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SUMMARY WITH CRITICAL APPRAISAL

Botulinum Toxin for Temporomandibular Disorders: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Abbreviations

n/a	Not applicable
NR	Not reported
NSS	Not statistically significant
RCT	randomized controlled trial
RDC	Research Diagnostic Criteria
SD	Standard deviation
SS	Statistical significance
TMD	Temporomandibular Disorders
TMJ	Temporomandibular joint
VAS	Visual analog scale

Context and Policy Issues

Temporomandibular disorder (TMD) is a term used to describe disorders that involve the temporomandibular joint, the muscles of mastication and associated structures.[1] Patients with TMD have a heterogeneous clinical presentation that can include facial pain, ear discomfort, headache and/or temporomandibular joint dysfunction. Causes of TMD include structural malalignment, joint trauma, psychiatric illness, head and cervical posture. TMD affects between 5-10% of the adult population and is associated with pain and dysfunction that can impact quality of life and reduce individual work productivity.[2,3] Treatment approaches have included medications (analgesics, muscle relaxants, nonsteroidal anti-inflammatory drugs), physiotherapy (exercises, massage), laser, psychological interventions, occlusal appliances, surgery and trigger point injections (local anaesthetics, corticosteroids, botulinum toxin).[1]

Botulinum toxin type A is a neurotoxin that inhibits the release of the neurotransmitter acetylcholine at the neuromuscular junction with a goal to reduce excessive contraction of the target muscle.[4] Botulinum toxin type A is currently available in Canada under several names (e.g. Botox, Dysport, Xeomin) and is indicated for both cosmetic and therapeutic purposes.[5] No botulinum toxin product has received approval from Health Canada for the management of TMD.

Evidence to support coverage decisions for botulinum toxin in Canadian jurisdictions is required. A previous CADTH report[6] examined a broad range of interventions for TMD. The current report aims to summarize evidence regarding the clinical effectiveness of botulinum toxin and to identify clinical practice guidelines and evidence on cost effectiveness.

Research Questions

1. What is the clinical effectiveness of botulinum toxin A for temporomandibular disorders?

2. What is the cost-effectiveness of botulinum toxin A for temporomandibular disorders?

3. What are the evidence-based guidelines regarding the treatment of temporomandibular disorders?

Key Findings

None of the included systematic reviews expressed confidence in the clinical effectiveness of Botox for treating temporomandibular disorder (TMD). While there were some primary studies indicating improvements in pain scores for botulinum toxin relative to saline injections, this finding was not consistently reported across all studies and the clinical significance of the improvements was uncertain. The evidence suggests that botulinum toxin is not superior to occlusive devices, dry needling or fascial manipulation.

In the primary studies, there was heterogeneity in TMD clinical presentation, botulinum toxin administration techniques and comparator treatment approaches and this creates significant uncertainty about the clinical utility for Botox in TMD. Assessing generalizability of the results to the Canadian context is difficult given these issues.

While there have been no consistent signals of increased risk of harm for botulinum toxin relative to control groups in the data reviewed, none of the primary studies were rigorously designed to study harms. This is an important issue to be addressed in future research since botulinum toxin treatment for TMD is an invasive procedure with some risks inherent in its administration.

There was no evidence to inform the cost effectiveness of botulinum toxin in TMD and no clinical practice guidelines were identified.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were botulinum toxin type A and temporomandibular disorders. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, any types of clinical trials or observational studies, economic studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2015 and January 27, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Q1-3: Adults with temporomandibular disorders, specifically masticatory muscle disorders (e.g., muscle myalgia and myofascial pain of the muscles of mastication [myofascial pain syndrome])
Intervention	Q1, 2: Intra-muscular injection with Botulinum Toxin Type A
Comparator	Q1, 2: Intra-muscular injection with a placebo (e.g., saline) Occlusal appliances (e.g., splint, mouth guard, bite plane) Physiotherapy (e.g., massage, fascial manipulation, posture) Q3: Not applicable

Outcomes	Q1: clinical effectiveness and adverse events (e.g., pain, muscle soreness, mouth opening, quality of life) Q2: cost effectiveness (e.g., cost-per health benefit gained, cost per adverse event avoided) Q3: guidelines for the appropriate treatment, guidelines on the appropriated use botulinum toxin A
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations and guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2015. Guidelines with unclear methodology were also excluded. Studies without a control group were excluded. Hemi facial spasm, bruxism, temporomandibular joint (TMJ) dislocation and dystonia are separate disorders and therefore studies of populations with these conditions were excluded. Systematic reviews were excluded if there was complete overlap with a more recent systematic review or if the review's analyses focused on data from studies that did not have a comparator group or if the review's analyses was predominantly focused on the use of botulinum toxin in populations other than TMD (e.g. bruxism, arthralgia, clicking, TMJ dislocation).

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using the AMSTAR 2 checklist.[7] The network meta-analysis was critically appraised using the ISPOR Task Force's Indirect Treatment Comparison/Network Meta-Analysis Study Questionnaire to Assess Relevance and Credibility to Inform Health Care Decision Making.[8] The randomized controlled trial (RCT) was critically appraised using the Downs and Black checklist.[9] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 366 citations were identified in the literature search. Following screening of titles and abstracts, 325 citations were excluded and 41 potentially relevant reports from the electronic search were retrieved for full-text review. Five potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 41 publications were excluded for various reasons, and 5 publications met the inclusion criteria and were included in this report. These comprised four systematic reviews and one RCT. Appendix 1 presents the PRISMA[10] flowchart of the study selection.

No economic evaluations or clinical practice guidelines were identified that met the criteria for this report.

Summary of Study Characteristics

Study characteristics are summarized below, and details are available in Appendix 2.

Study Design

Four systematic reviews were included[11-14] including three systematic reviews without meta-analysis[11-13] and one systematic review with a network meta-analysis.[14] One open-label, parallel group RCT[15] was included. All five reports were published in 2019. The four systematic reviews had overlapping studies but they contained at least one

unique study or reported unique results or comparisons not present in the other reviews (Appendix 5).

Country of Origin

The first authors of the systematic reviews were from the UK,[11] USA,[12] Brazil,[13] and China.[14] The authors of the RCT were from Turkey.[15]

Patient Population

The scope of some of the included systematic reviews was broader than the PICO for this CADTH report. All four systematic reviews included primary studies of adults with TMD but not all included studies reflected the population of interest for this review. One systematic review also included studies on patients with bruxism without a TMD diagnosis,[11] and one systematic review included studies in trigeminal neuralgia.[13] Three systematic reviews[11-13] included at least one study that had a mixed TMD/bruxism population and for one systematic review, it was not clear if the population included patients with bruxism.[14] The number of patients in the primary TMD studies that were included in the systematic reviews and were also relevant to this CADTH report ranged from 24 to 90.[11-14]

The RCT enrolled 40 adults (mean age 34 years, 72% women) with a diagnosis of TMD from a single clinic.[15]

Interventions and Comparators

The botulinum toxin intervention in the primary studies of the systematic reviews was one injection into the masseters and/or temporalis muscles bilaterally.[11-14] The dose of botulinum toxin used for each injection ranged from 70-300U. The comparators in primary studies of the systematic reviews included fascial manipulation, saline injection, laser, conservative treatment, lidocaine injection, dry needling, splints, physiotherapy, oral pharmacotherapy, placebo, acupuncture, psychological therapy, and complementary therapy. The authors did not provide a detailed description of the comparators.

The intervention in the RCT was botulinum toxin 25-150U injected once intramuscularly into a trigger point on the lateral pterygoid muscle bilaterally.[15] The control group received dry needling consisting of rapid needling (8-10 times) into the trigger point bilaterally with a needle mounted to an empty syringe.

Outcomes

The clinical outcomes of interest for this report were pain, muscle soreness, mouth opening, quality of life and adverse events. All four systematic reviews reported pain score result.[11-14] Two systematic reviews reported on mouth opening.[11,12] Two systematic reviews reported on adverse events.[12,13] No systematic reviews reported data on muscle soreness or quality of life.

The RCT reported on pain score and mouth opening.[15]

Summary of Critical Appraisal

Systematic Reviews

The quality assessment of three systematic reviews (AMSTAR2), one systematic review with network meta-analysis (ISPOR questionnaire) and the RCT (Downs and Black), is presented in Appendix 3.

The included systematic reviews had several strengths. Four systematic reviews contained statements specifying the population, intervention, comparator and

outcomes.[11-14] Four systematic reviews[11-14] described a comprehensive literature search strategy and authors of one systematic review registered the review protocol.[12] All four systematic reviews applied the Cochrane Risk of Bias tool to assess the quality of the primary studies[11-14] and three of these systematic reviews discussed the results in the context of the risk of bias assessment.[12-14] The systematic review with network analysis included a broad range of relevant comparator groups including splints and physiotherapy, two comparators of interest for this report.

There were also some limitations to the included systematic reviews. One systematic review included studies in patients with bruxism and TMD or bruxism but did not comment on the potential impact of population heterogeneity on the interpretation of the results.[11]

The systematic reviews were lacking information on the techniques of botulinum toxin injection such as how the dose was selected and how the injection sites were identified. The various methods for botulinum toxin administration may introduce heterogeneity in the analyses and reduce the generalizability of the findings. Administration technique variation and its potential impact on study outcomes was not adequately explored in any of the reviews. Similarly, no systematic reviews provided a detailed description of the comparator interventions. This is an important limitation because of the potential heterogeneity in how the interventions such as physiotherapy, fascial manipulation and occlusive devices, were applied in the individual studies.

There was inadequate reporting of results and statistical testing from the individual trials in all four systematic reviews.[11-14] Two systematic reviews provided no numerical data for individual study outcomes.[13,14] Three systematic reviews provided no statistical test results from individual trials.[11,13,14] One systematic review focused on adverse event data but provided no quantitative analyses of adverse events.[13] Administration of botulinum toxin is an invasive procedure and there are risks inherent in administering intramuscular injections into facial muscles but the primary studies do not appear to have been designed to quantify these risks.[16,17]

The systematic review with network meta-analysis reported very little information on the populations, study design features or results of the individual studies.[14] Therefore, it was not possible to adequately assess the validity of the pain score output from the network. In addition to these limitations to internal validity, the generalizability of the network meta-analysis was limited by the small number of studies.

Randomized Clinical Trial

In the RCT, botulinum toxin was compared with dry needling, which was a comparator of interest in this report.[15] Strengths included a clear description of botulinum toxin injection technique and the dry needling method and the use of randomized group assignment. Significant limitations of this study were its open-label design and the lack of clear reporting of the baseline characteristics of the enrolled patients.

Summary of Findings

Clinical Effectiveness of Botulinum Toxin

Pain Scores

Botulinum toxin versus saline injection

Three systematic reviews without meta-analyses and one systematic review with a network meta-analysis reported similar results on pain scores from overlapping trials.[11-14] One systematic review reported that in 5/6 studies that compared botulinum toxin to saline there were numerical improvements in pain scores with botulinum toxin

compared to saline from baseline up to 3 months, but the data were poorly reported, no statistical test results were provided and there was no discussion about whether the differences observed were clinically meaningful.[11] One systematic review reported 2/5 studies had statistically significant improvements in pain for botulinum toxin relative to saline, and 3/5 studies showed no difference.[12] One systematic review with meta-analysis reported no statistically significant difference between botulinum toxin and placebo for pain scores. There was no discussion in any of the systematic reviews regarding the validity of pain scores and the minimal clinically important difference in the context of TMD.

Botulinum toxin versus occlusal appliances

One systematic review with a network meta-analysis reported that there was no statistically significant difference between botulinum toxin and occlusal splint therapy on pain score.[14]

Botulinum toxin versus physiotherapy (including fascial manipulation, dry needling)

Two systematic reviews reported data from the same study that found no statistically significant difference between botulinum toxin and fascial manipulation on pain scores.[11,12] One systematic review with network meta-analysis reported no statistically significant difference between botulinum toxin and physiotherapy.[14]

One systematic review reported no statistically significant difference in pain scores for botulinum toxin versus dry needling based on one study.[12] One RCT reported a statistically significant difference in pain scores after 6 weeks follow-up for botulinum toxin versus dry needling, favouring dry needling.

Mouth Opening

Botulinum toxin versus saline injection

Two systematic reviews reported no statistically significant differences in mouth opening between botulinum toxin and saline injections from baseline to the end of the follow up period (between 1-6 months).[11,12] Mouth opening data were incompletely reported, making interpretation of these data uncertain.

Botulinum toxin versus physiotherapy (fascial manipulation)

Two systematic reviews reported no statistically significant differences in mouth opening between botulinum toxin and fascial manipulation from the same single study.[11,12]

Adverse Effects of Botulinum toxin

Two systematic reviews reported adverse events.[12,13] Adverse event data were reported in aggregate, with no attribution of the event to a specific treatment group and no comparisons between the intervention group and the control. The results presentation was mostly qualitative; there were very few numerical and no statistical analyses on the occurrence of adverse events in the primary studies were provided. Reported adverse events included temporary regional weakness, tenderness over the injection sites, minor discomfort during chewing, asymmetric smile, reduction in the size of the masticatory muscle (masseter), paresthesia, eye drooping or muscle weakness, difficulty swallowing, speech changes, perioral swelling and bruising.

No relevant reports were identified that reported data on muscle soreness or quality of life.

No relevant reports were identified that compared botulinum toxin to mouth guards, bite planes, massage or posture as therapy.

Limitations

The main limitations of this review are related to the quality of the available evidence and the heterogeneity of the condition and existing treatment approaches.

Through the quality assessment of the systematic reviews it was evident that they were of low to moderate quality. In the included systematic reviews, the descriptions of populations, interventions, comparators and results were often incomplete. TMD has a heterogeneous clinical presentation and there are also many possible differences in techniques for administration of botulinum toxin and other treatments.[1,16,17] This heterogeneity and the lack of information about these key aspects of the primary studies limit our ability to generalize the findings of the systematic reviews reviewed in this report.

A significant weakness of the primary studies in the included systematic reviews is that, like the included RCT, many of them used open-label designs. Placebo effect has been shown to impact outcome evaluation in TMD treatment and an open-label approach would be expected to introduce bias into pain assessments.[18] The generalizability of the results of the RCT is also limited because it was performed at a single center study located in Turkey and the interventions were administered by one clinician.

Future research could reduce uncertainty and would include well-designed RCTs with blinded methodology. In addition, many of the primary studies described in the systematic reviews were small (N<30) and therefore future studies should have adequate statistical power to detect differences between botulinum toxin and other treatment approaches.

Conclusions and Implications for Decision or Policy Making

A total of five relevant publications were identified that met the inclusion criteria for this report including four systematic reviews,[11-14] and one RCT.[12] These reports included comparisons of botulinum toxin to occlusive splints, physiotherapy (fascial manipulation, dry needling), pharmacotherapy, placebo, acupuncture, psychological approaches, complementary therapies, saline injections, lidocaine and laser.

None of the included systematic reviews expressed confidence in the efficacy of botulinum toxin for treating TMD. There were some primary studies that reported improvements in pain scores relative to saline injections. However, this result was not reproduced in several primary studies, and the clinical significance of observed changes is uncertain. No systematic reviews reported improvements in mouth opening for botulinum toxin. In the primary studies, there was heterogeneity in TMD clinical presentation, botulinum toxin administration techniques and comparator treatment approaches and this creates significant uncertainty about the clinical utility for botulinum toxin in TMD. Assessing generalizability of the results to the Canadian context is difficult given these issues.

While there have been no consistent signals of increased risk of harm for botulinum toxin relative to control groups in the data reviewed, none of the primary studies were rigorously designed to study harms. This is an important issue to be addressed in future research since botulinum toxin treatment for TMD is an invasive procedure with risks inherent in its administration.

There was no evidence to inform the cost effectiveness of botulinum toxin in TMD and no clinical practice guidelines were identified.

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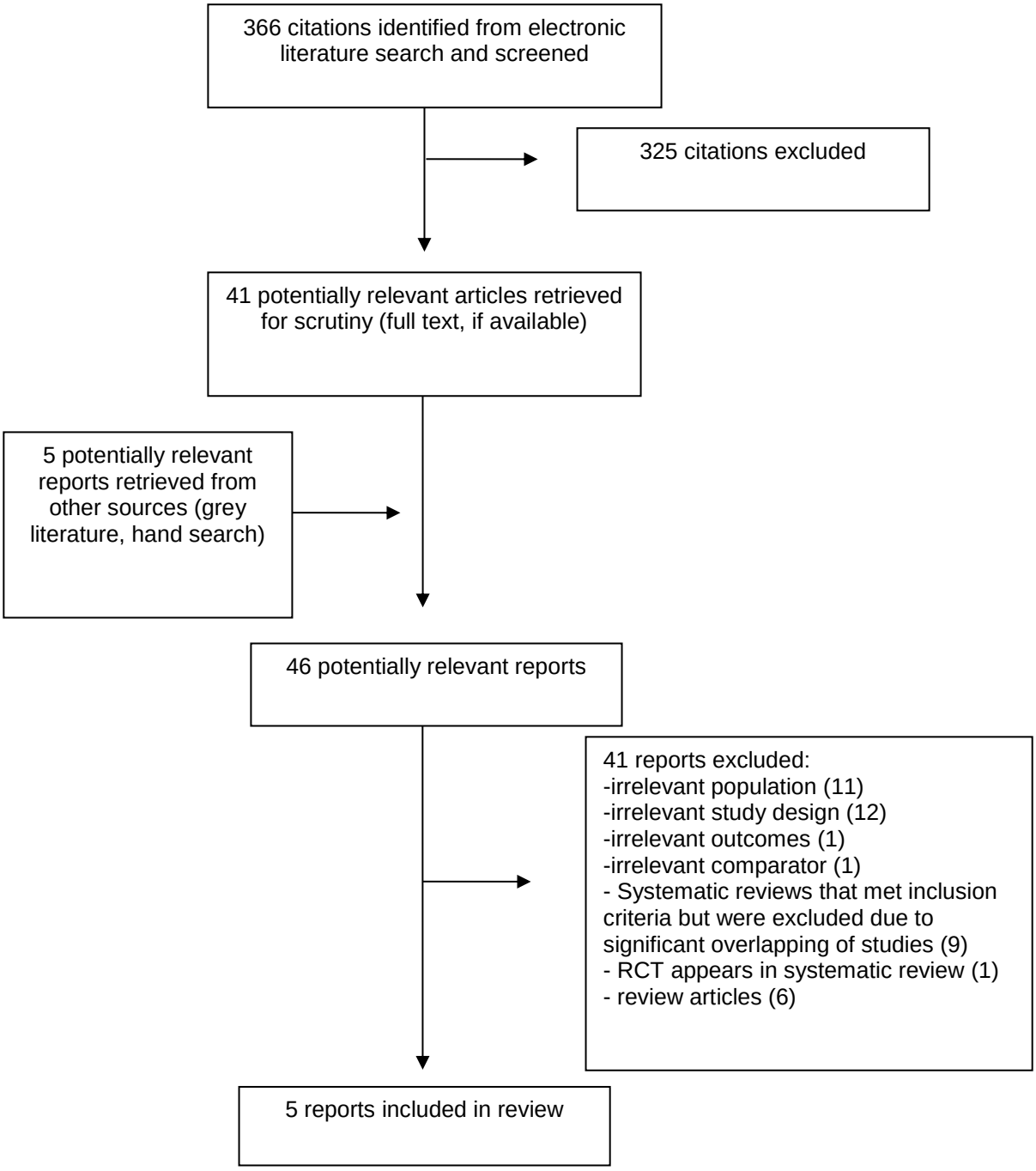
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included, N	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Patel, 2019[11] **United Kingdom**	11 studies (including 8 studies that met the PICO criteria for this CADTH report, N=219) All studies were prospective; treatment assignment methods were not described, 3/8 studies were crossover designs; 5/8 were parallel group studies Sample sizes ranged from 12-90 patients	TMD (myofascial pain) with or without bruxism; bruxism. 5/8 studies used the RDC standardized criteria for TMD diagnosis. 3/8 studies enrolled subjects unresponsive to 'conservative treatment'	BTX injected into both masseters and temporalis muscles (8 studies); masseters only (3 studies) Comparators: fascial manipulation, saline, laser, no treatment, or 'conservative treatment'	Pain VAS (8 studies); reductions in mouth opening; bruxism events; Follow up time ranged from 1-6 months.
Awan, 2019[12] **USA**	7 studies (including 7 studies that met the PICO criteria for this CADTH report, N=245) All studies were randomized; 5 used parallel group design, 2 were crossover designs; 5 studies report using blinding techniques	TMD (myofascial pain) 4/7 studies used the RDC standardized criteria for TMD diagnosis.	BTX injection 70-300U in one session. (masseter and temporalis in all studies, except one study was masseter only) Comparators: saline; fascial manipulation, lidocaine, dry needling	Improvement in pain, mouth opening, adverse events Follow up time ranged from 1 month (2 studies), 1-3 months (4 studies), 6 months (1 study)
Canales 2019[13] **Brazil**	17 studies (including 5 studies that met the PICO criteria for this CADTH report, N=105)	TMD (myofascial pain) 5/5 studies used the RDC standardized criteria for TMD diagnosis.	BTX injection, doses up to 150U (4/5 studies: masseter and temporalis, 1/5 studies masseter only) Comparators: saline; fascial manipulation	Adverse events were the primary outcome of interest Follow up time ranged from 1-6 months.
Feng 2019[14] **China**	12 studies (including 2* studies that met	TMD (myofascial pain)	BTX injection	Quantitative report of pain intensity

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included, N	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
(Network Meta-Analysis)	the PICO criteria for this CADTH report, N=51	All studies used the RDC standardized criteria for TMD diagnosis.	Comparators: splints, physiotherapy, pharmacotherapy, placebo, acupuncture, psychological, complementary, bi-physiotherapy	Follow up time: 3 months (2 studies)

BTX = botulinum toxin; CADTH = Canadian Agency for Drugs and Technologies in Health; NR= not reported; RCT = randomized controlled trial; RDC= Research Diagnostic Criteria; TMD=temporomandibular disorder;

* Feng et al cite “Manfredini 2012” but did not provide the full citation for this study. The authors of this CADTH report believe that this study was labelled incorrectly and it is in fact the 2012 study by Guarda-Nardini mentioned within the other systematic reviews in this table (see Table 9).

Table 3: Characteristics of Included Primary Clinical Study

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Kutuk 2019[15] Turkey	RCT Open-label Parallel group design	Diagnosis of TMD myofascial pain N=40 (29 women) Mean age (SD): 34(8)	BTX 25-150U injected intramuscularly into trigger points Dry needling	VAS pain at rest and on chewing, crepitation, maximal mouth opening, jaw functional limitation, strength of jaw, muscular spasms

BTX= botulinum toxin; SD= standard deviation; RCT = randomized controlled trial

Appendix 3: Critical Appraisal of Included Publications

Table 4: Quality Assessment of the Systematic Reviews Using AMSTAR2[7]

Strengths	Limitations
Patel, 2019[11]	
• The statement of objective and inclusion criteria included the population, interventions, and outcomes of interest. • The authors described the search strategy and databases used for identifying relevant studies. • The authors assessed risk of bias using the Cochrane Risk of Bias tool.	• The descriptions of the included studies were limited and did not describe the study populations, interventions, comparators or results in sufficient detail. • Authors did not explain their decision to not perform meta-analysis. • Authors did not account for risk of bias in the context of results discussion. • Overall risk of bias for included studies was not reported • There was incomplete reporting of statistical test results associated with the data presented from the individual studies. • There was no statement regarding author funding or potential conflict of interest. • Sources of funding for the individual studies were not described. • The authors did not provide sufficient analysis of the clinical heterogeneity between the included studies. • The authors did not critically assess the outcomes used in the included studies. • Authors did not provide a list of excluded studies. • Authors did not provide a detailed description of the comparators
Awan, 2019[12]	
• The protocol for the review was registered in the PROSPERO database. • The inclusion criteria included the population, interventions, and outcomes of interest. • The authors described the search strategy and databases used for identifying relevant studies. • Two independent reviewers screened studies and extracted data. • The authors assessed risk of bias using the Cochrane Risk of Bias tool, and presented overall risk of bias for the included studies. • Conflict of interest section states “none declared.” • Authors explained the reasons for not performing meta-analysis. • Authors discussed the results in the context of the risk of bias.	• There reporting of the results was unclear. • There was incomplete reporting of statistical test results (e.g. p-values, 95% confidence intervals, standard deviation) associated with the data presented from the individual studies. • Authors did not provide a list of excluded studies. • Authors did not provide a detailed description of the comparators
Canales 2019[13]	
• The statement of objective included the population, interventions, and outcomes of interest. • The authors described the search strategy and databases used for identifying relevant studies. • Two independent reviewers screened studies. • The authors assessed risk of bias using the Cochrane Risk of Bias tool and summarized overall risk of bias for the included RCTs	• There was no description of how data were extracted from the primary studies. • Adverse event data were reported in aggregate, with no comparisons between the intervention group and the control. • The results presentation was mostly qualitative; there were very few numerical or statistical descriptions of the occurrence of adverse events in the included studies

Strengths	Limitations
• Authors discussed some the results in the context of the risk of bias assessment.	• Many of the included trials were not specifically designed to monitor adverse events, which was the outcome of focus for Canales et al. • Authors did not provide a detailed description of the interventions or comparators of the primary studies

RCT= randomized controlled trial;

Table 5: Quality assessment of the Feng 2019[14] Network Meta-Analysis using the ISPOR Task-Force questionnaire[8]

Question	Feng 2019[14]
Relevance	
1. Is the population relevant?	Cannot answer – incomplete reporting of patient characteristics
2. Are any relevant interventions missing?	No, but authors did not provide a detailed description of the comparators
3. Are any relevant outcomes missing	Yes, this analysis only considered pain. No information on mouth opening, quality of life, adverse events.
4. Is the context (settings and circumstances) applicable?	Cannot answer
Credibility	
5. Did the researchers attempt to identify and include all relevant RCTs?	No. Feng did not include several relevant studies (Table 9)
6. Do the trials for the interventions of interest form one connected network of RCTs?	Yes
7. Is it apparent that poor quality studies were included, thereby leading to bias?	Most of the studies rated low for risk of bias. Overall quality of the studies was moderate.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	Cannot answer
9. Are there systematic differences in treatment effect modifiers across the different treatment comparisons in the network?	Cannot answer
10. Were these imbalances in effect modifiers across the different treatment comparisons identified before comparing individual study results?	Cannot answer
Analysis	
11. Were statistical methods used that preserve within-study randomization?	Yes
12. If both direct and indirect comparisons are available for pairwise contrasts was agreement in treatment effects evaluated or discussed?	Inconsistency was assessed by the authors. The authors concluded that the direct and indirect estimates were ‘relatively consistent’ for splint therapy, physiotherapy, placebo, complementary therapy, and botulinum toxin.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Yes
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of	Not applicable

Question	Feng 2019[14]
comparisons in the network of trials, did the researchers attempt to minimize bias with the analysis?	
15. Was a valid rationale provided for the use of random-effects or fixed-effect models?	No
16. If a random-effects model was used, were assumptions about heterogeneity explored or discussed?	Cannot answer
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	No
Reporting quality and transparency	
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes
19. Are the individual study results reported?	No
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	No
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	Yes
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	Yes
23. Is the effect of important patient characteristics on treatment effects reported?	No
Interpretation	
24. Are the conclusions fair and balanced?	Cannot answer
Conflict of interest	
25. Were there any potential conflicts of interest?	None reported
26. If yes, were there steps taken to address these?	n/a

Table 6: Strengths and Limitations of Clinical Studies using Downs and Black[9]

Downs and Black Item		Kutuk 2019[15]
Reporting		
Is the hypothesis/aim/objective of the study clearly described?		⊕
Are the main outcomes to be measured clearly described in the Introduction or Methods section?		⊕
Are the characteristics of the patients included in the study clearly described?		X
Are the interventions of interest clearly described?		⊕
Are the distributions of principal confounders in each group of subjects to be compared clearly described?		X
Are the main findings of the study clearly described?		X
Does the study provide estimates of the random variability in the data for the main outcomes?		⊕
Have all important adverse events that may be a consequence of the intervention been reported?		X
Have the characteristics of patients lost to follow-up been described?		X
Have actual probability values been reported for the main outcomes?		X
External Validity		
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?		?
Were those subjects who were prepared to participate representative of the entire population from which they were recruited?		?
Were the staff, place, and facilities where the patients were treated, representative of the treatment the majority of patients receive?		X
Internal Validity – Bias		
Was an attempt made to blind study subjects to the intervention they have received?		X
Was an attempt made to blind those measuring the main outcomes of the intervention?		X
In trials and cohort studies do the analyses adjust for different lengths of follow-up of patients or in case-control studies is the time period between the intervention and outcome the same for cases and controls?		?
Were the statistical tests used to assess the main outcomes appropriate?		?
Was compliance with the intervention/s reliable?		⊕
Were the main outcome measures used accurate (valid and reliable)?		⊕
Internal Validity – Confounding		
Were the patients in different intervention groups or were the cases and controls recruited from the same population?		⊕
Were study subjects in different intervention groups or were the cases and controls recruited over the same period of time?		⊕
Were study subjects randomized to intervention groups?		⊕
Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?		?
Was there adjustment for confounding in the analyses from which the main findings were drawn?		X
Were losses of patients to follow-up taken into account?		?
Power		
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?		?
Additional Critical Appraisal Points		
Was conflict of interest mentioned?		⊕

Legend: ⊕ = Yes, X = No, ? = Unclear

Appendix 4: Main Study Findings and Authors' Conclusions

Table 7: Summary of Findings Included Systematic Reviews and Meta-Analyses

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">Patel, 2019[11]</td></tr>
<tr><td>

No pooled analyses of studies were performed. Results summaries focused on change from baseline, rather than difference between treatment groups.

Pain

5/6 studies that compared BTX to saline there were numerical improvements in pain scores with botulinum toxin compared to saline from baseline up to 3 months, but the data were poorly reported, no statistical test results were provided and there was no discussion about whether the differences observed were clinically significant.
One study that compared BTX to fascial manipulation showed improvements favouring fascial manipulation at 3 months.
No statistical test results were provided for any of the pain score results
Results from unique study Chaurand 2017 (N=22):

Mean BTX VAS baseline: 8.5

Mean Reduction at 1 month: -19.2%

Mean conservative therapy VAS at baseline: 8.5

Mean Reduction at 1 month: -5.2%

Results from unique study Patel et al 2017 (N=20):

Mean BTX score baseline: 5.4

Mean Reduction at 1 month: -4.5 points

Mean saline score baseline: 5.4

Mean Reduction at 1 month: -1.7 points

Maximal mouth opening increases from baseline
<table>
<tr><th>Trial/Timepoint</th><th>BTX</th><th>Fascial manipulation</th></tr>
<tr><td>Guarda 2012</td><td></td><td></td></tr>
<tr><td>Baseline</td><td>NR</td><td>NR</td></tr>
<tr><td>1 month</td><td>Increased 2.7mm</td><td>Increased 0.4mm</td></tr>
<tr><td></td><td>BTX</td><td>Saline</td></tr>
<tr><td>Ernberg</td><td></td><td></td></tr>
<tr><td>Baseline</td><td>NR</td><td>NR</td></tr>
<tr><td>1 month</td><td>Increased1.6mm</td><td>Increased 0.9mm</td></tr>
<tr><td>3months</td><td>Increased 1.6mm</td><td>Increased 0.1mm</td></tr>
<tr><td>Guarda 2008</td><td></td><td></td></tr>
<tr><td>Baseline</td><td>NR</td><td>NR</td></tr>
<tr><td>6 months</td><td>Increased 0.3mm</td><td>Increased 2.1mm</td></tr>
<tr><td>deCarli</td><td></td><td></td></tr>
<tr><td>Baseline</td><td>38mm</td><td>42mm</td></tr>
<tr><td>1 month</td><td>36mm</td><td>42mm</td></tr>
<tr><td>Chaurand</td><td></td><td></td></tr>
<tr><td>Baseline</td><td>42.3mm</td><td>42.3mm</td></tr>
<tr><td>1 month</td><td>43.4mm</td><td>42.3mm</td></tr>
</table>
</td><td>"The evidence to support the use of Botox in the management of TMD and/or bruxism is not entirely unequivocal…..Given the current evidence, Botox should certainly be considered but due to financial implications and possible side effects, it seems appropriate that conservative options, such as self-management with explanation and physical therapies, should be exhausted first."(p667)</td></tr>
<tr><td colspan="2">Awan, 2019[12]</td></tr>
<tr><td>

No pooled analyses of studies were performed.

Pain

2/5 studies comparing BTX to saline reported statistically significant improvements in pain for BTX compared to saline
3/5 studies comparing BTX to saline reported no statistically significant difference between treatment groups for pain, pressure pain threshold and maximal mouth opening

</td><td>"…the therapeutic efficacy of Botox was unclear. Randomized controlled trials with better methodological criteria need to be carried out to evaluate the real effectiveness of Botox." (p192)</td></tr>
</table>

Main Study Findings	Authors' Conclusion
• One study reported no improvement in pain for BTX relative to fascial manipulation • One study reported 'positive outcomes' for BTX in a study that compared BTX to dry needling and lidocaine, but the authors did not specify which comparison this applied to	"It was difficult to have a definitive conclusion about Botox efficacy due to the lack of adequate quality studies. To assess the real effectiveness of Botox, it is important to perform new RCTs that have better methodological criteria in terms of standardized diagnostic methods, large sample size, and longer follow-up periods." (*p199*)

Mean VAS[1] Pain Score Results (SD)

Trial/Timepoint	BTX	Fascial Manipulation	SS	Adverse Events
Guarda 2012				Mild discomfort when chewing (n= NR)
Baseline	7.3(1.1)	6.0(2.0)		
3 months	4.8(2.0)	2.5(2.2)	NSS	
	BTX	**Dry Needle**		
Venancio				NR
Baseline	0.44(0.19)	0.52(0.09)		
3 months	0.44(0.19)	0.36(0.17)	NSS	
	BTX	**Saline**		
Nixdorf				pain worsening (n=3); paralysis(n=2)
Baseline	56(NR)	56(NR)		
2 months	Decrease 19	Decrease 1	NSS	
vonLindern				Dysphagia and paralysis (n=1)
Baseline	NR	NR		
6 months	NR	NR	P<0.01[2]	
Guarda 2008				NR
Baseline	6.2(2.8)	4.1(2.9)		
6 months	3.6(2.4)	4.7(2.8)	P<0.02[2]	
Kurtoglu				'no evident adverse events'
Baseline	56.1(17.1)	58.9(14.7)		
1 month	43.9(24.2)	51.4(23.0)	NSS	
Ernberg				NR
Baseline	61(11)	67(14)		
3 month	58(14)	65(11)	NSS	

1 Kurtoglu and Venancio used the bio-behavioural questionnaire and modified symptom severity index, respectively (not the VAS)
2 favouring BTX

Mean Mouth Opening, mm

Trial/Timepoint	BTX	Fascial Manipulation	Statistical Significance
Guarda 2012			
Baseline	48.7(8.3)	52.0(9.5)	
3 month	51.4(NR)	52.4(NR)	NSS
	BTX	**Saline**	
Guarda 2008			
Baseline	46.3(9.7)	43.8(9.4)	
6 months	48.4(7.6)	43.5(9.1)	NSS
Ernberg			
Baseline	42.7(11.3)	43.4(7.3)	
3months	44.3(7.2)	44.2(8.7)	NSS
Nixdorf			
Baseline	43(NR)	43(NR)	
2 months	Worsen 3(5)	Improve 5(7)	NSS

Canales 2019[13]

Most common adverse events (these events were reported in the TMD studies; authors did not attribute these events to a specific treatment group) • Temporary regional weakness	"Botox has been increasingly diffused in dentistry, being used for the management of masticatory myofascial pain and trigeminal neuralgia. Nonetheless, there is no consensus about its efficacy

Main Study Findings	Authors' Conclusion
• Tenderness over the injection sites • Minor discomfort during chewing • Asymmetric smile • Reduction in the size of the masticatory muscle (masseter) • Paresthesia • Eye drooping or muscle weakness • Difficulty swallowing, speech changes • Perioral swelling • Bruising • Pain with digital pressure Authors stated that muscle weakness was the most reported adverse effect, but none of the studies evaluated this outcome objectively	and adverse effects that could occur when this treatment is applied." (*p3411*) "…even though none of the included studies aimed to assess objectively Botox on adverse effects, this treatment in general was reported as well tolerated, since self-reported minor adverse effects with a spontaneous resolution were the most prevalent. Notwithstanding, it is recommended that future studies assess Botox adverse effects mainly produced from multiple or high-dose applications, as well as the ratio between the effectiveness and the probability of developing adverse effects when this substance is the treatment choice." (*p3419*)
Feng 2019[14]	
Network meta-analysis used data extracted from the studies on pain from the numerical rating scale and visual analog scale. Scores were transformed and change in pain score was used. Authors did not clearly report how this transformation was accomplished and what the numbers in the table below represent. There were no statistically significant differences when BTX was compared to any other comparator in the network for change in pain score. **BTX pain score change relative to comparators in the network:**	"Based on the limited evidence of available trials, complementary therapy seemed to be slightly more effective than remaining treatment modalities for pain reduction in TMD patients with masticatory muscle pain." (*p1*)

Comparator	Mean Difference	95%CI
Splint therapy	-0.25	-2.09,1.59
Physiotherapy	-0.13	-1.55,1.30
Pharmacotherapy	-0.14	-2.39,2.10
Placebo	-0.07	-1.56,1.42
Acupuncture	-2.49	-5.39,0.40
Psychological	-1.11	-3.41,1.20
Complementary Therapy	0.45	-1.38,2.28
Bi-physiotherapy	-1.21	-3.18,0.76

NR= not reported; NSS= not statistically significant (authors did not provide p-values);SD= standard deviation; SS= statistical significance; VAS= visual analog scale;

Table 8: Summary of Findings of the Included Primary Clinical Study

Main Study Findings	Authors' Conclusion
Kutuk 2019[15]	
• No pooled analyses of studies were performed.	"Botulinum injection and dry needling treatments provided significant improvement in VAS scores during rest and chewing, mouth opening, muscle spasm, and protrusion angle. Dry needling was superior to botulinum injection when compared pain at rest and laterally protrusion angles." (*p1558*)

Time	BTX	Dry Needling	Statistical Significance
Mean VAS pain at rest (SD)			
Baseline	5.3(1.7)	5.4(1.7)	
Week 6	4.2(1.4)	3.1(1.8)	P=0.048
Mouth opening(SD)			
Baseline	42.8(5.0)	42.2(5.8)	
Week 6	43.7(5.0)	45.0(5.8)	P=0.44
Functional limitation at week 6			

Main Study Findings				Authors' Conclusion
None	8(40%)	10(50%)		
Mild	6(30%	6(30%)		
Moderate	5(25%)	4(20%)		
Severe	1(5%)	1(5%)	P=0.63	

BTX= botulinum toxin; SD=standard deviation; VAS= visual analog scale

CADTH

Appendix 5: Overlap between Included Systematic Reviews

Table 9: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review*													
	Included				Excluded									
	Patel 2019[11]	Canales 2019[13]	Awan 2019[12]	Feng 2019[14]		Machado 2019[19]	Machado 2018[20]	Haggman 2017[21]	Awan 2017[22]	Bowens 2017[23]	Khawaja 2017[24]	Khalifeh 2016[25]	Calixtre 2015[26]	Chen 2015[27]
Ernberg 2011	X	X	X	X		X	X	X		X	X	X		X
Guarda-Nardini 2012	X	X	X	X		X	X			X	X		X	X
Venancio 2009			X				X							
Guarda-Nardini 2008	X	X	X			X	X	X	X		X	X		
Kurtoglu 2008	X	X	X			X	X				X	X		X
VonLindern 2003	X		X			X	X		X		X			X
Nixdorf 2002	X	X	X			X					X	X		X
Patel 2017	X					X								
Chaurand 2017	X													

*This table presents studies included in the published systematic reviews that used botulinum toxin in TMD patients and were of interest to this CADTH report. Only studies included in the published systematic reviews that were of interest for this CADTH review are listed in this table. For example, some systematic reviews contained studies in other indications (e.g. neck and shoulder pain, general myofascial disorders, bruxism), or studies that did not use a control group, or studies that included comparators that were not relevant; these studies are not listed in this table.

Table 10: Systematic Reviews Excluded Due to Overlapping Studies

Author, year	Unique studies that meet the PICO criteria for this CADTH report	Reason for exclusion
Machado 2019[19]	0	Complete overlap of relevant studies. Meta-analyses were performed in mixed populations and did not distinguish between patients with or without bruxism.
Machado 2018[20]	0	Complete overlap of relevant studies.
Khawaja 2017[24]	0	Complete overlap of relevant studies.
Bowens 2017[23]	0	Complete overlap of relevant studies. Several systematic reviews were also described but did not contain any analyses of TMD populations.
Haggman-Henrikson 2017[21]	0	Complete overlap of relevant studies. Some network meta-analyses were performed but no data were available regarding the relative effects of botulinum toxin in the network.
Awan 2017[22]	0	Complete overlap of relevant studies
Khalifeh 2016[25]	0	Complete overlap of relevant studies
Calixtre 2015[26]	0	Complete overlap of relevant studies
Chen 2015[27]	0	Complete overlap of relevant studies