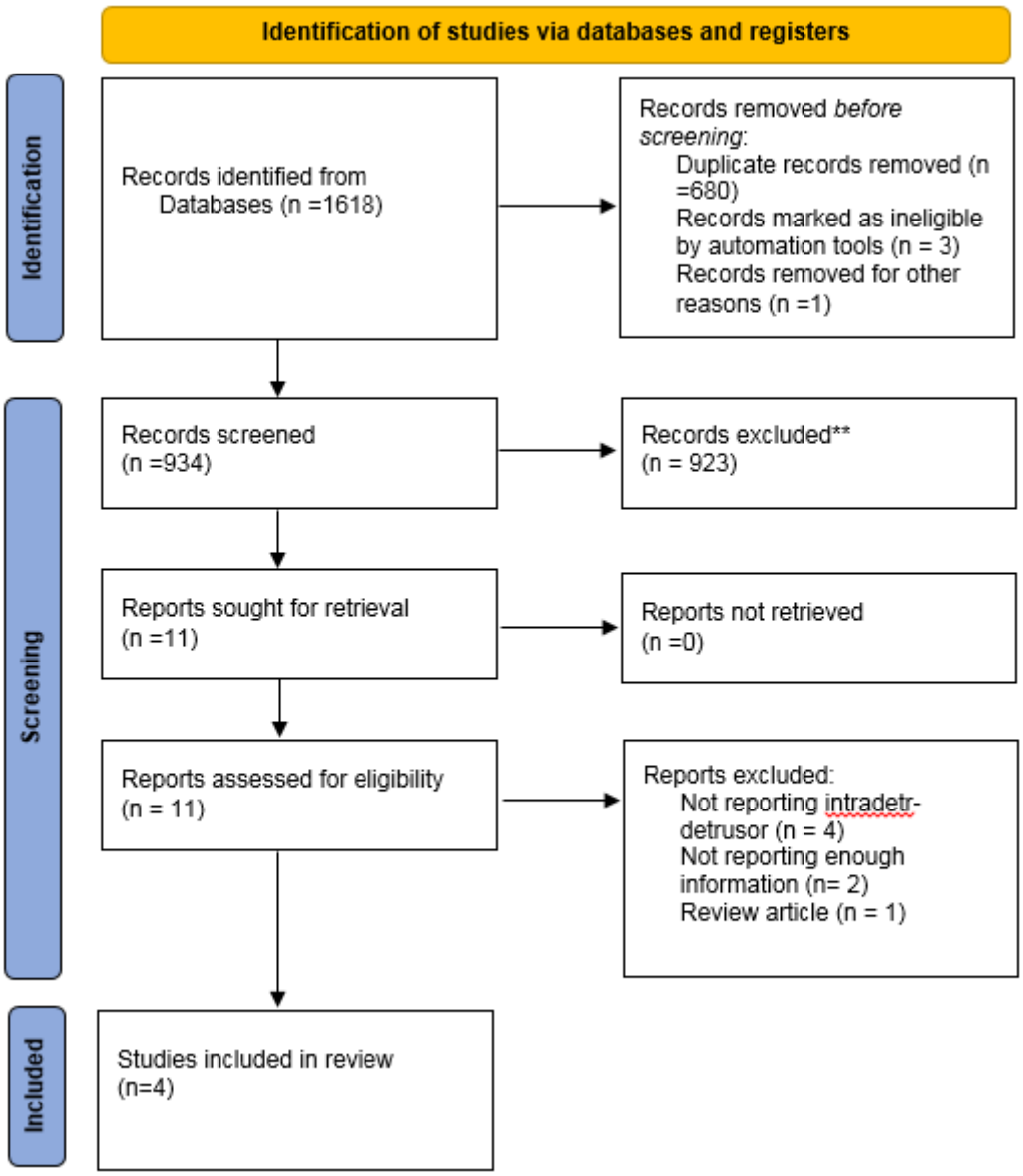

Figure 1. Flow diagram summarizing the selection of eligible studies.

Table 1. Data extracted from included studies

Author	Country/year	Type of botox/Dosage	Number of patients/ MS type	Female/Male	Mean age of patients	Mean Disease duration	Mean EDSS	Follow up (month)	Main finding	Side-effect
E.S. Philippova (12)	Russia/2020	Botulinum toxin A/(200U)	36/ RRMS:23, SPMS:10, PPMS:3	25/11	36.2 (15.3)	15.2 (10.5)	2.93 (1.05)	3	Intra-detrusor injection of Botulin toxin had resulted in significant improvement in patients (MDP (cmH2O)= baseline:23.61 (14.1), week12:7.52 (5.2)) (MCC (mL)= baseline:158 (61.4), week12:367 (101.3)) (Vfirst IDC (mL)= baseline:155 (82.3), week12:320 (96.5))	NR

Author	Country/year	Type of botox/Dosage	Number of patients/ MS type	Female/Male	Mean age of patients	Mean Disease duration	Mean EDSS	Follow up (month)	Main finding	Side-effect
R. Khavari (13)	USA/ 2019	Onabotulinum toxin A/100-200U	12/NR	12/0	43.9 (38-71)	14.9 (2-38)	NR	1.5-2.5	(MCC (mL)= baseline:134.5 (14-251), post:195.5 (51-401)) (PVRV (mL)= baseline:116.2 (0-350), post:377.9 (120-600)) (UI per day= baseline:1.64 (0-4), post:0.42 (0-1))	NR
M. Tullman (14)	USA/ 2018	Onabotulinum toxin A/100U	66/ RRMS:45, SPMS:12, PPMS:6, PRMS:3	57/9	51.5 (10.4)	14.7 (8.5)	4.5 (1.4)	3	OnabotulinumtoxinA 100 U had resulted in significant improvement of Urinary Incontinency and other urinary symptoms, urodynamics, Qulatiy of life with CIC, and UTI rate in non-catheterizing patients with MS and neurogenic detrusor overactivity, in comparison of onabotulinumtoxinA 200 U (UE per day=baseline:6.8 (3.8), changes in week 6:-4.3 (95%,-5.3 to -3.3CI)) (ME per day= aseline:10.0 (2.9), changes in week 6: -2.5 (95%,-3.3 to -1.6CI)) (VV (mL)= baseline:163.7 (62.6), changes in week 6:67.6 (95%,43.4 to 91.7CI)) (MCC (mL)= baseline:246.4 (138.5), changes in week 6:127.2 (95%,91.8 to 162.5CI)) (MDP during storage phase (cm H2O)= baseline:43.4 (32.5), changes in week 6:-27.8 (95%,-35.2 to -20.4CI)) (MDP during first IDC (cm H2O) =baseline:35.9(34.9), changes in week 6:-19.6(95%,-35.1 to -4.0CI))	UTI:17, Residual urine volume:11, Urinary retention:10, Bacteriuria:6, Dysuria:3, Diarrhea:1, Arthralgia:2, Bladder discomfort:2, Ear infection:2, Fall:2, Hematuria:2, Renal cyst:2, Leukocyturia:2, Vulvovaginal mycotic infection:2, CIC:10
		Placebo	78/ RRMS:51, SPMS:18, PPMS:9, PRMS:0	70/8	51.7 (10.3)	14.3 (8.5)	4.8 (1.5)		(UE per day= baseline:7.5 (4.1), changes in week 6:-1.6 (95%,-2.3 to -0.9CI)) (ME per day= baseline:10.4 (3.6), changes in week 6: -0.8 (95%,-1.5 to -0.1CI)) (VV (mL)= baseline:158.2 (64.6), changes in week 6:5.1 (95%,-7.6 to 17.8CI)) (MCC (mL)= baseline:245.7 (133.9), changes in week 6:-1.8(95%,-23.7 to 20.1CI)) (MDP during storage phase (cm H2O) =baseline:44.6 (35.1), changes in week 6:-0.5 (95%,-7.9 to 6.9CI)) (MDP during first IDC (cm H2O)= baseline:36.1 (37.2), changes in week 6:-3.7 (95%,-5.7 to 13CI))	UTI:5, Residual urine volume:1, Urinary retention:1, Bacteriuria:4, Dysuria:1, Diarrhea:3, Arthralgia:1, Bladder discomfort:0, Ear infection:0, Fall:1, Hematuria:5, Renal cyst:1, Leukocyturia:4, Vulvovaginal mycotic infection:0, CIC:2
D. Ginsberg (15)	USA/ 2013	Onabotulinum toxin A/200U	130/NR	104/26	49.7 (12.1)	14.6 (10.2)	NR	3	There was a significant improvement of urinary incontinency and urodynamic factors in patients after OnabotulinumtoxinA injection. (MDP (cmH2O)= baseline:41.6 (29.9), changes in week6:-22.1 (34.1)) (MCC (mL)= baseline:251.3 (160.6), changes in week6:149.3 (169.2))	UTI:69, Urinary retention:38, Hematuria:8, Diarrhea:5, Fatigue:15, Constipation:9, Nasopharyngitis:6, Pyrexia:7, Muscular weakness:10, Dysuria:7, Headache:2, Nausea:5, MS relapse:4, Upper respiratory tract infection:4, Back pain:7, Hypertension:6, Influenza:2, Bladder pain:2, Decubitus ulcer:0, Muscle spasms:4, Renal cyst:0, Autonomic dysreflexia:2,
		Onabotulinum toxin A/300U	120/NR	107/13	49.9 (10.7)	13.2 (7.9)	NR		(MDP (cmH2O)= baseline:36.6 (29.8), changes in week6:-24.1 (27.8)) (MCC (mL)= baseline:250.8 (156.2), changes in week6:165.1 (174.0))	UTI:69, Urinary retention:46, Hematuria:8, Diarrhea:10, Fatigue:7, Constipation:7, Nasopharyngitis:7, Pyrexia:2, Muscular weakness:12, Dysuria:5, Headache:6, Nausea:6, MS relapse:12, Upper respiratory tract infection:2, Back pain:3, Hypertension:2, Influenza:3,

Author	Country/year	Type of botox/Dosage	Number of patients/ MS type	Female/Male	Mean age of patients	Mean Disease duration	Mean EDSS	Follow up (month)	Main finding	Side-effect
		Placebo	131/NR	100/31	50.2 (10.7)	14.0 (7.8)	NR		(MDP (cmH2O)= baseline:40.6 (29.6), changes in week6:10.7 (41.2)) (MCC (mL)= baseline:240.5 (141.9), changes in week6:6.8 (120.2))	Bladder pain:6, Decubitus ulcer:0, Muscle spasms:6, Renal cyst:2, Autonomic dysreflexia:0, UTI:38, Urinary retention:6, Hematuria:2, Diarrhea:4, Fatigue:6, Constipation:2, Nasopharyngitis:6, Pyrexia:3, Muscular weakness:5, Dysuria:7, Headache:0, Nausea:0, MS relapse:6, Upper respiratory tract infection:4, Back pain:1, Hypertension:0, Influenza:1, Bladder pain:0, Decubitus ulcer:0, Muscle spasms:1, Renal cyst:3, Autonomic dysreflexia:0,
S. Deffontaines-Rufin (16)	France/ 2011	Botulinum toxin A/300U	71/NR	52/19	47.6 (11.2)	(n=33(13.8(9)), (n=22(11.7(9)),	NR	3	Botulinum toxin A injection resulted in decrease of refractory neurogenic detrusor overactivity symptoms in MS patients, based on clinical and urodynamic parameters. (MCC (mL)= baseline:240 (130), week12:328 (114)) (MDP (cm H2O)= baseline:61 (23), week12:36 (27)) (FCV (mL)= baseline:159 (83), week12:301 (120))	None
F. Cruz (17)	Portugal/ 2011	Onabotulinum toxin A/200U	53/NR	44/9	50.1 (12.2)	14.8 (9.8)	4.9 (1.5)	3	OnabotulinumtoxinA 200 U and 300 U had a significant result in improvement of incontinency and urodynamic factors. (UI per week=baseline:34.5 (18.5), changes in week 2:-23.8 (16.7), changes in week 6:-25.9 (18.8), changes in week 12:-24.2 (18.9)) (VV (mL)= baseline:115.3 (80.1), changes in week 2:75.1 (115.7), changes in week 6:128.5 (117.7), changes in week 12: 119.8 (117.5)) (MCC (mL)= baseline:239.1 (161.5), changes in week 6:159.2 (156.9)) (MDP (cmH2O)= baseline:38.7 (31.5), changes in week 6:-14.6 (36.0)) (VfirstIDC(mL)= baseline:181.2 (131.9), changes in week 6:191.0 (152.1))	UTI:35, Urinary retention:27
		Onabotulinum toxin A/300U	51/NR	41/10	49.4 (10.2)	14.0 (8.6)	5.1 (1.5)		(UI per week= baseline:33.1 (21.1), changes in week 2:-19.2(21.0), changes in week 6:-24.4 (22.8), changes in week 12:-23.7 (17.8)) (VV (mL)= baseline:130.6 (68.1), changes in week 2:75.1(136.7), changes in week 6:112.9 (148.6), changes in week 12:108.6 (142.9)) (MCC (mL)= baseline:251.0 (167.3), changes in week 6:168.7 (179.0)) (MDP (cmH2O)= baseline:36.5 (32.2), changes in week 6:-20.2 (22.9)) (VfirstIDC(mL)= baseline:190.1 (132.1), changes in week 6:217.3 (213.5)),m	UTI:31, Urinary retention:16

Author	Country/year	Type of botox/Dosage	Number of patients/ MS type	Female/Male	Mean age of patients	Mean Disease duration	Mean EDSS	Follow up (month)	Main finding	Side-effect
		Placebo	50/NR	38/12	50.0 (10.9)	14.1 (7.6)	5.1 (1.3)		(UI per week= baseline:35.8 (30.9), changes in week 2:-13. 8(19.6), changes in week 6:-18.1 (23.3), changes in week 12:-15.5 (27.4)) (VV (mL)= baseline:121.8(64.4), changes in week 2:19.0 (55.2), changes in week 6:27.5 (75.6), changes in week 12:27.4 (69.7)) (MCC (mL)= baseline:236.2 (141.6), changes in week 6:28.4 (121.6)) (MDP (cmH2O)= baseline:37.8 (27.4), changes in week 6:8.8 (43.0)) (VfirstIDC(mL)= baseline:191.3 (128.5), changes in week 6:17.2 (117.2)),	UTI:16, Urinary retention:2
U. Mehnert (18)	Switzerland/ 2010	Botulinum toxin A/100U	12/NR	11/1	51.5 (9.3)	NR	5.0 (1.5)	3	Botulinum toxin A resulted in obvious improvement in urgency, frequency, and maximum detrusor pressure, and maximum cytometric capacity in MS patients. (FDV (mL)= baseline:340.3 (233), week6:453.1 (200)) (UI per day = baseline:3.8 (5.1), week6:1.9 (3.2), week12:1.0 (1.4)) (UE per day = baseline:9.1 (5.7), week6:2.8 (3.8), week12:4.4 (5.2)) (VV (mL)= baseline:337.4 (256.5), week6:330.8 (186.2), week12:221.3 (132.4)) (Qmas (mL/sec)= baseline:27.9 (21), week6:23.1 (13.0), week12:18.7 (13.5)) (PVRV (mL)= baseline:98.3 (77.6), week6:222.1 (113.2), week12:135.2 (94.8))	Hematuria:6, injection site pain:8
V. Kalsi (19)	UK/ 2007	Botulinum toxin A/(300U)	43/NR	39/4	45.8 (33-61)	NR	NR	4	There was a significant decrease of overactive bladder symptoms in MS patients after Botulinum toxin A injection. However, minimal side effects were reported in patients. (MCC (mL)= baseline:235.6 (22.1), week4:602.9 (33.47), week16:456.5 (33.53)) (MDP (cmH2O)= baseline:51.3 (4.1), week4:26.6 (3.1), week16:26.4 (2.4)) (ME per day= baseline:12.5 (0.7), week4:6.6 (0.4), week16:6.9 (0.4)) (UI per day= baseline:3.9 (0.5), week4:0.36 (0.1), week16:0.7 (0.2)) (UE per day= baseline:7.7 (0.7), week4:1.7 (0.4), week16:1.3 (0.3))	UTI:7, hematoma:1, urethral caruncle:1, heavy legs:1, leg weakness:1,
A. Nasseff (20)	Egypt/ 2006	Botulinum toxin A/(300U) Botulinum toxin A/(100-200U)	9/RRMS:9 6/RRMS:6	5/4 3/3	21-39	2-7	2-5	6	Botulinum toxin type A was effective in improvement of urinary dysfunction of MS patients. (MDP (cmH2O)= baseline:56.7 (10.2), week24:53.4 (6.9)) (MCC (mL)= baseline:146 (10.8), week24:248 (11.2)) (ME per day= baseline:15.7 (2.29), week24:9.67 (2.0)) (PVRV (mL)=baseline:226 (19.8), week24:92.8 (7.25)) (MDP (cmH2O)=baseline:85.5 (5.36), week24:52.2 (3.49)) (MCC (mL)=baseline:199 (16.8), week24:217.8 (22.1))	Stool incontinence: 1

Author	Country/year	Type of botox/Dosage	Number of patients/ MS type	Female/Male	Mean age of patients	Mean Disease duration	Mean EDSS	Follow up (month)	Main finding	Side-effect
H. Schulte-Baukloh (21)	Germany/ 2006	Botulinum toxin A/(300U)	16/NR	11/5	48.6 (34-69)	NR	NR	6	Botulinum toxin A had decreased neurogenic detrusor overactivity symptoms in MS patients. (MCC (mL)=baseline:265.40 (36.13), week4:359.67 (39.44), week12:336.07 (42.25), week24:360.75 (50.40)) (MDP (cmH2O)=baseline:57.11 (7.99), week4:37.18 (5.02), week12:44.36 (6.94), week24:24.38 (5.55))	NR
P. Gallien (22)	France/ 2005	Botulinum toxin A/(100U)	45/NR	28/17	50 (11)	14.4 (9.8)	5.4 (1.9)	4	A single injection of Botulinum A toxin didn't have significant effect on post-voiding residual urine volume in MS patients with detrusor sphincter dyssynergia. (MDP (cmH2O)=baseline:67 (26), week4:52 (22)) (VV (mL)=baseline:135 (92), week4:197 (143)) (Qmas (mL/sec)=baseline:13 (10), week4:15 (7)) (PVRV (mL)=baseline:220 (99), week4:186 (158)) (MCC (mL)=baseline:344 (194), week4:355 (168))	MS relapse:4, uterine leiomyoma:1, drug-induced confusion:1, dyspnoea:1, UTI:16, Urinary leakages:2
		Placebo	41/NR	30/11	51 (10)	17.8 (11)	6.0 (1.3)		(MDP (cmH2O)=baseline:62 (23), week4:66 (25)) (VV (mL)=baseline:166 (166), week4:128 (95)) (Qmas (mL/sec)=baseline:16 (12), week4:13 (9)) (PVRV (mL)=baseline:217 (96), week4:206 (145)) (MCC (mL)=baseline:374 (171), week4:346 (138))	MS relapse:2, pyelonephritis:1, lumbar radicular pain:1, femoral fracture:1, UTI:12, Urinary leakages:2

RRMS=relapsing-remitting, SPMS=secondary-progressive, PPMS=primary-progressive, PRMS=progressive-relapsing, CIC = clean intermittent catheterization, IDC = involuntary detrusor contraction, I-QOL = incontinence–quality of Life, MCC = maximum cystometric capacity, MDP or (P det. max.) = maximum detrusor pressure, MID = minimally important difference, MS = multiple sclerosis, PVR or PVRV = postvoid residual, QOL = quality of life, TEAE = treatment-emergent adverse event, UI = urinary incontinence, UTI = urinary tract infection, UE= Urgency episodes, FCV=volume at first involuntary bladder contraction, UDI=urogenital distress inventory, IIQ=incontinence impact questionnaire, FDV=first desire to void, Qmax=maximum flow, MVP=maximum voiding pressure, (UF= urinary frequency,= ME= Micturition episodes), MVV=maximal voided urine volume, RV=re£lex volume, VfirstIDC= bladder volume at first involuntary detrusor contraction, VV= volume per voide.

Table 2. Quality assessment of non-randomized studies (ROBINS-I)

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall Bias
Philippova et al.	Low	Low	Low	Low	Moderate	Low	Low	Moderate
Khavari et al.	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Deffontaines-Rufin et al.	Low	Low	Low	Low	Low	Low	Low	Low
Mehnert et al.	Low	Low	Low	Low	Moderate	Low	Low	Moderate
Kalsi et al.	Low	Low	Low	Low	Low	Low	Low	Low
Nassef et al.	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Schulte-Baukloh et al.	Low	Moderate	Low	Low	Low	Low	Low	Moderate

Table 3. Quality assessment of randomized trials (ROB2)

Study	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
Tullman et al.	Low	Low	Low	Low	Low	Low
Ginsberg et al.	Low	Low	Low	Low	Low	Low
Cruz et al.	Some concerns	Low	Low	Low	Low	Some concerns
Gallien et al.	Low	Low	Low	Low	Low	Low

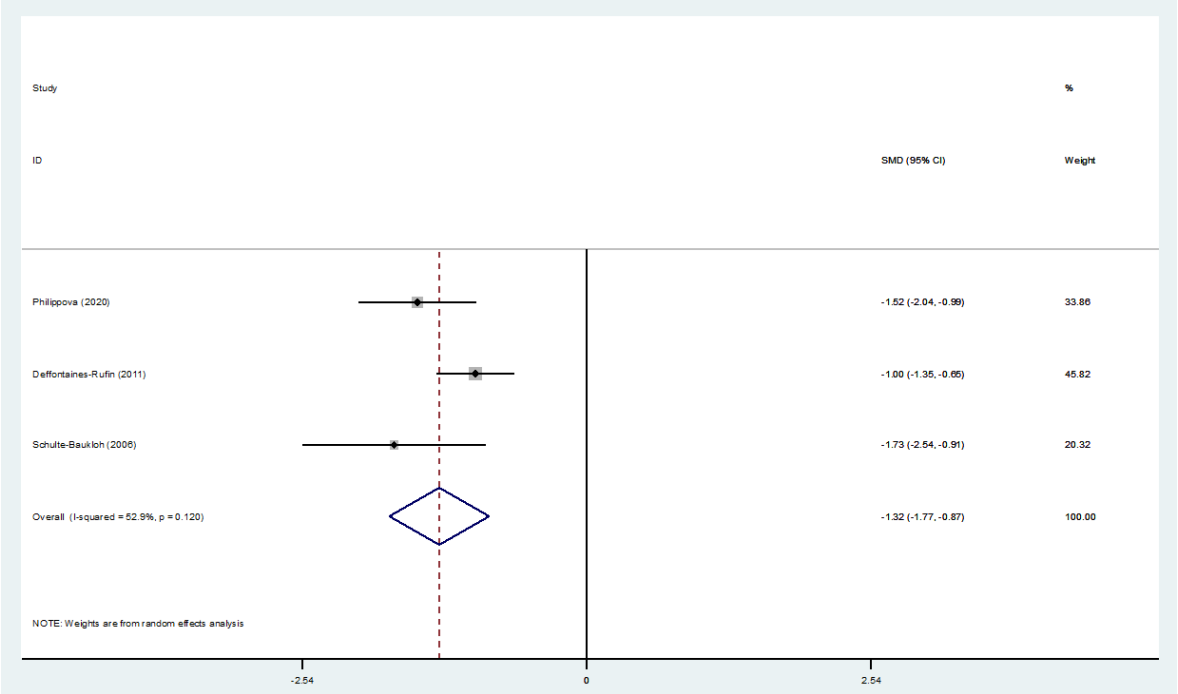

Figure 2. The SMD of MDP (MDP $_{\text{week 12}}$-MDP $_{\text{baseline}}$)

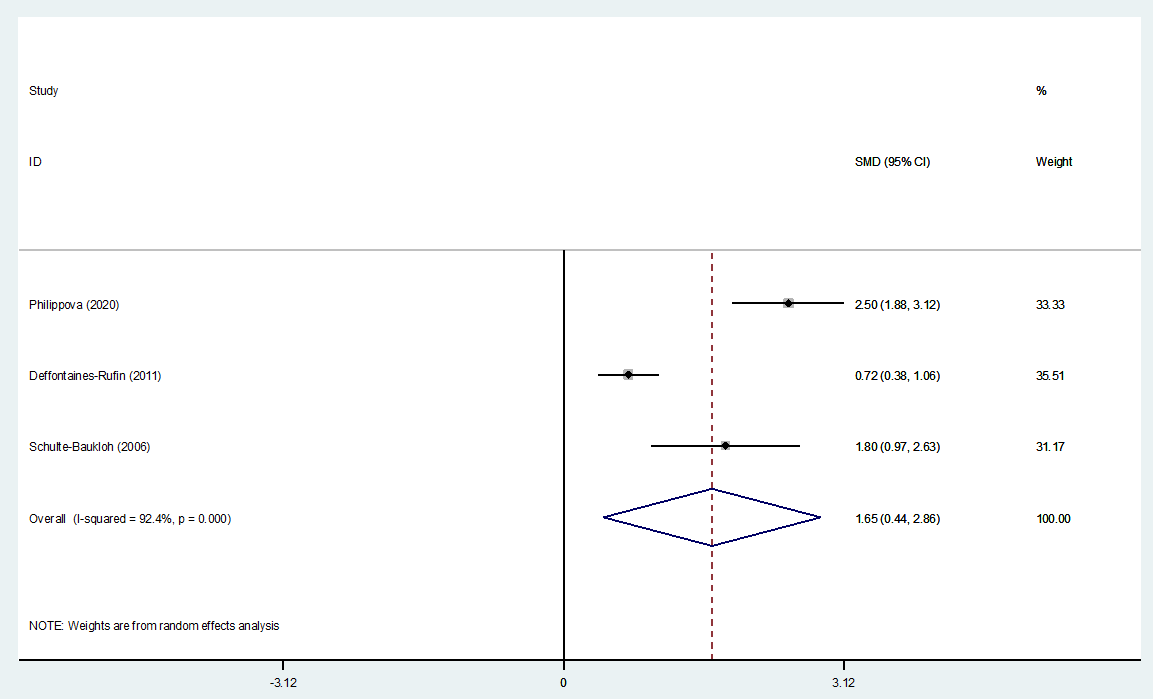

Figure 3. The SMD of MCC (MCC $_{\text{week 12}}$-MCC $_{\text{baseline}}$)

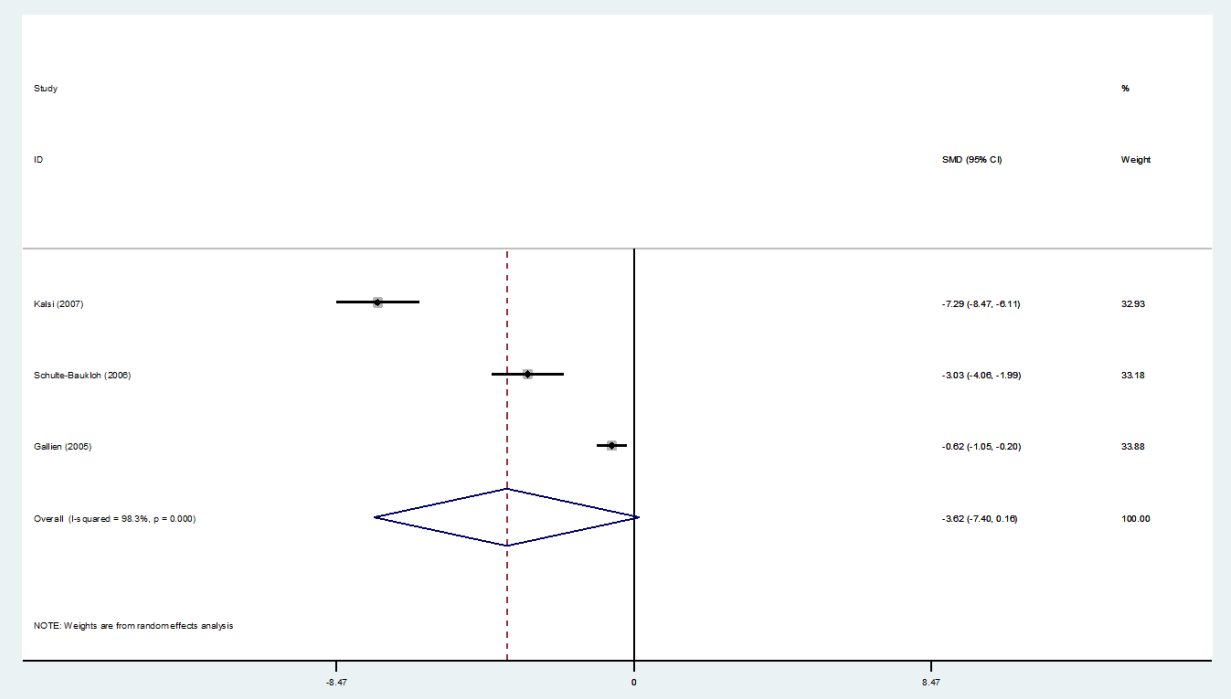

Figure 4. The SMD of MDP (MDP $_{\text{week 4}}$-MDP $_{\text{baseline}}$)

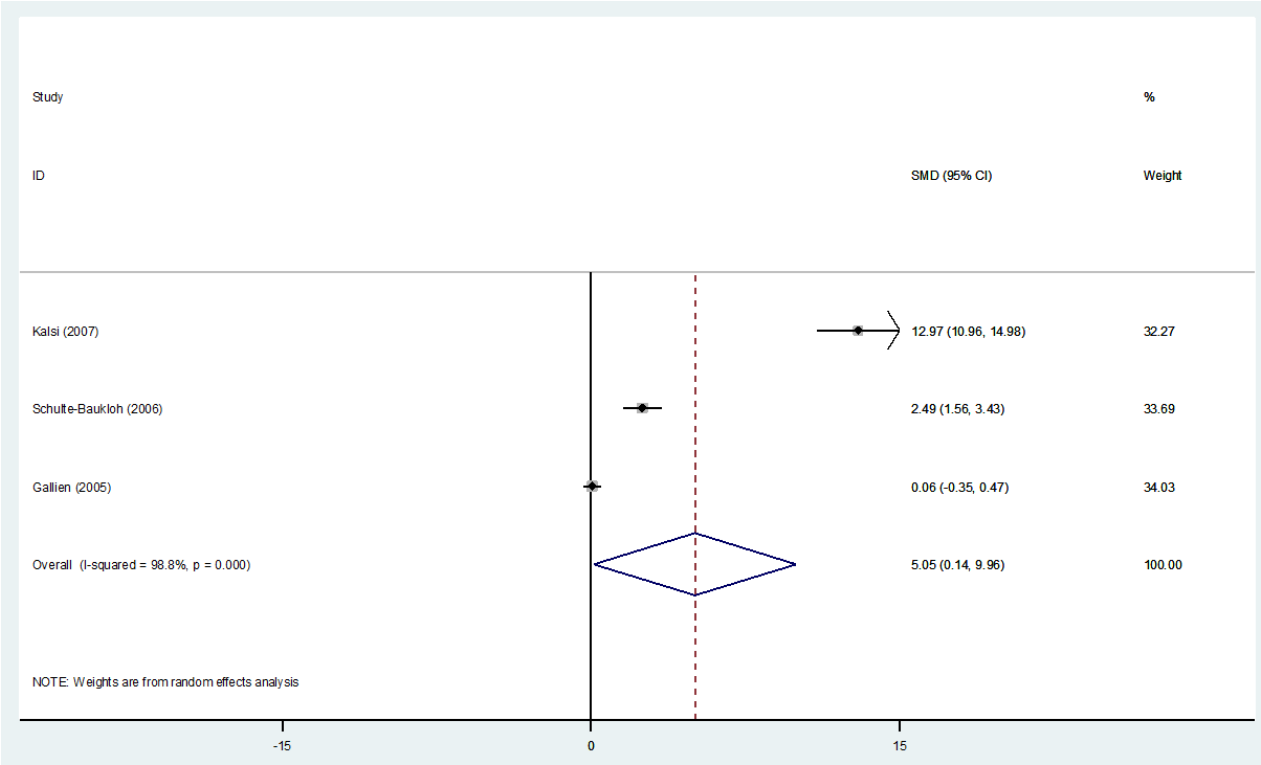

Figure 5. The SMD of MCC (MCC $_{\text{week 4}}$-MCC $_{\text{baseline}}$)

Philippova et al., enrolled 36 patients with MS and neurogenic lower urinary tract dysfunction who received 200 U intra-detrusor injection of BoNTA. Their results showed that MCC significantly increased while MDP decreased significantly after intervention (12). By enrolling 43 patients with MS and severe urgency incontinence, Kalsi et al. administered 300 U intra-detrusor BoNTA. They found that incontinency, urgency, frequency, and nocturia improved significantly after intervention. MCC improved significantly 4 weeks after injection compared with the final evaluation (16 weeks after intervention) (19). Our results show SMDs of MCC and MPD were higher after 4 weeks

than 12 weeks after intervention which indicate that the effect of intra-detrusor BoNTA injection is higher one month after administration.

In a prospective study, Schulte-Baukloh et al. injected 300 U of BTX-A into the bladder and external sphincter. They reported a 29%, and 44% reduction of frequency after 4 and 12 weeks of injection, while MDP decreased by 35 and 22%, four and twelve weeks after injection, respectively and MCC increased significantly(21). Mehrnet et al. included 12 patients with MS and overactive bladder. They found that all cytometric and voiding parameters (except incontinency) improved significantly after the administration of 100 U botox. Their results also demonstrated that urgency and frequency increased after a 12-week follow-up (18). Lower urinary tract symptoms (LUTS) are prevalent in patients with MS including frequency, urgency, nocturia, and incontinency. Literature shows that between 50% and 90% of patients with MS suffer from LUTS that affects their well-being and the quality of life (23, 24). The first-line treatment of LUTS in MS is an anti-cholinergic medication that has no satisfactory efficacy and various side- effects (25).

Other therapies include physiotherapy, desmopressin spray, pelvic floor muscle training, and posterior tibial nerve stimulation (PTNS) (26, 27). In a recent systematic review and meta-analysis, Guitynavard et al. showed that PTNS is very effective in treating nocturia, and leakage per day in patients with MS (1). Botox is the second-line treatment for urinary complications in MS. It is suggested to start the botox at a lower dose and increase the dose gradually. In most intra-detrusor administrations, 300 U dose is used which may lead to high (pressure/vacuum relief valves) PVRV or urinary retention (UR) (18). Further large, multi-centric studies should be done to evaluate short- and long-term effects of botox and proper dosage in patients with MS who suffer from urinary symptoms. This study had some limitations. First, the number of studies that reported urodynamic findings was limited. Second, the dosage was not similar in all studies. This systematic review and meta-analysis demonstrated that injection of intra-detrusor Onabotulinumtoxin had a positive effect on improving urodynamic findings in patients with MS.

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