



## Original Article

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# Efficacy and Safety of OnabotulinumtoxinA in Patients With Neurogenic Detrusor Overactivity Caused by Spinal Cord Injury: A Systematic Review and Meta-Analysis

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**Purpose:** OnabotulinumtoxinA (BoNT-A) is a promising therapy for treating neurogenic detrusor overactivity (NDO) in individuals with spinal cord injury (SCI). This systematic review and meta-analysis aimed to carry out an in-depth review and to make an objective estimation of the efficacy and safety of BoNT-A on NDO after SCI.

**Methods:** The PubMed, Embase, and Cochrane databases were searched for all relevant articles published from 2001 to 2016 that referred to NDO, SCI, and BoNT-A or botulinum toxin A. All data were recorded in an Excel spreadsheet by 2 individual reviewers. Review Manager version 5.3 was used to carry out the meta-analysis.

**Results:** This analysis included 17 studies involving 1,455 patients. Compared with placebo and baseline, BoNT-A was effective in increasing maximum cystometric capacity, volume at first involuntary detrusor contraction, cystometric bladder capacity (all  $P < 0.00001$ ), compliance ( $P = 0.001$ ), and the number of patients with complete dryness ( $P = 0.0003$ ), and decreasing detrusor pressure, the number of patients with no involuntary detrusor contractions, the maximum flow rate, the incidence of detrusor overactivity (all  $P < 0.00001$ ), and the number of urinary incontinence episodes ( $P = 0.001$ ). There were no statistically significant differences between doses of 200 U and 300 U or between injections into the detrusor and submucosa. There were no life-threatening adverse events.

**Conclusions:** BoNT-A is effective and safe in treating NDO after SCI. There were no statistically significant differences between doses of 200 U and 300 U or between injecting into the detrusor and submucosa. However, more high-quality randomized controlled trials are still needed.

**Keywords:** OnabotulinumtoxinA; Meta-analysis; Neurogenic detrusor overactivity; Spinal cord injury

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- **Conflict of Interest:** No potential conflict of interest relevant to this article was reported.

## INTRODUCTION

Spinal cord injury (SCI) is a devastating event that can cause far-reaching effects on individuals' health, with further economic and social ramifications [1]. The incidence rate of SCI

hospitalizations was found to be 4.8 per 1,000 person-years [2].

In patients with severe SCI, the micturition reflex from the spinal cord segment is released from supraspinal modulation. This reflex increases the concentration of nerve growth factor distributed in the bladder wall. Subsequently, hyperexcitability

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of afferent nerves and detrusor overactivity (DO) occur in the bladder [3]. Then, patients often complain of lower urinary tract symptoms such as urinary frequency, urgency, and urinary incontinence (UI) [4]. Therapies for neurogenic detrusor overactivity (NDO), which is a complex and multilevel process, include medications (such as anticholinergic drugs and onabotulinumtoxinA [BoNT-A]), surgical procedures (such as sacral nerve stimulation), functional exercises, and psychological therapies. Since the causes of NDO are diverse, therapies should be chosen on an individualized basis [5,6].

In August 2011, BoNT-A was approved for patients with NDO after SCI by the U.S. Food and Drug Administration (FDA) [7]. To date, many studies have focused on the efficacy and safety of BoNT-A in improving urodynamic parameters and reducing the number of UI episodes. However, the absence of high-quality studies, especially randomized controlled trials (RCTs), has made it challenging to conduct a systematic review of this issue. Therefore, the efficacy and safety of BoNT-A have remained controversial. With this in mind, the purpose of this meta-analysis was to further evaluate the efficacy and safety of BoNT-A.

## MATERIALS AND METHODS

### Search Strategy

We searched the PubMed, Embase, and Cochrane databases for all relevant articles published from 2001 to June 2016. The references of the retrieved studies were also reviewed. We used the following keywords: “neurogenic detrusor overactivity,” “spinal cord injury,” “botulinum toxin A,” “BoNT-A” and “BOTOX.” Articles were restricted to clinical trials.

### Inclusion Criteria

All identified clinical trials were screened by 2 reviewers and had to meet the following criteria for inclusion in our analysis: (1) The participants were older than 18 years. (2) NDO was mainly caused by SCI (50% or more of participants). (3) BoNT-A was administered by injection into the bladder wall. (4) The study contained accessible data on maximum cystometric capacity (MCC), volume at first involuntary detrusor contraction (VFIDC), detrusor pressure (Pdet), UI episodes, compliance, voiding volume, postvoid residual volume (PVR), maximum flow rate (Qmax), mean functional bladder capacity, the number of patients with complete dryness (CD), incidence of DO, incontinence-specific quality of life (I-QoL), and the number of

patients with no involuntary detrusor contraction (IDC). (5) The full text of the study could be found. Studies not meeting any of those criteria were excluded.

### Exclusion Criteria

Studies meeting any of the following criteria were excluded from this analysis: (1) The full text was not accessible. (2) It was not a clinical trial (i.e., reviews, basic science). (3) It contained duplicate data from the same trial; in such cases, where findings from the same trial were published in multiple journals, only the most useful publication was used for this analysis. (4) Studies without sufficient subjects (i.e., case reports of single cases) or accessible data were also excluded from this analysis. After the selection, we regathered all the articles, both included and excluded, to perform a confirmatory assessment of the reasons for inclusion or exclusion.

### Quality Assessment

All the studies were graded according to the Cochrane Handbook for Systematic Reviews of Interventions 5.1. Eight entries represented 5 biases: selection bias, performance bias, detection bias, attrition bias, and reporting bias. Random sequence generation, double-blinding of participants and studiers, and double-blinding of outcomes indicated low risk. Allocation concealment, incomplete outcome data addressed, and selective reporting corresponded to high risk. Based on these criteria, all studies were classified using 3 grades, from A to C: (A) If all the key domains, and most information, met the low-risk criteria, the study was seen as having a low risk of bias. (B) If  $\geq 1$  key domains had an unclear risk of bias, and most information was at low or unclear risk, the study was viewed as having an unclear risk of bias. (C) If  $\geq 1$  key domains met the high-risk criteria and some information, with a significant influence on the results, was at a high risk of bias, the study was considered to have a high risk of bias [8].

### Data Extraction

Two reviewers read all the full texts, including the content of the publications and abstracts. The following information was collected from all included studies: (1) the first author's name and the year of publication; (2) the nations of the participants; (3) the sample size and numbers of each group; (4) the dose and location of administration; (5) baseline, index after at least 1 injection, or changes in urodynamic parameters and clinical outcomes; and (6) the type and number of adverse events (AEs). If

there was controversy over any aspects of the studies, a third reviewer was invited to review the study. If necessary, a fourth reviewer was included.

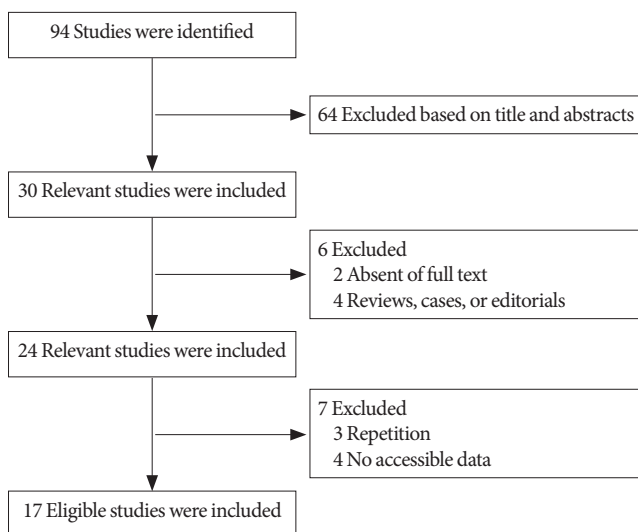
### Statistical Analysis

All data were recorded in an Excel spreadsheet by 2 individual reviewers. After this procedure, Review Manager ver. 5.3 (Cochrane Collaboration, Oxford, UK) was used to carry out the meta-analysis. In this process, the mean difference (MD) and 95% confidence interval (CI) were calculated using the software. Meanwhile,  $I^2$  was used to measure heterogeneity across trials. If  $I^2$  did not reach 50%, we chose a fixed-effects model. When  $I^2$  exceeded 50%, a random-effects model was more suitable. All types of AEs and the overall number of each AE in both the experimental and control groups were recorded.

## RESULTS

### Characteristics of Individual Studies

Fig. 1 shows the process of selection in this meta-analysis. After reading the abstracts and full texts, the 70 studies excluded involve (1) 64 excluded based on title and abstracts; (2) 2 excluded due to absent of full text; (3) 4 reviews, cases or editorials in Fig. 1. The remaining 24 studies involve 7 excluded (3 repetition and 4 no accessible data) and 17 eligible studies included. Ultimately, 17 studies with 1,455 patients were included in the meta-analysis. Eleven studies were RCTs. Eight studies investigated BoNT-A versus placebo, 4 investigated BoNT-A doses of 200 U versus 300



**Fig. 1.** The process of selection for this meta-analysis.

U, 2 investigated injections into the detrusor versus submucosa, and 2 investigated sparing the trigone versus avoiding the trigone. According to the Cochrane Handbook for Systematic Reviews of Interventions 5.1, 5 studies were evaluated as grade A, 5 as grade B, and 7 as grade C. The primary characteristics and quality assessment of the included studies are shown in Table 1. The funnel plot provided an estimation of the publication bias of the studies, and no evidence of bias was found (Fig. 2).

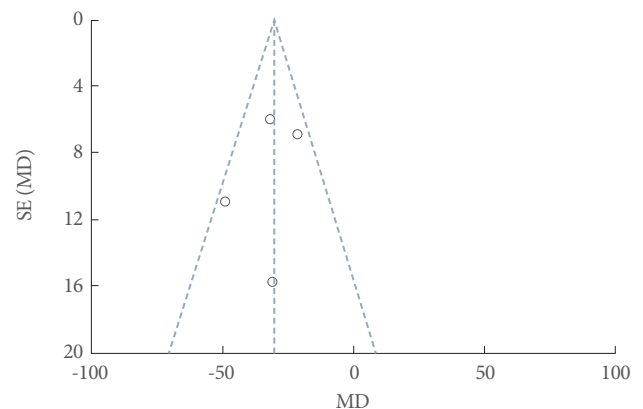
### The Efficacy of BoNT

#### BoNT-A versus placebo

Five studies involving 961 participants included data for a comparison of BoNT-A versus placebo [9-14]. Compared with placebo, BoNT-A increased the MCC (MD, 134.75; 95% CI, 105.06–164.44;  $P < 0.00001$ ), VFIDC (MD, 163.42; 95% CI, 96.41–230.43;  $P < 0.00001$ ), and the number of participants with no IDC and decreased Pdet (MD, -30.48; 95% CI, -38.38 to -22.58;  $P < 0.00001$ ) and UI episodes (MD, -12.45; 95% CI, -19.90 to -5.00;  $P = 0.001$ ). However, the PVR (MD, 95.97; 95% CI, 60.10–131.84;  $P < 0.00001$ ) increased more in the BoNT-A group than in the placebo group (Fig. 3).

#### Baseline versus after treatment

Ten studies involving 386 participants included data representing baseline versus posttreatment outcomes [10,15-24]. The results presented above were confirmed in the comparison between baseline and posttreatment values (Fig. 4) [9-21,24,25]. In addition, BoNT-A was effective in increasing the voiding volume (MD, 51.01; 95% CI, 37.75–64.27;  $P < 0.00001$ ), compliance (MD, -14.34; 95% CI, -23.18 to -5.49;  $P = 0.001$ ), and the number of patients with CD (odds ratio [OR], 0.02; 95% CI,



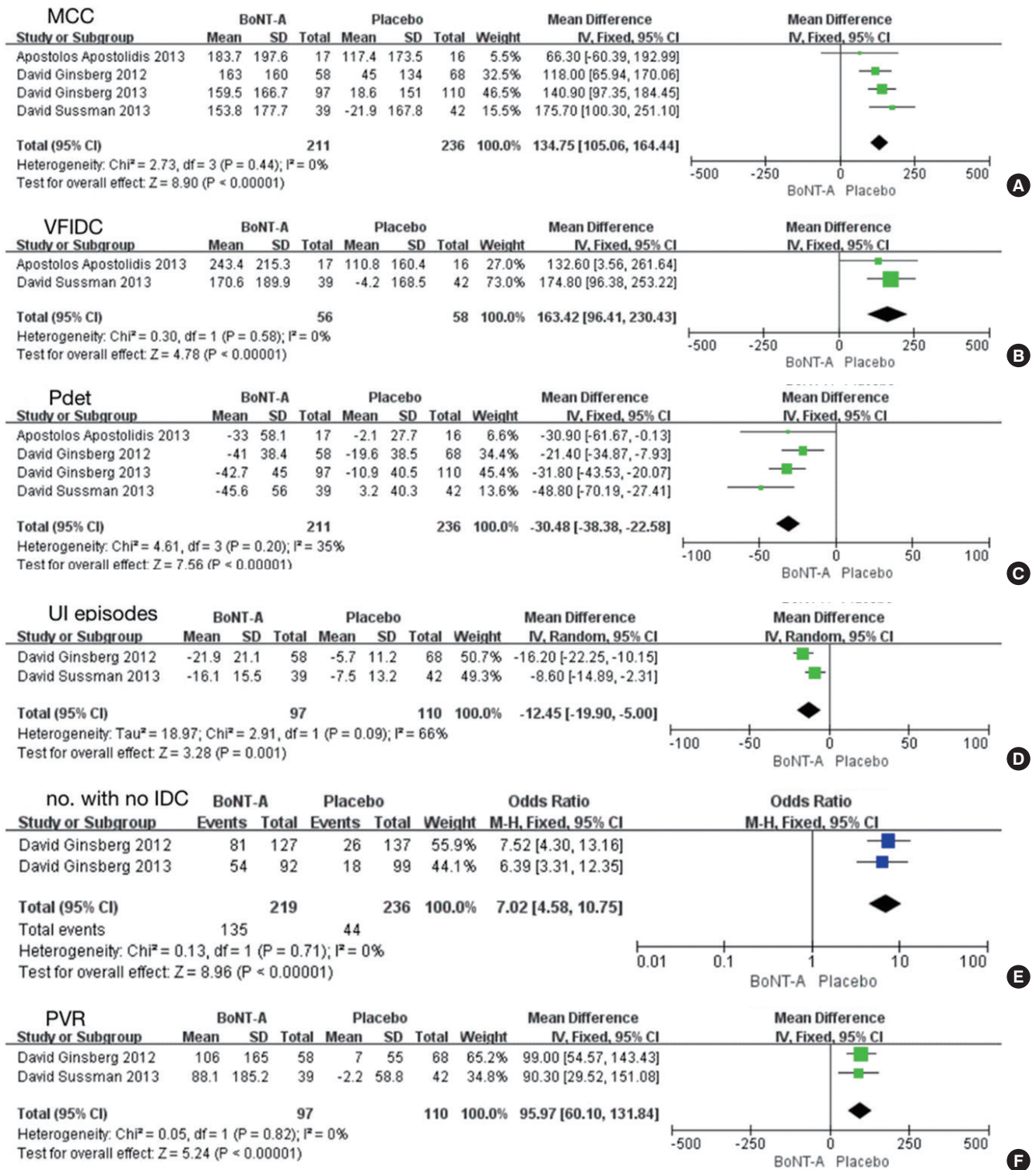
**Fig. 2.** Funnel plot of the studies included in the meta-analysis. SE, standard error; MD, mean difference.

**Table 1.** Primary characteristics and quality assessment

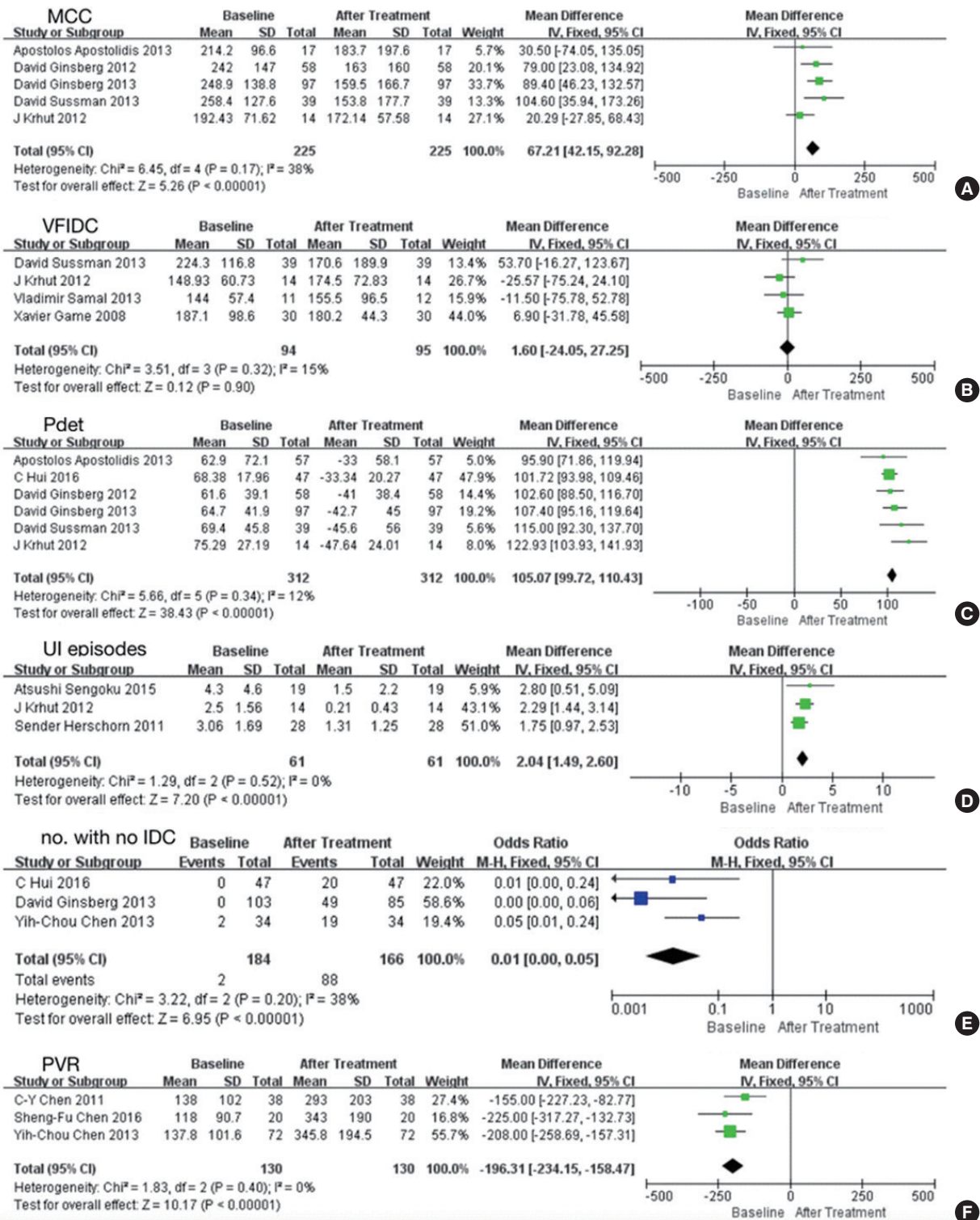
Study	Sample size	Study design	Country	Age (yr)	Time since SCI	Induction	Outcome measures	Follow-up (mo)	Quality assessment <sup>a)</sup>
Ginsberg, 2013 [9]	310	Prospective	International multicenter	41.5 ± 14.5	10.9 ± 11.4 yr	200 U, 300 U into the detrusor avoiding the trigone, +30 sites	MCC, Pdet, no. with no IDC	13	A
Jia, 2013 [10]	41	Prospective	China	36.0 ± 8.8	21.5 ± 17.3 mo	300 U into the detrusor sparing the trigone, +30 sites	Compliance, incidence of DO	N	C
Apostolidis, 2013 [11]	73	Prospective	International multicenter	33.6 ± 10.8	31.4 mo	200 U into the detrusor avoiding the trigone, +30 sites	MCC, VFIDC, Pdet, compliance	13.5	B
Sussman, 2013 [12,13]	121	Prospective	International multicenter	43.1 ± 15.2	8.1 ± 7.1 yr	200 U, 300 U into the detrusor avoiding the trigone, +30 sites	MCC, VFIDC, Pdet, UI episodes, PVR	13	A
Ginsberg, 2012 [14]	416	Prospective	International multicenter	46 ± 13	14 ± 9 yr	200 U, 300 U into the detrusor sparing the trigone, +30 sites	MCC, Pdet, UI episodes, no. with no IDC, I-QoL, PVR	13	A
Chen, 2016 [15]	30	Prospective	Germany	48.2 ± 18.41	NA	300 U into the detrusor, +30 sites	PVR, voiding volume, Qmax	18	C
Hui, 2016 [16]	91	Prospective	China	29.83 ± 11.77	20.04 ± 6.56 mo	160 into the wall and 40 into the trigone vs. 200 into the wall, avoiding the trigone, +30 sites	Pdet, voiding volume, VFIDC, I-QoL, UI episodes, etc.	3	B
Sengoku, 2015 [17]	19	Prospective	Japan	41.1 ± 14.2	11 yr + 5 mo	200 U into the subepithelial bladder wall sparing the trigone, +30 sites	UI episodes, incidence of DO	12	C
Chen, 2014 [18]	72	Prospective	Taiwan	41.5	8.7 ± 8.1 yr	200 U, 300 U into the detrusor, avoiding the trigone, +30 sites	PVR, voiding volume, Qmax, I-QoL, compliance	12	C
Krhtut, 2012 [19]	32	Prospective	International multicenter	20-48	NA	300 U into the detrusor and suburothelial, +30 sites	MCC, VFIDC, Pdet, voiding volume, etc.	3	B
Chen, 2011 [20]	38	Prospective	Taiwan	40.1 ± 12.4	10.3 yr	300 U into the detrusor sparing the trigone, +40 sites	PVR, Qmax, I-QoL	6	C
Gamé, 2008 [21]	30	Prospective	France	39.4 ± 12.1	13.3 ± 19.1 yr	300 U into the detrusor sparing the trigone, +30 sites	VFIDC, incidence of DO	6	C
Klaphajone, 2005 [22]	10	Prospective	Thailand	32.5	55.5 mo	300 U into the detrusor sparing the trigone, +15-30 sites	Compliance,	9	C
Abdel-Meguid, 2010 [23]	36	Prospective	Egypt	25 ± 3.1	31 ± 13.7 mo	300 U into the detrusor avoiding the trigone vs. 200 U into the detrusor and 100 U into the trigone	Mean volume of first reflex, UI episodes, etc.	4.5	B
Šámal, 2013 [24]	23	Prospective	Liberec	20-58	47 mo	300 U into the detrusor avoiding the trigone +submucosa, +30 sites	VFIDC, Pdet, UI episodes	3	B
Herschorn, 2011 [25]	57	Prospective	Canada	42.8	7.0 ± 6.8 yr	300 U into the detrusor sparing the trigone, +30 sites	UI episodes	15	A
Schurch, 2007 [26-28]	56	Prospective	Switzerland	41.6 ± 12.8	63 mo	200 U, 300 U into the detrusor sparing the trigone, +30 sites	AEs	6	A

SCI, spinal cord injury; MCC, maximum cystometric capacity; Pdet, detrusor pressure; IDC, involuntary detrusor contraction; DO, detrusor overactivity; VFIDC, volume at first involuntary detrusor contraction; UI, urinary incontinence; PVR, postvoid residual volume; I-QoL, incontinence-specific quality of life; Qmax, maximum flow rate; AEs, adverse events; NA, not applicable.

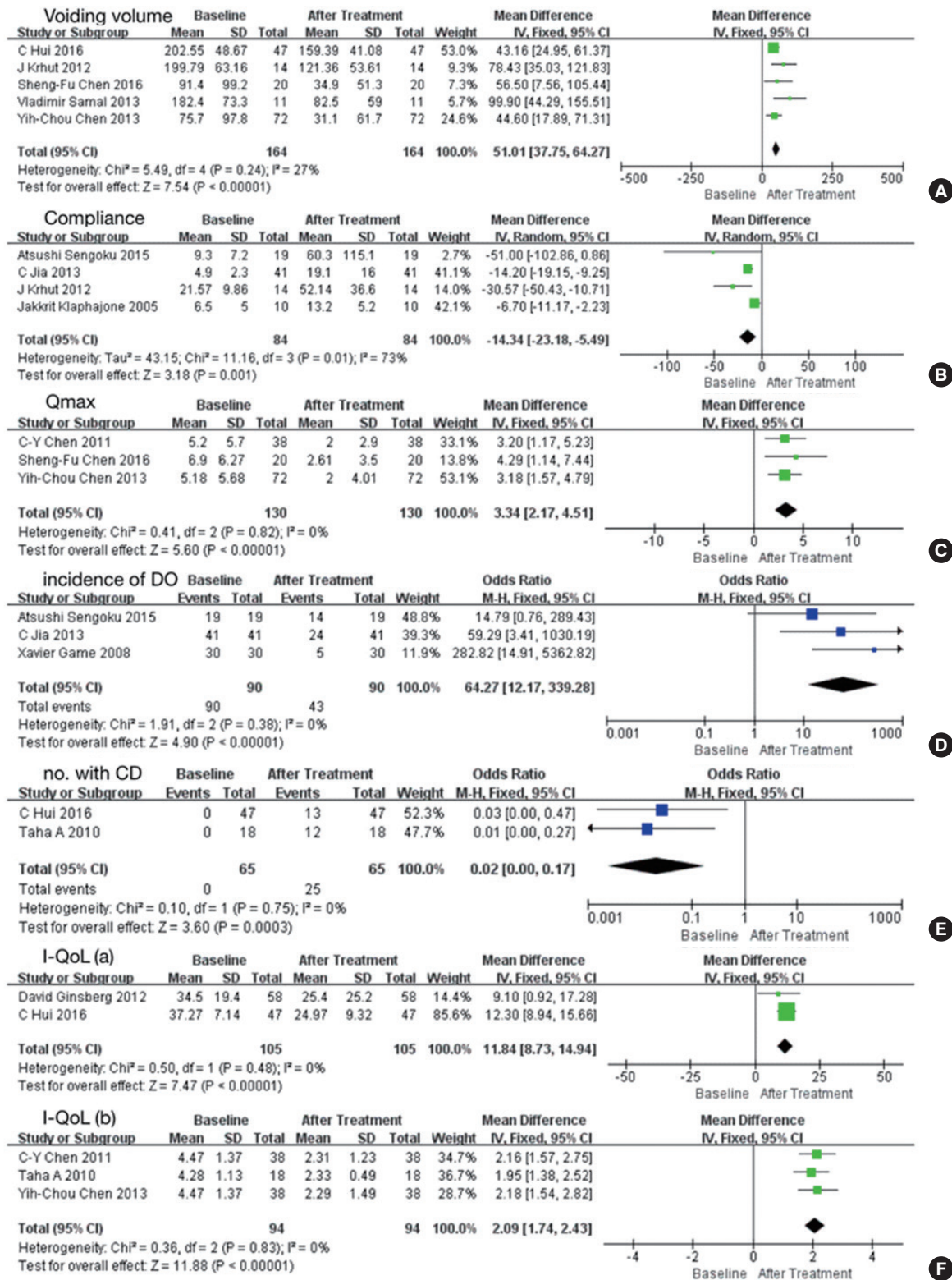
<sup>a)</sup>Quality assessment: (A) If all the key domains, and most information, met the low-risk criteria, the study was seen as having a low risk of bias. (B) If ≥ 1 key domains had an unclear risk of bias, and most information was at low or unclear risk, the study was viewed as having an unclear risk of bias. (C) If ≥ 1 key domains met the high-risk criteria and some information, with a significant influence on the results, was at a high risk of bias, the study was considered to have a high risk of bias.



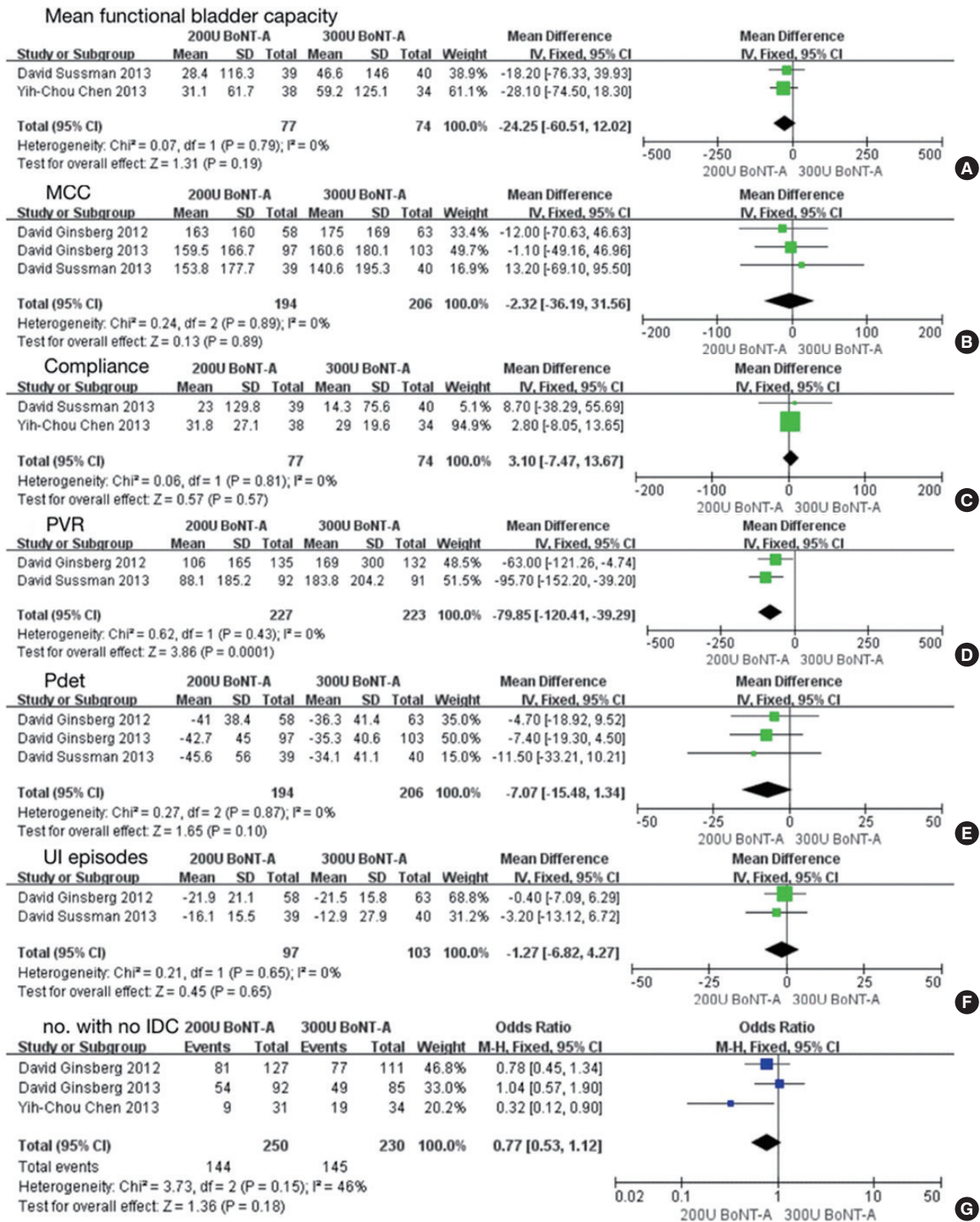
**Fig. 3.** Forest plots comparing the effects of onabotulinumtoxinA (BoNT-A) versus placebo on maximum cystometric capacity (MCC) (A), volume at first involuntary detrusor contraction (VFIDC) (B), detrusor pressure (Pdet) (C), urinary incontinence (UI) episodes (D), number of patients with no involuntary detrusor contraction (IDC) (E), and postvoid residual volume (PVR) (F). SD, standard deviation; CI, confidence interval; df, degrees of freedom.



**Fig. 4.** Forest plots comparing the effect of onabotulinumtoxinA (BoNT-A) on baseline values versus posttreatment values of maximum cystometric capacity (MCC) (A), volume at first involuntary detrusor contraction (VFIDC) (B), detrusor pressure (Pdet) (C), urinary incontinence (UI) episodes (D), number of patients with no involuntary detrusor contraction (IDC) (E), and postvoid residual volume (PVR) (F). SD, standard deviation; CI, confidence interval; df, degrees of freedom.

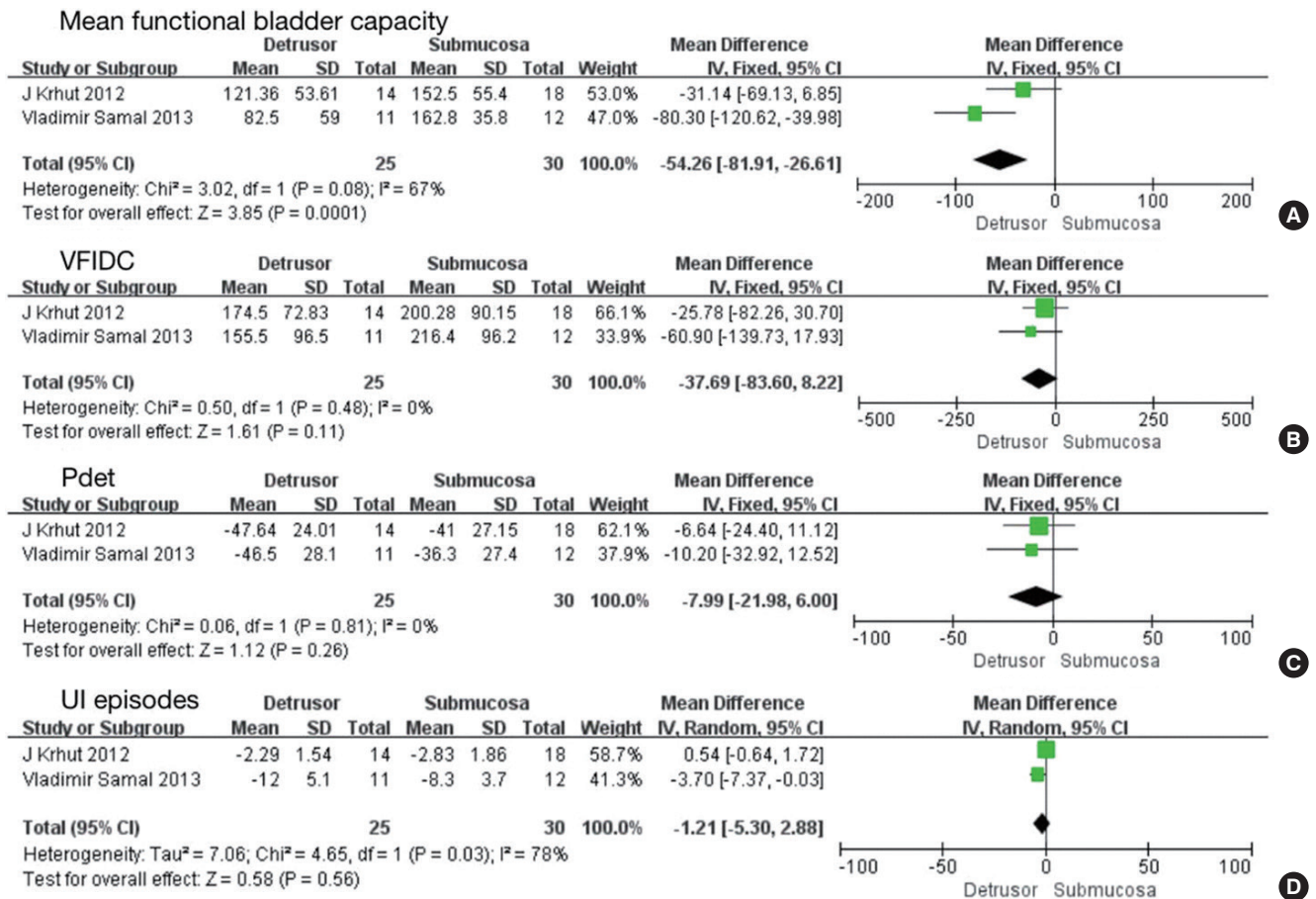


**Fig. 5.** Forest plots comparing the effect of onabotulinumtoxinA (BoNT-A) on baseline values versus posttreatment values of voiding volume (A), compliance (B), maximum flow rate (Qmax) (C), incidence of detrusor overactivity (DO) (D), number of patients with complete dryness (CD) (E), and incontinence-specific quality of life (I-QoL) (F). SD, standard deviation; CI, confidence interval; df, degrees of freedom.



**Fig. 6.** Forest plots comparing the difference between 200 U and 300 U of onabotulinumtoxinA (BoNT-A) on mean functional bladder capacity (A), maximum cystometric capacity (MCC) (B), compliance (C), postvoid residual volume (PVR) (D), detrusor pressure (Pdet) (E), urinary incontinence (UI) episodes (F), and number of patients with no involuntary detrusor contraction (IDC) (G). SD, standard deviation; CI, confidence interval; df, degrees of freedom.





**Fig. 7.** Forest plots comparing the difference between injections into the detrusor versus submucosa on mean functional bladder capacity (A), volume at first involuntary detrusor contraction (VFIDC) (B), detrusor pressure (Pdet) (C), and urinary incontinence (UI) episodes (D). SD, standard deviation; CI, confidence interval; df, degrees of freedom.

0.00–0.17;  $P = 0.0003$ ), reduced Qmax (MD, 3.34; 95% CI, 2.17–4.51;  $P < 0.00001$ ), and reduced incidence of DO (OR, 64.27; 95% CI, 12.17–339.28;  $P < 0.00001$ ) (Fig. 5).

Five other studies presented the effects of BoNT-A on I-QoL [14,16,18,20,23]. They were divided into 2 groups because they used different tools to evaluate I-QoL: a 22-item questionnaire and the International Prostatic Symptom Score questionnaire. Their results showed that BoNT-A was effective in improving I-QoL, and this improvement was significant (Fig. 5F).

#### **BoNT-A dose: 200 U versus 300 U**

Four studies involving 919 participants included data comparing doses of 200 U of BoNT-A versus 300 U [9,12,14,18,25]. No significant difference was found between 200 U and 300 U of BoNT-A in mean functional bladder capacity (MD, 24.5; 95% CI, -60.51 to 12.02;  $P < 0.19$ ), MCC (MD, -2.32; 95% CI, -36.19

to 31.56;  $P < 0.89$ ), compliance (MD, 3.10; 95% CI, -7.47 to 13.67;  $P < 0.57$ ), PVR (MD, -79.85; 95% CI, -120.41 to -39.29;  $P = 0.0001$ ), Pdet (MD, -7.07; 95% CI, -15.48 to 1.34;  $P < 0.10$ ), UI episodes (MD, -1.27; 95% CI, -6.82 to 4.27;  $P = 0.65$ ) and the number of patients with no IDC (MD, 0.77; 95% CI, 0.53–1.12;  $P = 0.18$ ) (Fig. 6).

#### **Injections into the detrusor versus submucosa**

Two studies involving 55 participants included data comparing injections into the detrusor versus submucosa [19,24]. No significant difference was found in mean functional bladder capacity (MD, -54.26; 95% CI, -81.91 to -26.61;  $P = 0.0001$ ), VFIDC (MD, -37.69; 95% CI, -83.60 to 8.22;  $P < 0.00001$ ), Pdet (MD, -7.99; 95% CI, -21.98 to 6.00;  $P = 0.26$ ) and UI episodes (MD, -1.21; 95% CI, -5.30 to 2.88;  $P = 0.56$ ) (Fig. 7).

**Table 2.** Complications of BoNT-A and placebo

Adverse event	BoNT-A	Placebo	P-value <sup>a)</sup>
Symptomatic UTI	432/861 (50.17)	160/425 (37.65)	0.00002
Urinary retention	150/732 (20.49)	15/409 (3.67)	0.00000
Hematuria	57/861 (6.62)	15/425 (3.53)	0.02334
Diarrhea	41/732 (5.60)	19/409 (4.65)	0.48799
Nausea	40/732 (5.46)	8/409 (1.96)	0.00464
Constipation	38/732 (5.19)	18/409 (4.40)	0.55348
Pyrexia	38/761 (4.99)	16/396 (4.04)	0.34073
Fatigue	35/704 (4.97)	13/380 (3.42)	0.23639
Headache	34/732 (4.64)	15/409 (3.67)	0.43487
Autonomic dysreflexia	29/776 (3.74)	2/380 (0.53)	0.00150

Values are presented as number (%).

BoNT-A, onabotulinumtoxinA; UTI, urinary tract infection.

<sup>a)</sup>P-values were the outcomes of the chi-square tests for independence of each adverse event between the 2 groups.

## Safety

We recorded all types of AEs and their proportions [9-28]. The chi-square test was used to evaluate differences between pairs of groups. Table 2 lists the top 10 AEs, including symptomatic urinary tract infection, urinary retention, hematuria, diarrhea, nausea, constipation, pyrexia, fatigue, headache, and autonomic dysreflexia. Nearly half of the AEs were not considered to have been treatment-related. Others could recover spontaneously or with only symptomatic treatment, and no AEs were life-threatening.

## DISCUSSION

The neurotoxin Botulinum toxin, first described by van Ermenegem in 1897, was extracted from the bacterium *Clostridium botulinum* [29,30]. BoNT-A, as a subtype, received FDA approval for the clinical treatment of NDO in 2011 [31]. BoNT-A inhibits neurotransmitter release from efferent nerve and sensory nerve endings. After BoNT-A injections, the expression of bladder muscarinic receptors M2 and M3 is reduced in humans with NDO [32]. For the above reasons, BoNT-A can induce the inhibition of DO and cause Pdet to decrease. Recent studies have reported it to have significant benefits on urodynamic parameters and clinical indices [33].

According to this meta-analysis, compared with baseline, BoNT-A was effective in increasing MCC, VFIDC, the voiding volume, compliance, I-QoL, the number of patients with CD and no IDC, and in decreasing Pdet, UI episodes, Qmax, and

the incidence of DO [10,15-24]. Meanwhile, this meta-analysis further indicated that compared with placebo, BoNT-A was effective in increasing MCC, VFIDC, and the number of patients with no IDC, and in decreasing Pdet and UI episodes during 18 months of follow-up [8-14]. However, PVR was found to increase. The reason for this is that as MCC and VFIDC increased, the residual volume after voiding also increased. Additionally, since the dose used in clinical therapy remained controversial, our review mainly focused on comparing the most frequent doses (200 U and 300 U) [31]. Both doses were comparably effective in terms of outcomes for mean functional bladder capacity, MCC, compliance, PVR, Pdet, UI episodes, and the number of patients with no IDC [9,12,14,18,25]. Likewise, no significant difference was found between injection into the detrusor versus the submucosa in terms of mean functional bladder capacity, VFIDC, Pdet, and UI episodes [19,24].

In addition to the above-presented results, 2 RCTs involving 127 participants compared injection locations (sparing the trigone and excluding the trigone). One study compared 160 U of BoNT-A injected into the bladder wall combined with 40 U into the trigone versus the injection of 200 U into the bladder wall, avoiding the trigone [16]. Both methods increased the number of patients with CD (+13 vs. +5,  $P=0.01$ ), improved I-QoL ( $26.01 \pm 11.56$  vs.  $18.75 \pm 15.18$ ), decreased UI episodes ( $-5.22 \pm 0.91$  vs.  $-4.68 \pm 1.06$ ,  $P=0.01$ ), and Pdet ( $-33.34 \pm 20.27$  vs.  $-28.02 \pm 15.18$ ,  $P=0.04$ ). However, sparing the trigone was considered preferable [11]. The other study compared 200 U injected into the detrusor combined with 100 U into the trigone versus 300 U injected into the detrusor, avoiding the trigone [23]. Sparing the trigone was more obviously preferable in terms of increasing patients with CD (+12 vs. +6,  $P<0.001$ ) and decreasing UI episodes ( $0.98 \pm 0.45$  vs.  $2.38 \pm 0.79$ ,  $P<0.001$ ). However, no significant differences were found in MCC ( $384.6 \pm 49.7$  vs.  $406.5 \pm 55.4$ ,  $P=0.22$ ), Pdet ( $35.0 \pm 3.6$  vs.  $36.9 \pm 5.1$ ,  $P=0.21$ ), I-QoL ( $2.22 \pm 0.55$  vs.  $2.22 \pm 0.65$ ,  $P=0.44$ ) [22]. Considering the diversity of doses in the 2 studies, further research is needed.

Nevertheless, there were some limitations of our analysis. We considered conducting subgroup analyses based on quality assessment, as shown in Table 1. However, there were not enough data in each subgroup for such an analysis. Therefore, considering the same standard of quality assessments for all the studies and in order to avoid repeating our analyses, we summarized the primary characteristics and quality assessment results of all the included studies in Table 1. Furthermore, it seemed to be

better to evaluate the MD of differences instead of the MD of values when comparing the effect of BoNT-A on baseline versus posttreatment values. However, most of the raw data from the included studies only provided the values after treatment, instead of the difference between baseline and after treatment. Therefore, we only evaluated the MDs.

In addition, heterogeneity could be generated by the subjects chosen, the location and dose of each site, and the loss of some negative data. Heterogeneity can be reduced by applying conscientious and rigorous procedures and sensitivity analyses, but it cannot be eliminated. Meanwhile, due to differences in the follow-up periods, the long-term effects were somewhat difficult to evaluate. Furthermore, the data in the studies included in this meta-analysis were insufficient to determine which dose and injection site were better for patients, so more high-quality prospective trials are still needed [8].

In conclusion, BoNT-A is effective and safe in treating NDO after SCI in the short term. There were no significant differences between 200 U or 300 U of BoNT-A and between injecting into the detrusor or submucosa. More high-quality and refined RCTs are needed.

## AUTHOR CONTRIBUTION STATEMENT

- Full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis: *GPL, XYW, YZ*
- Study concept and design: *GPL, XYW, YZ*
- Acquisition of data: *GPL, XYW*
- Analysis and interpretation of data: *GPL, XYW*
- Drafting of the manuscript: *GPL*
- Critical revision of the manuscript for important intellectual content: *GPL, XYW, YZ*
- Statistical analysis: *GPL, XYW*
- Study supervision: *YZ*

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