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[Intervention Review]

Botulinum toxin for motor and phonic tics in Tourette's syndrome

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ABSTRACT

Background

Gilles de la Tourette syndrome, or Tourette's syndrome, is defined as the presence of both motor and vocal (phonic) tics for more than 12 months, that manifest before the age of 18 years, in the absence of secondary causes. Treatment of motor and phonic tics is difficult and challenging.

Objectives

To determine the safety and effectiveness of botulinum toxin in treating motor and phonic tics in people with Tourette's syndrome, and to analyse the effect of botulinum toxin on premonitory urge and sensory tics.

Search methods

We searched the Cochrane Movement Disorders Group Trials Register, CENTRAL, MEDLINE, and two trials registers to 25 October 2017. We reviewed reference lists of relevant articles for additional trials.

Selection criteria

We considered all randomised, controlled, double-blind studies comparing botulinum toxin to placebo or other medications for the treatment of motor and phonic tics in Tourette's syndrome for this review. We sought both parallel group and cross-over studies of children or adults, at any dose, and for any duration.

Data collection and analysis

We followed standard Cochrane methods to select studies, assess risk of bias, extract and analyse data. All authors independently abstracted data onto standardized forms; disagreements were resolved by mutual discussion.

Main results

Only one randomised placebo-controlled, double-blind cross-over study met our selection criteria. In this study, 20 participants with motor tics were enrolled over a three-year recruitment period; 18 (14 of whom had a diagnosis of Tourette's syndrome) completed the study; in total, 21 focal motor tics were treated. Although we considered most bias domains to be at low risk of bias, the study recruited a small number of participants with relatively mild tics and provided limited data for our key outcomes. The effects of botulinum toxin injections on tic frequency, measured by videotape or rated subjectively, and on premonitory urge, are uncertain (very low-quality evidence). The quality of evidence for adverse events following botulinum toxin was very low. Nine people had muscle weakness following the injection, which could have led to unblinding of treatment group assignment. No data were available to evaluate whether botulinum injections led to immunoresistance to botulinum.

Authors' conclusions

We are uncertain about botulinum toxin effects in the treatment of focal motor and phonic tics in select cases, as we assessed the quality of the evidence as very low. Additional randomised controlled studies are needed to demonstrate the benefits and harms of botulinum toxin therapy for the treatment of motor and phonic tics in patients with Tourette's syndrome.

PLAIN LANGUAGE SUMMARY

Botulinum toxin for motor and phonic tics

Review question: How safe and effective is botulinum toxin, compared to placebo or other medications, in treating motor and phonic tics in Tourette's syndrome?

Background: People with Tourette's syndrome often make repetitive and sudden movements (motor) or vocal noises (phonic) called tics. Botulinum toxin injections are used to treat motor and phonic tics in patients with Tourette's syndrome. They are thought to weaken the mechanism in the body that makes the tics happen. There are conflicting reports regarding their effectiveness.

Study characteristics: The review authors summarised information from one clinical trial that compared botulinum toxin to a placebo, to treat tics in adults with Tourette's syndrome.

Key results: We found one small study. The study was limited by the number of participants (N = 18), who mainly had mild tics. We are very uncertain about the effects of botulinum toxin injections on reducing tic frequency and severity, and measures of overall well-being. Some participants experienced harms, which included weakness, restlessness, and neck discomfort following the injection. We do not know from the study whether participants who received the injection developed resistance to the botulinum injections, which would make them less effective over time.

The evidence is current to 25 October 2017.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Botulinum toxin compared to Placebo for motor and phonic tics in Tourette's syndrome

Botulinum toxin compared to placebo for motor and phonic tics in Tourette's syndrome

Patient or population: Tourette's syndrome with motor and phonic tics

Setting: hospital

Intervention: botulinum toxin injections

Comparison: placebo injections

Outcomes	Net effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
Severity of motor tics (measured by video-tape of tic count)	Median proportional change in treated tics: with Botulinum toxin -39%; with placebo +5.8%; net effect -37% (IQR -77% to -15%)	18 (1 RCT)	⊕⊕⊕⊕ VERY LOW 1, 2
Severity of phonic tics	Phonic tics were not measured.		
Premonitory Urge (treated tics)	The net effect for urge in treated tics was -0.94 (-1.71 to -0.17) and for premonitory sensation in treated tics was 0.03 (-0.86 to 0.92)	18 (1 RCT)	⊕⊕⊕⊕ VERYLOW 1, 2
Sensory tics	Senory tics were not measured in this trial.		
Adverse events	There were 32 adverse events reported in the Botulinum group;with placebo group only five adverse events were reported which includes weakness and neck discomfort.	18 (1 RCT)	⊕⊕⊕⊕ VERY LOW 1, 2
Development of immunoresistance against botulinum toxin	This outcomes were not reported in this included study.		

Net effect: proportional change in the intervention arm - proportional change in the control arm; **CI:** confidence interval

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹ Downgraded one level due to indirectness: The majority of participants had a mild tic disorder, limiting the results from generalisation to everyone with Tourette's syndrome.

² Downgraded two levels due to very serious imprecision: Very small sample size in the study (18 participants) and wide confidence intervals.

BACKGROUND

Gilles de la Tourette syndrome, which is more commonly known as Tourette's syndrome (TS), is diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria as the presence of both motor and vocal (phonic) tics for more than 12 months, which manifest before the age of 18 years, in the absence of secondary causes (APA 2013). Tics resemble voluntary actions and can vary significantly. They manifest as repetitive, out of context, and exaggerated movements (Ganos 2015). TS is now recognized as a neuropsychiatric spectrum disorder, in which tics are commonly associated with attention deficit hyperactivity disorders (ADHD) and obsessive-compulsive disorders (OCD; (Kurlan 2014)).

Description of the condition

In people with TS, tics are classified as either motor or vocal (phonic). Motor tics have been further categorized as either simple (focal involvement of a single muscle group) or complex (purposeless but goal directed behaviour; (Kurlan 2014)). Motor tics may affect any part of the body, but face muscles are most commonly affected (e.g. eye blinking). Dystonic (or tonic) tics are long lasting, and characterized by sustained abnormal postures (Jankovic 1994). Tics are labelled as blocking tics when they interfere with normal motor movement. Vocal tics are also characterized as either simple or complex. Simple vocal tics include sniffing, grunting, or throat clearing. Complex vocal tics include words and phrases. The most disabling tics include motor movements that lead to self injury or injury to others, and vocal tics that manifest as coprolalia (such as swearing) or echolalia (repetition of word and phrases; (Cheung 2007)). An unpleasant preceding sensation or premonitory urge is an important feature of tics, and may be perceived as an inner tension of willingness to move (Hallett 2015). These are called sensory tics when the premonitory urge emanates from a specific body part (Kwak 2000; Shprecher 2009). A family history of TS is very common, but the disorder is generally believed to be multifactorial (Kurlan 2014).

Treatment of the condition

Treatment depends upon the severity of symptoms. In many people with TS, tics are self-limited and do not require treatment (Kwak 2000; Kurlan 2014). Therapy is indicated if symptoms are bothersome and chronic. Habit reversal therapy is a type of behavioural therapy that is commonly used to avoid drug treatment. In this therapy, people are taught to recognize the urges and to deal with them, by doing something other than making a tic (Hallett 2015). Pharmacological treatments include drug therapy and focal injection of botulinum neurotoxin. Drug therapy includes alpha-adrenergic agonists (e.g. clonidine, guanfacine), dopamine depletors (e.g. tetrabenazine), atypical antipsychotics (e.g. risperidone and aripiprazole), and typical antipsychotics (e.g. pimozide, haloperidol, and fluphenazine; (Ganos 2015)). Botulinum toxin injections can also be useful to control both motor and phonic tics, and to reduce sensory tics (Hallett 2015; Kurlan 2014). The surgical treatment option, of deep brain stimulation, has been very useful in people with severe symptoms. However, the optimal target to treat people with TS is still debated, and stimulation of different sites of the brain have been tried (globus pallidus internus, anterior limb of the internal capsule, medial thalamus, nucleus accumbens, and subthalamic nucleus, (Hallett 2015)).

Description of the intervention

Botulinum toxin injections are well-tolerated and reported to be an effective treatment for motor and phonic tics in people with TS (Aguirregomozcorta 2008). Injection sites depend upon the specific types of tics, and the body parts involved (Marras 2001). Complications are usually mild and transient. In most studies to date, botulinum toxin type A has been used, but studies have used a wide range of doses (Jankovic 1994; Marras 2001).

How the intervention might work

The main pharmacological effect of botulinum neurotoxins is the inhibition of acetylcholine release from peripheral motor nerve terminals (Sellin 1981). At motor nerve terminals, the blockade of acetylcholine release results in neuromuscular paralysis. Botulinum toxins also exert a paralysing effect at autonomic cholinergic nerve terminals (MacKenzie 1982). In addition to its cholinergic effects, botulinum neurotoxins inhibit the release of other neurotransmitters (Ashton 1988; McMahon 1992). Some of these additional actions by the toxins are thought to impede neurotransmission of sensory neurons, and underlie its antinociceptive properties (Aoki 2003). Studies have also shown that botulinum neurotoxins can be retrogradely transported by motor neurons to the central nervous system (CNS), and may also be able to reach the CNS through the bloodstream (Boroff 1975). However, the most likely way peripheral injections of the botulinum toxins exert effects on the CNS is through perturbation of peripheral sensory neurons (Trompetto 2009).

The primary therapeutic effect of botulinum neurotoxin in tics is believed to stem from blocking neuromuscular transmission and weakening hyperactive muscles fibres involved in the production of involuntary movements. In addition to alleviating excessive muscle activity, botulinum neurotoxins also appear to reduce the premonitory sensations and pain associated with tics (Kwak 2000). Similar mechanisms may underlie the therapeutic effects of botulinum toxin injected into the vocal cords, which reduce phonic tics and coprolalia.

Why it is important to do this review

Oral pharmacological agents (typical and atypical antipsychotics, α -2-agonists, baclofen etc.) are associated with a number of adverse side effects (including exercise intolerance, weight gain, sedation, fatigue, tardive dyskinesia, and birth defects). Also, oral medications fail to treat all tics, so additional treatment options are required.

A Cochrane review is needed to help establish whether botulinum toxin treatment is safe and effective in the treatment of motor and phonic tics in people with TS.

OBJECTIVES

To determine the safety and effectiveness of botulinum toxin in treating motor and phonic tics in people with Tourette's Syndrome, and to analyse the effect of botulinum toxin on premonitory urge and sensory tics.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) that used botulinum toxin to treat motor and phonic tics in people with TS.

Types of participants

We included people of all age groups, who were diagnosed with TS and had motor and phonic tics.

Types of interventions

Intervention

We included trials that injected botulinum toxin, of any dose and for any duration, to treat motor and phonic tics in participants with TS. The number of injections depended upon the number and severity of tics a person had.

Control

The control comparison was either placebo, or any other pharmacological agent.

Types of outcome measures

Primary outcomes

1. Severity of motor and phonic tics as measured by one of the rating scales listed below.
 - Tourette Syndrome Severity Scale.
 - Yale Global Tic Severity Scale.
 - Videotape review of tic count or rate.
 - Tic Symptom Self Report.

Secondary outcomes

1. Premonitory urge.
2. Sensory tics as measured by one of the following rating scales.
 - Tic Symptom Self Report.
 - Clinical Global Impression Tic Severity Scale.
 - The Gilles de la Tourette Syndrome–Quality of Life Scale.
3. Adverse events (weakness, injection site reaction, muscle discomfort, dysphagia, and worsening or addition of urge or tic).
4. Development of immunoresistance against botulinum toxin (i.e. the failure of botulinum toxin efficacy due to antibodies formed by the host against botulinum toxin).

Search methods for identification of studies

Electronic searches

We searched the following databases from inception onwards:

- The Cochrane Movement Disorder Review Group Specialized Register (searched 25 October 2017);
- The Cochrane Central Register of Controlled Trials (CENTRAL, 2017, Issue 10) in the Cochrane Library (searched 25 October 2017). This database comprises trial reports from a wide variety of sources, including Embase;
- MEDLINE Ovid (from 1946 to 25 October 2017).

We cross-referenced botulinum toxin and its proprietary names with Tourette's syndrome and its derivations, as MeSH headings and as text words. We outlined our search strategy for MEDLINE in [Appendix 1](#). We modified this for use with the other databases.

We did not impose any language restrictions.

Searching other resources

We checked the reference lists of the reports we identified in our literature searches for additional reports of relevant studies. We also contacted the study authors and experts in the field of Tourette's syndrome. We searched BIOSIS previews and conference proceedings (International Congress of Parkinson's Disease and Movement Disorders) for the past five years.

We checked for ongoing studies in ClinicalTrials.gov (<https://clinicaltrials.gov>) and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; www.who.int/ictip/en/).

Data collection and analysis

Selection of studies

One review author (SP) screened the publications identified by the search strategy by title, abstract, and keyword, and selected studies that potentially satisfied the inclusion criteria of the review. Three review authors (PS, RK, BB) independently evaluated the selected studies for inclusion or exclusion. We obtained full-text copies of all potential included studies. Three review authors (PS, RK, BB) independently evaluated them, and we resolved any differences by discussion. We presented the study selection process in a PRISMA flow diagram ([Figure 1](#)).

Figure 1. Study flow diagram

Data extraction and management

Three review authors (SP, PS, BB) independently extracted data from the included studies using a pre-standardised data extraction form, based on a checklist of items considered in data collection or data extraction (Appendix 2). We made a final decision on inclusion of data, and resolved any differences by discussion. We reported each included study's details in the 'Characteristics of included studies' table.

Assessment of risk of bias in included studies

Two review authors (SP, RK) independently performed 'Risk of bias' assessments for each included study, and resolved any disagreements by consulting a third review author (BB). We performed 'Risk of bias' assessments for the following domains (Higgins 2011).

Random sequence generation (selection bias)

For each included study, we checked the method used to generate the random sequence list. We judged the study to be at one of the following levels of bias.

- Low risk of bias (any truly random process, e.g. random number table; computer random number generator).
- High risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number).
- Unclear risk of bias.

Allocation concealment (selection bias)

For each included study, we determined the method used to conceal the random sequence list prior to intervention assignment. We considered the study to be at one of the following levels of bias.

- Low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes).
- High risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth).
- Unclear risk of bias.

Also, we checked the baseline characteristics of each included study to check whether all the measured variables were equally balanced between the treatment arms.

Blinding of participants and personnel (performance bias)

We classified each included study as follows.

- Low risk of bias: participants and investigator(s) were both unaware of the assigned treatment;
- High risk of bias: participants or investigator(s) were aware of the assigned treatment (open-label studies).
- Unclear risk of bias: blinding was not reported, and we could not verify it by contacting the study investigators.

Blinding of outcome assessment (detection bias)

We classified each included study as follows.

- Low risk of bias: outcome assessors were unaware of the assigned treatment when they recorded the outcomes.
- High risk of bias: outcome assessors were aware of the assigned treatment when they recorded the outcomes.

- Unclear risk of bias: blinding of assessor(s) was not reported, and we could not verify it by contacting the study investigators.

Incomplete outcome data (attrition bias)

We classified each included study as follows.

- Low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups).
- High risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation). We considered attrition bias of 20% and above as high risk of bias.
- Unclear risk of bias.

Selective reporting (reporting bias)

We used the criteria below for reporting bias.

- Low risk of bias (all of the pre-stated outcomes in the methods section or in a clinical trials registry are reported properly, without modifying the expected outcomes of interest).
- High risk of bias (not all the pre-stated outcomes have been reported; one or more reported primary outcomes were not pre-stated as primary outcomes; the pre-stated outcomes are reported inadequately).
- Unclear risk of bias.

Other bias (any other bias that is not covered by the above)

We assessed whether the included study was free of potential conflicts of interest, or other biases that could have influenced the study results and put it at risk of bias:

- Low risk of other bias (e.g. study author has declared a conflict of interest, and his or her role in the study doesn't influence the results of the study);
- High risk of other bias (e.g. study author is on the payroll of the funding company or agencies);
- Unclear risk of other bias.

In cases of missing information, we attempted to contact the trial authors for clarification. We resolved any disagreements by discussion.

Measures of treatment effect

Dichotomous data

For dichotomous data, we had planned to record the number of events and the total participants in each study arm for each outcome. We had planned to express the results as risk ratios (RRs) with 95% confidence intervals (CIs).

Continuous data

For continuous data, we had planned to record the mean, standard deviation (SD), and total number of participants in each study arm. We had planned to express the results as the mean difference (MD) with 95% CIs, or standardised mean difference (SMD) with 95% CIs when the same outcome was measured using different scales.

However, in our included study, the data were not reported as dichotomous or continuous outcomes. Instead, the trialists measured the treatment effect as net effect, which was calculated

as proportional change in the intervention arm and the control arm. So, we used these values as the effect measure in the [Effects of interventions](#) and [Summary of findings for the main comparison](#).

Unit of analysis issues

We did not find any cluster-randomised or multiple-arm trials for this review. We included a placebo-controlled, double-blind cross-over study design trial, but we did not perform any adjustments to the data, as the investigators allowed an adequate washout period before crossing over.

Dealing with missing data

There was no information missing from the included study. We used the complete case analysis data reported. We did not make any assumptions regarding participants lost to follow-up. However, we used the incomplete outcome information to assess the risk of attrition bias, and the overall quality of the evidence.

Assessment of heterogeneity

We did not perform a meta-analysis, due to insufficient data from a single RCT, and therefore, there was no need to assess heterogeneity. In future, if we find more than one included study, we will assess statistical heterogeneity by visually inspecting the forest plots for overlapping CIs, and use the χ^2 test to determine heterogeneity (with $P < 0.10$ for significance). The χ^2 test may be underpowered to prove the presence of heterogeneity, therefore, if the number of included studies is low, we will use the I^2 statistic as a measure of inconsistency across the included studies. The observed value of the I^2 statistic and its interpretation will be:

- 0% to 30%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 60% to 80%: may represent substantial heterogeneity;
- 80% to 100%: considerable heterogeneity.

If we find the I^2 statistic to be more than 50%, we will perform the meta-analysis with a random-effects model rather than a fixed-effect model, to provide more conservative pooled estimates. Otherwise, we will use a fixed-effect model. If there is a substantial amount of heterogeneity, we will investigate the source of heterogeneity, using subgroup analysis.

Assessment of reporting biases

Because we only included a single RCT, the method suggested to assess reporting bias was not applicable. In future, if we include more than 10 studies, we plan to analyse the primary and secondary outcomes for reporting bias, using funnel plot asymmetry.

Data synthesis

We had planned to follow the guidance provided by the *Cochrane Handbook for Systematic Reviews of Interventions* for data analysis ([Higgins 2011](#); [Higgins 2011a](#)).

As we included only one study, we did not perform a meta-analysis. Hence, we presented the results qualitatively. In future, we plan to perform meta-analyses only when the included studies have similar participants, interventions, and outcomes.

In future, if we have more included studies, we will use the Mantel-Haenszel method to pool dichotomous outcome data, and the inverse variance method to pool continuous data, with a fixed-effect model. We will use the generic inverse variance method when we combine data from parallel-arm trials with adjusted data from cross-over trials

Subgroup analysis and investigation of heterogeneity

Due to insufficient data, we did not perform a subgroup analysis. We had planned to explore if the effects were different for motor versus vocal tics separately.

Sensitivity analysis

We did not perform sensitivity analyses because we only included a single RCT. However, if we have more studies in future updates, we plan to explore the difference in the estimate of the effect if we:

- exclude studies at high risk of bias (i.e. one of: random sequence, allocation concealment, or blinding were judged at high risk);
- exclude studies having more than 20% loss to follow-up; or
- remove cross-over trials if they only present first period data.

Assessing the quality of evidence

We followed the GRADE approach to determine the quality of the evidence ([Schünemann 2011](#)). We used GRADEpro GDT software to import statistical data from RevMan 5, and to create '[Summary of findings for the main comparison](#)' for the following outcomes ([GRADEpro GDT 2015](#); [RevMan 5](#)).

Primary outcome

Severity of motor and phonic tics, as measured by one of the following rating scales:

- Tourette Syndrome Severity Scale.
- Yale Global Tic Severity Scale.

Secondary outcomes

- Premonitory urge (treated tics)
- Sensory tics
- Premonitory sensation (treated tics)
- Adverse events (weakness, injection site reaction, muscle discomfort, dysphagia, and worsening or addition of urge or tic)
- Development of immunoresistance against botulinum toxin

We assessed the quality of the evidence based on the following domains: risk of bias, inconsistency of results, indirectness, imprecision, and publication bias. The quality of evidence can vary from high to very low.

High-quality evidence means confidence in the estimates is almost certain, while very low-quality evidence indicates an uncertainty of the estimates. We used all five domains in the GRADE tool to assess the quality of evidence, and provided justification in footnotes for downgrading or upgrading.

RESULTS

Description of studies

See the [Characteristics of included studies](#) for details.

Results of the search

Our literature search identified 78 records. We excluded 67 after screening the titles and abstracts. We retrieved the full text for 11 studies, and excluded 10. We included one randomised, cross-over trial in the review.

Included studies

We included one randomised, cross-over study on the use of botulinum toxin injections for the treatment of tics in Tourette's syndrome (TS; (Marras 2001). Inclusion criteria included: (i) the presence of at least one simple and bothersome motor tic affecting the face, neck, or shoulder, due to an idiopathic tic disorder and considered to be amenable to being injected, (ii) stable medications for the month prior to starting the trial.

They recruited 20 participants over three years, 18 of whom completed the study. Fourteen participants had a diagnosis of TS, with relatively mild and non-disabling tics (21 treated tics), eight participants were taking oral medication.

At the initial visit, the target tic-involved muscle(s) were injected with either botulinum toxin (Onabotulinum toxin A)

or saline placebo, at doses that were considered typical for dystonic disorders affecting the same muscle or sets of muscles. Participants subsequently underwent repeat videotaping and clinical assessments at weeks 2, 6, and 12, and then every four weeks thereafter, until participants and examiners agreed the tic disorder had returned to its baseline severity. Once back to baseline, participants crossed over to receive the opposite treatment.

Excluded studies

See the 'Characteristics of excluded studies' table for details.

We excluded four non-randomised studies (three motor tics and one phonic tics; (Jankovic 1994; Kwak 2000; Porta 2004; Rath 2010)), five case reports (two motor tics and three phonic tics; (Aguirregomez 2008; Salloway 1996; Scott 1996; Srirompotong 2007; Trimble 1998)), and one case series (phonic tics; (Vincent 2008)), as they did not fulfil the inclusion criteria.

Risk of bias in included studies

There was only one included study, and we assessed it to be free from all risk of bias, except for allocation concealment, which was unclear (Figure 2; Figure 3).

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

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

The included study reported adequate methods of sequence generation, which was computer-generated by EPI-STAT Research Inc, The study nurse, who had no role in the assessment of

participants, kept the randomisation schedule, thus we rated it as low risk of bias. However, there was no description of how the participants were allocated into the study arms, therefore, we rated it as unclear risk of bias for allocation concealment.

Blinding

The report stated the study was double-blinded, but it was not clear whether the participants were blinded. However, the physicians who treated and assessed the participants were blinded, so it is likely safe to assume the participants were also unaware of their treatment allocation. Therefore, we rated the study at low risk of performance and detection bias.

Incomplete outcome data

Twenty patients were enrolled in the study and two patients were (one each from the treatment and the placebo arm) lost to follow-up. Since a 10% rate of loss to follow-up was equally distributed across both the groups, we felt it would not likely have any effect on results, and we judged this to be at low risk of bias.

Selective reporting

All the pre-stated outcomes in the methods were reported. Although we could not assess the outcomes and methods against the study protocol, we considered the risk of reporting bias to be low.

Other potential sources of bias

We judged there to be no other potential sources of bias in the included study (low risk of bias).

Effects of interventions

See: [Summary of findings for the main comparison Botulinum toxin compared to Placebo for motor and phonic tics in Tourette's syndrome](#)

We have presented the findings in [Summary of findings for the main comparison](#).

Comparison 1: Botulinum toxin versus placebo.

The effects of the intervention were taken from the report of a single, small (N = 18), randomised cross-over trial ([Marras 2001](#)).

Primary outcome

Severity of motor and phonic tics

The primary outcome measure was the proportional change between baseline and week two, in the number of treated tics per minute, as observed by blinded videotape review. A statistically significant reduction in tic frequency was seen in 15 of 18 patients (net effect -0.37, -39% in the treatment phase to +5.8% in the placebo phase; P = 0.0007; [Table 1](#)).

Phonic tics were not measured.

Secondary outcomes

Premonitory urge (treated tics)

There was a significant change in premonitory urge scores between the two treatments (net effect 0.94, -0.46 in the treatment phase to +0.49 in the placebo phase; P = 0.02).

Sensory tics

Sensory tics were not measured in this trial.

Adverse events

Nine participants reported subjective, non-disabling weakness following botulinum toxin treatment (two during the placebo phase), although on examination, assessors noted weakness in 12 participants during treatment and two during the placebo phase, and neck discomfort in three participants during treatment and one during the placebo phase). Other adverse effects during the active treatment phase included: blurred vision in one participant, difficulty swallowing in two participants. Two participants reported their inability to perform the treated tic led to the emergence of a new tic in its place, and two participants reported experiencing 'fidgetiness' following botulinum toxin treatment, one of whom reported this feeling led to an increased urge to perform the treated tic.

Development of immunoresistance against botulinum toxin

This was not measured in the trial.

Although not original outcomes of interest in our protocol, [Marras 2001](#) also measured the change in frequency of untreated tics, change in severity of tics, change in premonitory sensation for treated tics, and change in global impression of improvement between baseline and week two. They found no significant differences between treatment groups

DISCUSSION

Summary of main results

We found very low-quality evidence from one small (N = 18) cross-over trial that botulinum toxin significantly reduced the severity (measured as number per minute) and premonitory urge of simple focal motor tics in people with mild tics. Additional randomised controlled trials that address the limitations of this study are needed to examine the clinical effectiveness of botulinum toxin more thoroughly.

Overall completeness and applicability of evidence

We set out the purported reasons why botulinum toxin injections might be considered in the symptomatic treatment of motor and phonic tics in patients with Tourette's syndrome (TS). However, at the present time, only one study met our inclusion criteria ([Marras 2001](#)).

Although Marras and colleagues found a positive effect of botulinum toxin injections on reducing the frequency of simple motor tics and the urge to perform those tics, they did not find that it improved global measures of tic severity, or measures of overall patient well-being. The study reported a placebo-controlled study design and included quality control measures, such as assessing intra-rater variability, through a delayed, repeated review of some of the patient videotapes. Nevertheless, the study and its conclusions were limited by a small sample size and the inclusion of a population who predominantly had a mildly affected tic disorder, limiting the power to detect an effect on global measures, and the ability to extrapolate findings to more severely affected patients. Another limitation in the study was the un-blinding that could have occurred as a result of the botulinum toxin therapy inducing weakness, which was perceived by half of the patients.

While in essence this was a positive randomised controlled trial, the study's limitations preclude the ability to make broad conclusions

about the role of botulinum toxin therapy in the treatment of tics in TS. The findings suggest that botulinum toxin injections may be beneficial for some simple motor tics, but additional randomised controlled trials that address the limitations of this study are needed to more thoroughly demonstrate the clinical effectiveness of botulinum toxin therapy for the treatment of tics in TS. Data on immunoresistance was not available for the study and further studies should measure this outcome.

Quality of the evidence

We could include only one randomised controlled trial in our review, which presented very low-quality of evidence for the improvement in the primary outcome. There were several factors that led us to downgrade the evidence to very low-quality, mainly due to indirectness, since the patient population represented in the study experienced milder tics than would otherwise be indicated by this intervention. The small sample size and associated wide confidence interval reduced our confidence in the evidence for all of our key outcomes.

Potential biases in the review process

We did not identify any potential bias in the review process.

Agreements and disagreements with other studies or reviews

There are several other uncontrolled studies and case reports examining the use of botulinum toxin in motor and phonic tics, although their level of evidence is considered weak. An uncontrolled study of 35 participants showed an improvement in motor tics (mean peak effect response was 2.8 on a scale of 0 to 4), with mean duration of benefit for 14.4 weeks (Kwak 2000). Participants with focal tics involving eye and neck muscles were likely to benefit more. In a case report, a patient described the effect of botulinum toxin treatment with dystonic 'whiplash' neck tics as life changing (Aguirregomez 2008). There were no controlled trials showing the efficacy of botulinum toxin in phonic

tics, however, an uncontrolled study of 30 participants with TS with phonic tics, by Porta and colleagues, documented improvement in 95% of participants, with a mean response duration of 5.8 days (Porta 2004). Fifty percent of patients became tic free, and premonitory experiences dropped from 53% to 20%. Hallett and colleagues published an evidence-based review of botulinum neurotoxin for the treatment of movement disorders including tics and they classified the current evidence as class II (Hallett 2013). They concluded that although botulinum toxin did appear to improve focal tics, because of a lack of class I studies, the treatment should only be considered in select cases (Hallett 2013). They gave a Level U recommendation for botulinum toxin in the management of tics (data inadequate or conflicting; given current knowledge, treatment is unproven). Their evidence rating and recommendation were in line with what we concluded.

AUTHORS' CONCLUSIONS

Implications for practice

The limitations of only one small included study preclude the ability to make broad conclusions about the effects of botulinum toxin therapy in the treatment of motor and phonic tics in Tourette's syndrome.

Implications for research

There is uncertain evidence that the intervention may be effective. Future placebo-controlled trials selecting participants sufficiently impaired by the target tic(s) through explicit symptom scales are needed to evaluate the benefits and harms of this intervention. Studies should consider how to reduce the risk of unmasking of treatment group assignment and evaluate immunoresistance.

ACKNOWLEDGEMENTS

We thank the Editorial Team of the Cochrane Movement Disorders Group for their assistance with this review.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Marras 2001

Methods	Randomised controlled cross-over trial
Participants	<p>Number of individual randomised: 20</p> <p>Inclusion criteria:</p> <p>Patients were invited to participate if they had at least one simple motor tic due to an idiopathic tic disorder, and performed by a muscle amenable to injection.</p> <p>Exclusion criteria:</p> <p>Not mentioned</p> <p>18 participants completed the study.</p>
Interventions	<p>Intervention: botulinum toxin</p> <p>Mode of Delivery: injection</p> <p>Control: placebo</p> <p>Mode of delivery: injection</p>
Outcomes	<p>Videotaped tic count rates (treated and untreated tics)</p> <p>Urge (treated tics)</p> <p>Premonitory sensation (treated tics)</p> <p>TS Global Score (all tics)</p>

Marras 2001 (Continued)

Yale - Yale Global Tic Severity Scale

Shapiro - Shapiro Tourette Syndrome Severity Scale

Notes	Botulinum toxin supplied by Botox Allergan Canada at no charge.
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "after the above observations at the first visit, patients were randomised by a computer generated randomisation schedule (EPI-STAT Research Inc) to receive initial injections of botulinum toxin or placebo. Comment: adequate method of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Quote: "The randomisation schedule was prepared and record of it kept by a study nurse who had no role in the assessment of the patients." Comment: no clarity around how the randomisation schedule was used to allocate participants to treatment arms
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The randomisation schedule was prepared and record of it kept by a study nurse who had no role in the assessment of the patients." Comment: Intervention was administered by the treating physician who was not aware of the treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote : "The nurse prepared the medication and delivered unlabeled syringes to the treating physician; this same physician was responsible for the physical examination at each visit." Comment: adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Only two participants (10%) were lost to follow-up, one from each arm.
Selective reporting (reporting bias)	Low risk	All the pre-stated outcomes in the methods were reported.
Other bias	Low risk	No other potential source bias were identified in this study.

Characteristics of excluded studies [ordered by year of study]

Study	Reason for exclusion
Jankovic 1994	A non randomised pilot study included 10 male patients diagnosed with Tourette's syndrome, manifested by disabling focal tics
Scott 1996	A case report of a boy with Tourette's syndrome, manifested chiefly by severe coprolalia, obsessive compulsive disorder, and attention deficit hyperactivity disorder, treated with botulinum toxin injection into his vocal cord.
Salloway 1996	A case report of a patient with refractory vocal tics treated with botulinum toxin

Study	Reason for exclusion
Trimble 1998	A case report of a patient with Tourette's syndrome with vocal tics treated with botulinum toxin injections
Kwak 2000	A non randomised study where 35 patients (30 male, 5 female) were treated with botulinum toxin in the sites of their most problematic tics
Porta 2004	A non-randomised study where authors assessed the effect of botulinum toxin type A on phonic tics in patients with Tourette's syndrome
Srirompotong 2007	A case report of a patient with ear wiggling tics treated with botulinum toxin type A
Aguirregomez-corta 2008	A case report of a patient with Tourette's syndrome with tetraparesis and cervical myelopathy, secondary to violent dystonic tics involving the neck, in which a more aggressive course of treatment with botulinum toxin injection, in addition to neuroleptic medication, resulted in complete resolution of dystonic tics at 12 months of follow-up
Vincent 2008	A case series of two patients with laryngeal tics treated with botulinum toxin type A
Rath 2010	A non-randomised study in which 15 consecutive patients (18 tics) with simple motor tics were treated with botulinum toxin type A.

ADDITIONAL TABLES

Table 1. Videotape tic counts per minute

Items	Median proportional change in those receiving botulinum toxin	Median proportional change in those receiving placebo	Net effect	Interquartile range
Treated tics	-39%	+5.8%	-37%	(-77 % to -15%)
Untreated Tics	-21%	-12%	-5%	(-48% to 21%)

APPENDICES

Appendix 1. Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE® (1946 to present) search strategy

- 1 Tics/ or Tourette Syndrome/ (4652)
- 2 tourette*.mp. (5434)
- 3 (tic or tics).mp. (8039)
- 4 1 or 2 or 3 (10941)
- 5 exp Botulinum Toxins/ (15207)
- 6 (botul* and toxi*).mp. (19713)
- 7 (botul* and inject*).mp. (9225)
- 8 botox.mp. (1784)

Botulinum toxin for motor and phonic tics in Tourette's syndrome (Review)

9 6 or 7 or 8 (20133)

10 4 and 9 (127)

11 (randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab. (4324533)

12 exp animals/ not humans.sh. (4680953)

13 11 not 12 (3733808)

14 10 and 13 (78)

15 remove duplicates from 14 (74)

Appendix 2. Checklist of items considered in data collection or data extraction (Higgins 2011)

Source

- Study ID (created by review author);
- Report ID (created by review author);
- Review author ID (created by review author);
- Citation and contact details.

Eligibility

- Confirm eligibility for review;
- Reason for exclusion.

Methods

- Study design;
- Total study duration;
- Sequence generation;
- Allocation sequence concealment;
- Blinding;
- Other concerns about bias.

Participants

- Total number;
- Setting;
- Diagnostic criteria;
- Age;
- Sex;
- Country;
- Comorbidity;
- Socio-demographics;
- Ethnicity;
- Date of study.

Interventions

- Total number of intervention groups;
- Specific intervention.

Outcomes

- Outcomes and time points:
 - collected;
 - reported.

For each outcome of interest, we recorded the following.

- Outcome definition (with diagnostic criteria if relevant).
- Unit of measurement (if relevant).
- Scales: upper and lower limits, and whether high or low score is better.

Results

- Number of participants allocated to each intervention group.

For each outcome of interest, we reported the following.

- Sample size.
- Missing participants.
- Summary data for each intervention group (e.g. 2 × 2 table for dichotomous data; means and standard deviations for continuous data).
- Estimates of effect with confidence intervals and P values.
- Subgroup analyses.

Miscellaneous

- Funding source;
- Key conclusions of the study authors;
- Miscellaneous comments from the study authors;
- References to other relevant studies;
- Correspondence required.

CONTRIBUTIONS OF AUTHORS

All authors independently extracted the data onto standardised forms; disagreements were resolved by mutual discussion.

Sanjay Pandey wrote the first draft and revised the final draft.

Prachaya Srivanitchapoom contributed to writing the first draft, critiqued, and reviewed it.

Richard Kirubakaran contributed to writing the first draft, critiqued, and reviewed it.

Brian D Berman contributed to writing the first draft, critiqued, and reviewed it.

DECLARATIONS OF INTEREST

Sanjay Pandey has no known conflicts of interest

Prachaya Srivanitchapoom has no known conflicts of interest

Richard Kirubakaran has no known conflicts of interest

Brian D Berman has no known conflicts of interest

SOURCES OF SUPPORT**Internal sources**

- No internal source of support, Other.

External sources

- Department for International Development (DFID), UK.

Project funding for the Effective Healthcare Research Consortium; salary for Richard Kirubakaran during the review stage.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have initially planned to use Relative Risk (RR) as a effective measure for dichotomous data. However, the study did not report the data as required for analysis. Hence, we have used the effect measure of Net effect and 95% CI which is an absolute change value between the intervention group compared to the control group.

INDEX TERMS

Medical Subject Headings (MeSH)

Botulinum Toxins, Type A [adverse effects] [*therapeutic use]; Neuromuscular Agents [adverse effects] [*therapeutic use]; Tics [*drug therapy] [etiology]; Time Factors; Tourette Syndrome [complications] [*drug therapy]

MeSH check words

Humans