Efficacy and safety of botulinum toxin for treating motor dysfunction in patients with Parkinson’s disease: a systematic review and meta-analysis

Yuqi Yang,1,2 Tong Zhang,1,2 Liu Li,1,2 Xiaoli Wu,1,2 Hanzhi Li1,2

ABSTRACT
Objective To evaluate the efficacy and safety of botulinum toxin (BTX) for motor dysfunction in Parkinson’s disease (PD).

Design Systematic review and meta-analysis.

Data sources Searches of PubMed, EMBASE and the Cochrane Library, from database inception to 20 October 2022.

Eligibility criteria Studies reported in English with adult PD patients treated with BTX.

Data extraction and synthesis

Results Six randomised controlled trials (RCTs) and six non-RCTs (case series) were included (ntotal=224 participants, nRCT=165). No significant difference was found in pooled results of UPDRS-III (available in four RCTs and two non-RCTs, SMD=−0.19, 95% CI −0.98 to 0.60), UPDRS-II (four RCTs and one non-RCT, SMD=−0.55, 95% CI −1.22 to 0.13), FOG-Q (one RCT and one non-RCT, SMD=−0.53, 95% CI −1.93 to 2.98) or the risk of TRAEs (five RCTs, RR 0.87, 95% CI 0.37 to 2.01). Significant decreases were found in pooled VAS score (three RCTs and five non-RCTs, MD=−2.14, 95% CI −3.05 to −1.23) and TUG (MD=−2.06, 95% CI −2.91 to −1.20) after BTX treatment.

Conclusions BTX may not be associated with motor symptoms alleviation, although it benefits pain alleviation and functional mobility improvement.

INTRODUCTION
Parkinson’s disease (PD) is a degenerative disorder of the central nervous system. It is the second most common neurodegenerative disease worldwide, with incidence and prevalence increasing with age.1 During the course of the disease, the most pronounced symptoms are related to movement: tremor, rigidity, slowness of movement, postural instability and difficulty with walking and gait.2 Motor dysfunction in PD patients becomes more severe as PD progresses. Herein, patients are less likely to control their movements, which are often accompanied by serious physical pain.3 The motor dysfunction of PD is due to the death of dopamine-generating cells in the substantia nigra; however, the reason why these cells die is not known. Notably, the aetiology of PD has not been fully revealed at the neural network and anatomical level, resulting in the inability of the current medical technology to cure PD. Therefore, some related symptoms to motor dysfunction, such as tremors and dystonia, have been investigated in order to more effectively relieve the pain and improve the quality of life of PD patients.4 Current management strategies for motor dysfunction-related symptoms aim to relieve symptoms and slow disease progression, but no pharmacological breakthroughs have been made to protect dopaminergic neurons and related motor circuitry components.5
Levodopa, a prodrug to dopamine, is the standard and most common initial therapy for PD patients. Early responses of PD patients to levodopa are usually good, but as the disease progresses and the capacity of the system to store dopamine declines, most patients eventually experience a shorter duration of response to individual doses, alternative phases with good and poor response to medication, involuntary movements of the head, trunk or limbs, and other motor complications.\(^6\) Therefore, it is crucial to find a promising approach for the treatment of motor dysfunction-related symptoms.

Botulinum toxin (BTX) has been widely used for decades to treat motor and movement disorders, autonomic dysfunctions and neuropathic pain.\(^7\)\(^8\) BTX blocks the release of acetylcholine from presynaptic nerve terminals at the neuromuscular junction, thereby blocking muscle contraction and gland activity at the postganglionic synapses. It has become an important treatment option for movement disorders, especially for focal and generalised dystonia.\(^10\) Various studies have examined the efficacy of BTX in alleviating the severity of movement disorders in PD patients. Several studies have also evaluated the efficacy of BTX in improving drooling and sialorrhoea in PD patients, showing that BTX did not significantly improve the recovery or severity of drooling and sialorrhoea.\(^11\)\(^\text{–}^\text{14}\) In addition, studies evaluating the therapeutic efficacy of BTX on movement disorder in PD patients have reported ambiguous results.\(^15\)\(^\text{–}^\text{17}\)

Therefore, to determine the therapeutic efficacy and safety of BTX treatment for motor disorders in PD patients, this systematic review and meta-analysis was conducted to systematically evaluate the association between BTX treatment and motor disorders in PD patients.

### METHODS

We performed this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline.\(^18\)

### Search strategy

We conducted a comprehensive search in three databases, including PubMed, EMBASE and the Cochrane library, from the establishment date of these databases up to 20 October 2022. The publication language was limited to English, and subjects were limited to human. The following medical subject heading terms and their analogues were used to develop search strategy: “Parkinson Disease” and “Botulinum Toxins”. Detailed search strategies of three databases are summarised in online supplemental table I.

### Study selection criteria

We developed eligibility criteria for this study based on PICO acronym. Specifically, P, I, C and O represented participants, interventions, comparators, and outcomes, respectively.

### Participants

Eligible participants were adult patients with PD.\(^3\)

### Intervention

BTX, the administration, dose and course of the treatment were not limited.

### Comparison

All types of comparisons could be accepted, including the placebo or other treatment.

### Outcomes

The primary outcome included the scores of the United Parkinson’s Disease Rate Scale section (UPDRS) III\(^19\) and the Visual Analogue Scale (VAS). UPDRS, one of the bases of treatment and research in PD clinics, is a rating tool to gauge the course of PD patients. UPDRS includes a series of ratings for typical Parkinson’s symptoms that cover all the movement hindrances of PD. The third segment of UPDRS (UPDRS-III) is a motor section that grades and evaluates the mobile disability of PD patients. The intensity of distress (pain, cramp, muscle tension) because of motor dysfunction was measured with a VAS. The secondary outcomes included the scores of the UPDRS-II, Freezing of Gait Questionnaire (FOG-Q),\(^20\) Timed Up and Go test (TUG)\(^21\) and treatment-related adverse events (TRAEs). UPDRS-II assesses the activities of daily living of PD patients. FOG-Q evaluates the effect of treatment in PD patients with freezing of gait. A higher TUG score indicates an increased risk of falls.

### Study

Cohort studies, randomised control trials (RCTs), case–control studies, cross-over studies and case series. The studies could enrol participants without gender constraints. The studies combined with other treatments were excluded, as well as those studies that did not use motor dysfunction evaluations were also excluded. In addition, the present study also excluded abstracts that did not provide sufficient information for statistical analysis and methodological evaluation.

### Study selection procedures

Two investigators independently screened the titles and abstracts of the studies identified in the primary search based on prespecified exclusion and inclusion criteria. The full text of the remaining articles was reviewed to determine whether it contained relevant information. Any discrepancy was resolved by a consensus and discussion with a third investigator. The bibliographic sections of the selected articles, as well as the systematic and narrative articles on the topic, were manually searched.

### Data extraction

Data on study-related outcomes in the individual studies were abstracted onto a standardised form by two investigators and included study characteristics, including authors, year of publication, the country where the study was performed, study design, disease type, sample size, etc.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>Symptoms</th>
<th>Sample size (I/P)</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fernandez et al</td>
<td>USA</td>
<td>RCT</td>
<td>Freezing of gait</td>
<td>9/5</td>
<td>Intramuscular injections of 5000 units of BTX into the soleus-gastrocnemius complex of the predominantly affected leg</td>
<td>1 month</td>
<td>UPDRS-II, UPDRS-III, VAS, TRAEs</td>
</tr>
<tr>
<td>Gurevich et al</td>
<td>Israel</td>
<td>RCT</td>
<td>Freezing of gait</td>
<td>6/5</td>
<td>BTX was injected gastrocnemius/soleus muscles under EMG control at a total dose of 300 IU (150 IU per leg)</td>
<td>20 weeks</td>
<td>UPDRS-II, UPDRS-III, FOG-Q, TRAEs</td>
</tr>
<tr>
<td>Bonanni et al</td>
<td>Italy</td>
<td>RCT</td>
<td>Lateral axial dystonia</td>
<td>4/5</td>
<td>125 U of BTX toxin were injected under EMG control</td>
<td>3 months</td>
<td>VAS</td>
</tr>
<tr>
<td>Gupta and Visvanathan</td>
<td>Australia</td>
<td>CS</td>
<td>Foot dystonia</td>
<td>6/0</td>
<td>The involved muscles were injected with 250–400 units BTX</td>
<td>3 months</td>
<td>UPDRS-II, VAS, TUG, TRAEs</td>
</tr>
<tr>
<td>Lindholm et al</td>
<td>Sweden</td>
<td>CS</td>
<td>Striatal foot</td>
<td>10/0</td>
<td>15–60 U per one limb with EMG guidance</td>
<td>16 weeks</td>
<td>UPDRS-III, VAS, TUG</td>
</tr>
<tr>
<td>Vastik et al</td>
<td>Czech Republic</td>
<td>CS</td>
<td>Freezing of gait</td>
<td>10/0</td>
<td>Injected under EMG guidance, guidance, dosage 50 U per one leg</td>
<td>4 weeks</td>
<td>FOG-Q, TUG</td>
</tr>
<tr>
<td>Bruno et al</td>
<td>Canada</td>
<td>RCT</td>
<td>Pain in Parkinsonism</td>
<td>7/5</td>
<td>Up to 200 units in the upper painful limbs or up to 300 units in the lower painful limbs</td>
<td>12 weeks</td>
<td>UPDRS-II, UPDRS-III, VAS, TRAEs</td>
</tr>
<tr>
<td>Artusi et al</td>
<td>Italy</td>
<td>CS</td>
<td>Pisa syndrome</td>
<td>13/0</td>
<td>50–75 BTX for each paraspinal muscle injected, and from 25 to 50 units for each non-paraspinal muscle injected</td>
<td>2 months</td>
<td>VAS, TRAEs</td>
</tr>
<tr>
<td>Mittal et al</td>
<td>USA</td>
<td>RCT</td>
<td>Tremor</td>
<td>14/16</td>
<td>BTX was injected into muscles using sterile 27-gauge needle under EMG guidance, with the mean total dose of 100 U per patient</td>
<td>8 weeks</td>
<td>UPDRS-II, UPDRS-III, TRAEs</td>
</tr>
<tr>
<td>Zhu et al</td>
<td>China</td>
<td>RCT</td>
<td>Unclear</td>
<td>45/44</td>
<td>100 U BTX was diluted with 2 mL 0.9% saline, and was then injected into different sites</td>
<td>3 months</td>
<td>TRAEs</td>
</tr>
<tr>
<td>Datta Gupta et al</td>
<td>Australia</td>
<td>PPTC</td>
<td>Spatiotemporal</td>
<td>14/0</td>
<td>BTX was injected into dystonic muscles in the foot, with a maximum dose of 300 U</td>
<td>3 weeks</td>
<td>UPDRS-III, VAS, TUG, TRAEs</td>
</tr>
<tr>
<td>Huang et al</td>
<td>China</td>
<td>CS</td>
<td>Foot dystonia</td>
<td>6/0</td>
<td>BTX with a concentration of 50.0 U/mL was injected into different sites under EMG guidance</td>
<td>3 months</td>
<td>VAS, TUG</td>
</tr>
</tbody>
</table>

BTX, botulinum toxin; CS, case series; EMG, electromyography; FOG-Q, Freezing of Gait Questionnaire; PPTC, pretreatment and post-treatment comparison; RCT, randomised controlled trial; TRAEs, treatment-related adverse events; TUG, Timed Up and Go test; UPDRS-II, United Parkinson’s Disease Rating Scale Section II; UPDRS-III, United Parkinson’s Disease Rating Scale Section III; VAS, Visual Analogue Scale.
follow-up duration, treatment parameters, and primary and secondary outcomes. If a study used some items of UPDRS-II (eg, item 16 for evaluating symptomatic complaint of tremor) or UPDRS-III (eg, item 21 for evaluating action/postural tremor) to measure outcomes, we also extracted these data for meta-analysis.

We used the recognised formulas to calculate the required data based on the information reported in each study if necessary. If studies only displayed results using plots, we retrieved essential data using Plot Digitizer V.2.6.8. Discrepancies were rechecked with a third investigator until a consensus was achieved.

Quality assessment
Two reviewers independently assessed the methodological quality of included studies using different assessment tools according to study design. The quality assessment for RCT was conducted using the revised Cochrane risk of bias tool. In this tool, each domain was labelled with high, some concerns or low, and the overall methodological quality for each study was determined based on the results of all domains. Specifically, the overall methodological quality was high if all domains were labelled with low risk, was moderate if at least one domain was labelled with some concerns but no domain was labelled with high risk, or was low if at least one domains was labelled with high risk. For non-randomised studies, we used ROBINS-I to assess its methodological qualities from seven domains: confounding, selection of participants, classification of intervention, deviations from intervention, missing data, measurement of outcome and selection of reported results. Each domain of this tool was labelled with low, moderate, serious or critical risk of bias, and the overall methodological quality for each study was rated as non-critical and critical based on the results of all seven domains. Finally, we used an online programme, namely 'robvis', to graphically presented the results of risk of bias assessment. Disagreements between the two investigators were discussed until a consensus had been achieved.

Statistical analysis
We used risk ratio (RR) with 95% CI to express the estimate of TRAEs. For continuous variables, the mean difference (MD) with 95% CI was used to express the estimates if data were measured using the same tool at the same measurement scale. Conversely, if data were measured using different tools, using the same tool but on different measurement scales, or using different tools on different measurement scales, we expressed estimates using standardised MD (SMD) with 95% CI. We evaluated statistical heterogeneity between studies using the Cochrane Q and Higgins I², and there was significant for statistical heterogeneity if p<0.1 and I²>50%. Nevertheless, due to the anticipated heterogeneity of the included studies, particularly differences in study design, we performed meta-analysis using a random-effects model. When non-randomised studies were assessed as being at critical risk of bias, we adjusted the within-study variance-covariance matrix using a precision weight correction factor of 0.1 to provide a more conservative pooled estimate. We did not examine potential publication bias by funnel plots and Egger’s test because the number of studies included in this meta-analysis was less than 10, in which case the funnel plots and Egger’s test could yield misleading results and are not recommended. We first used Open Meta-Analyist software to conduct statistical analysis, then used Review Manager to derive forest plots.
RESULTS

The established search strategy identified 2795 publications. After removing 517 duplicates, 2278 records were screened according to the inclusion criteria. After initial screening, 2,256 publications were excluded based on the title and abstract. Then, 22 studies were kept for further eligibility evaluation based on full texts. After excluding 10 studies according to the following reasons: ineligible patients (n=5), ineligible aims (n=2), ineligible language (n=1) and unrelated to our topic (n=2), a total of twelve studies were included,15–17 34–42 including six RCTs and six non-RCTs (all case series). A flowchart of the search process is shown in online supplemental figure 1. All studies were published between 2004 and 2022. The symptom of freezing of gait was observed in three studies. Lateral axial dystonia, foot dystonia, striatal foot, tremor, spatiotemporal and pain Parkinsonism were observed in the remaining nine studies. The basic characteristics of the included studies are summarised in table 1.

Methodology quality

According to the revised Cochrane assessment tool, all RCTs were rated as low or some concerns in bias; however, all non-randomised studies were rated as critical risk in the overall methodological quality. The results of methodological quality assessment are displayed in online supplemental figure 2.

Primary outcomes

United Parkinson’s Disease Rate Scale Section III

Four RCTs and two non-randomised studies contributed with data for UPDRS-III. Adjusted pooled results showed that BTX treatment did not significantly change the score of the UPDRS-III (SMD=−0.19, 95% CI −0.98 to 0.60; I²=73%; figure 1). As shown in figure 1, subgroup analysis according to study design (p=0.10 for subgroup differences) was non-significant.

Visual Analogue Scale

Three RCTs and five non-randomised studies contributed with data for VAS. Adjusted pooled results showed that BTX treatment significantly changed the score of the VAS (MD=−2.14, 95% CI −3.05 to −1.23; I²=63%; figure 2). As shown in figure 2, subgroup analysis according to study design (p=0.25 for subgroup differences) was non-significant.

Secondary outcomes

United Parkinson’s Disease Rate Scale Section II

Four RCTs and one non-randomised study contributed with data for UPDRS-II. Adjusted pooled results showed that BTX treatment did not significantly change the score of the UPDRS-II (SMD=−0.55, 95% CI −1.22 to 0.13; I²=54%; figure 3). As shown in figure 3, subgroup analysis according to study design (p=0.11 for subgroup differences) was non-significant.

Timed Up and Go test

Five non-randomised studies contributed with data for TUG. Pooled results showed that BTX treatment...
significantly changed the TUG (MD=−2.06, 95% CI −2.91 to −1.20; I²=52%)

Freezing of Gait Questionnaire
One RCT and one non-randomised study contributed with data for FOG-Q. Adjusted pooled results showed that BTX treatment did not significantly change the score of the FOG-Q (SMD=0.53, 95% CI −1.93 to 2.98; I²=87%; Online supplemental figure 3). As shown in online supplemental figure 3, however, subgroup analysis according to study design (p=0.006 for subgroup differences) was significant.

Treatment-related adverse events
Five RCTs contributed with data for TRAEs. Pooled results showed that BTX treatment was not significantly associated with an increased risk of TRAEs (RR=0.87, 95% CI 0.37 to 2.01; I²=21%; figure 5).

DISCUSSION
To our knowledge, this is the first systematic review and meta-analysis to evaluate the therapeutic efficacy and safety of BTX for treating motor dysfunction in PD patients. A total of twelve studies including six randomised (n=165) and six non-randomised (n=59) studies that used BTX to treat motor dysfunction were included in the final data analysis. Pooled results showed that BTX treatment in PD patients significantly decreased the scores of VAS and shortened TUG, but did not increase the risk of TRAEs, although it did not significantly alter the scores of the UPDRS-III, UPDRS-II and FOG-Q.

It is estimated that up to 80% of dopaminergic cells in the nigrostriatal system are lost before the cardinal motor features of PD appear.43 The disease is usually diagnosed by the first motor symptoms and is considered to be of special significance. Therefore, it is crucial to effectively treat motor symptoms in PD patients. BTX is currently a first-line therapy for the treatment of cervical dystonia, blepharospasm and focal dystonia due to its effectiveness and its low risk of causing systemic side effects, as concluded in a review published in 2008.44 Nevertheless, throughout the review process, no clear and widely supported conclusions were found regarding the therapeutic efficacy of BTX on motor dysfunction in PD patients, nor did we find clear evidence that BTX was ineffective. However, in this systematic review and meta-analysis, we provided more information on the efficacy and safety of BTX for the treatment of motor symptoms.
in PD patients. Although the current evidence indicated that BTX might not benefit in improving motor symptoms, it helped alleviate pain and improve functional mobility without increasing the risk of TRAEs.

Injection schedules, doses and approaches (either ultrasound or anatomical landmark guidance) of BTX varies in clinical practice. Notably, studies have revealed that different injection schedules and doses of BTX might be associated with different efficacies and risks of TRAEs. In these eligible studies included in the present systematic review and meta-analysis, the injection dose of BTX can be as small as a few IU per limb in the study by Lindholm et al in 2017 and as large as intra-muscular injections of 5000 units of BTX into the soleus-gastrocnemius complex of the predominantly affected leg in the study by Fernandez et al in 2004. Meanwhile, the injection schedules and approaches varied in the included studies, there was no evidence on which dose, schedules or approaches was the most appropriate, so the variations due to doses, schedules and approaches could not be ignored.

BTX was first isolated from Clostridium botulinum which caused muscle paralysis after consuming contaminated sausages. In the following decades, BTX proved its efficacy in several neurologic conditions. Among the seven biological serotypes of BTX, only BTX types A and B are used for clinical therapy. In this study, most of the included studies used BTX type A, one study used BTX type B and one did not report the details of type of BTX. Due to the small sample of studies, subgroup analyses could not be conducted. Meanwhile, there were no studies that compared the effectiveness of BTX types A and B for treating PD, but it does not mean that there are no differences between BTX types A and B for the treatment of PD.

The patients suffered from various symptoms, including the freezing of gait, lateral axial dystonia, foot dystonia, striatal foot, pain and Pisa syndrome. Therefore, the BTX injections were performed according to the symptoms, contributing to heterogeneity. Indeed, although the BTX was administered by intramuscular injection in all studies, some were under electromyographic guidance, some trials injected the gastrocnemius/soleus muscles, and some injected the paraspinous muscles, dystonic muscles, tibialis posterior, extensor hallucis and flexor digitorum longus, increasing heterogeneity.

The present systematic review and meta-analysis have some methodological limitations. First, the study design was not limited, which would inevitably bias the pooled results when combining randomised and non-randomised studies if appropriate strategies were not used to correct weights of non-randomised studies with critical risk. However, we addressed this issue using a precise weight correction factor of 0.1 according to the strategy used in a previous study, thus reducing the risk of biased results to some extent. Second, some studies fell short in terms of quality, owing to small numbers of participants, unclear reporting of study methods and data reporting in a format that was not easy to combine with other data. Further research is required to clarify the efficacy and safety of BTX treatment for PD patients. Third, our analysis included patients with PD and different motor disorders, and BTX was injected into different sites according to the symptoms. The reaction of pain and functional assessment can differ by injection sites. Fourth, most studies additionally injected BTX without long-term follow-up. The outcomes were measured by physicians or the patients themselves, thus making the results highly subjective. The studies of BTX for treating motor dysfunction in patients with PD need to be normalised in the future. Above all, the standardisation related to RCTs should be considered. Fifth, we did not use any strategies to check for publication bias due to limited number of eligible studies for each outcome. Therefore, we must acknowledge that publication bias may negatively affect the pooled results. Sixth, all eligible studies enrolled only limited sample sizes, which significantly increased the risk of erroneous results. So, the sample size needs to be calculated formally, and long-term follow-up should also be considered in future studies.

**Conclusion**

The present meta-analysis showed that BTX may not improve motor symptoms in PD patients, although it may benefit pain alleviation and functional mobility improvement. However, our findings must be interpreted with more caution due to some limitations in terms of methodology and content. In addition, we also suggest that future
prospective comparative studies with a large sample size are required to validate our findings.

Contributors YL and LZ carried out the studies, participated in collecting data and drafted the manuscript. LS and XH, XX performed the statistical analysis and participated in its design. YJ and FG, HL participated in the acquisition, analysis or interpretation of data and drafted the manuscript. All authors read and approved the final manuscript.

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Provenance and peer review Not commissioned; externally peer reviewed.

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