Botulinum Toxin Type a for the Management of Masticatory Muscle Pain in Temporomandibular Disorders: A Systematic Review

Abstract

Background: Botulinum toxin type A (BoT-A) has gained significant clinical interest in the management of masticatory muscle pain in temporomandibular disorders (TMD). This may be due to clinical success of BoT-an in treatment of other neuromuscular and refractory chronic pain disorders in the head and neck region, and the limited understanding of the underlying pathophysiology of masticatory muscle pain.

Methods: A systematic review was conducted to determine the effectiveness of botulinum toxin type A in the management of masticatory muscle pain in temporomandibular disorders, specifically myalgia, or myofascial pain. Three reviewers separately identified the pertinent literature by searching MEDLINE via PubMed, Web of science and Cochrane databases and reference lists of relevant articles under the inclusion criteria of all studies in English language.

Results: Thirteen manuscripts met the inclusion criteria. Among these six were randomized controlled trials (RCT) and seven were case-series investigations. Two out of 6 RCT and all of the 7 case-series investigations have suggested BoT-A therapy being significantly better in management of masticatory muscle pain in TMD.

Conclusion: The effectiveness of BoT-A treatment for the management of masticatory muscle pain in TMD has yet to be established. Results of both types of investigations are convoluted by the presence of multiple methodological limitations and heterogeneity in protocol. Botulinum toxin injection therapy appears to effective in certain patients with masticatory muscle pain disorders in TMD. However, there is limited evidence regarding the characterization of participants that would benefit from this therapeutic modality.

Keywords: Temporomandibular disorders; Botulinum toxin; Myalgia; Masticatory muscle pain; Pain

Introduction

Temporomandibular disorders (TMD) encompass a group of musculoskeletal and neuromuscular conditions that involve the temporomandibular joints (TMJs), the masticatory muscles, and associated tissues [1]. The prevalence of pain-related TMD, such as, masticatory myalgia, masticatory myofascial pain and TMJ arthralgia, has been reported to be between 2.5 % to 10 % in the general adult population, making it the second most common musculoskeletal condition, after chronic back pain, which results in pain and disability [2,3]. Common manifestations of pain-related TMD consist of pain, of a persistent, recurring, or chronic nature [4,5], limitation in the range of mandibular motion, and joint noises [4-6]. Pain-related TMD can affect the individual’s daily activities, psychosocial functioning, and quality of life [7]. It has been estimated that the annual pain-related TMD management cost in the United States, excluding diagnostic imaging, in the last decade was approximately $4 billion [8]. Furthermore, in the United States, it is estimated that for every 100 million working adults, pain-related TMD contributes to 17.8 million lost workdays annually [9,10]. Although the pathophysiology of pain-related TMD is poorly understood, multiple risk factors have been identified, such as, gender, pain provoked during jaw function and/or palpation, oral parafunctions, other chronic pain conditions, pain sensitivity and psychosocial characteristics [11,12]. Multiple treatment modalities have been suggested as a treatment for masticatory muscle pain disorders, including patient education, behavioral management, physical therapy, occlusal splints, and pharmacotherapy [6-14]. However, no specific therapy has been proven uniformly effective in providing symptomatic relief [13]. Because of this, the search for effective and safe therapies has been topic of interest among researchers. An example of such therapy is the emergence of botulinum toxin type A (BoT-A) as a potential therapeutic modality for management of masticatory muscle pain in TMD. Botulinum toxin type A is a subtype of a potent biologic toxin produced by Clostridium botulinum, a presynaptic neurotoxin. It blocks the calcium ion-mediated release of acetylcholine at the neuromuscular junction. The primary effect is on alpha-motor neuron function. However, it has been suggested that it may also alter the functioning of gamma-motor neurons in the muscle.
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spindles [15,16]. Independent of the neuromuscular effects, BoT-A has been suggested to have analgesic properties [16,17]. However, the mechanism by which the analgesic effects are mediated is not fully understood. Animal-based investigations suggest BoT-A inhibits neurogenic inflammation by peripherally blocking the release of inflammatory neuropeptides, such as, substance P (SP) and glutamate [17,18]. In addition, BoT-A has been found to inhibit the release of Calcitonin Gene-Related Peptide (CGRP) [18], and reduce the vascular response to algogenic substances, such as capsaicin, applied to human skin [1]. Botulinum toxin type A may also act centrally, it has been suggested that it may undergo retrograde transportation by sensory neurons and inhibit the release of neurotransmitters at the central nerve terminals [17-20]. Intra-muscular administration of botulinum toxin has shown to be significantly useful in the management of muscle hyperactivity disorders, such as cervical dystonia, spasmodic dystonia, or blepharospasm [21,22]. In addition to the reduction in dystonia-associated muscle hyperactivity, it has been shown to reduce the associated pain [15-21]. Masticatory muscle hyperactivity in TMD and its associated pain have been suggested as self-perpetuating in nature [23]. However, based on multiple EMG-based investigations, current evidence suggests that TMD-associated pain is correlated with muscle hypoactivity [23-35]. Botulinum toxin has also been shown to be clinically beneficial in the management of refractory chronic pain disorders when injected into the soft-tissue (subcutaneously or intra-muscularly) as in case of chronic migraine headaches [26,27] and trigeminal neuralgia [28,29]. Likewise, it has been shown to be effective when injected intra-articularly for the management of refractory arthritis joint pain [30,31]. The proposed mechanism of relief has been attributed to the neuro-inhibitory and anti-nociceptive properties of the toxin along the peripheral and central nervous system [17]. The clinical success of BoT-A in treatment of neuromuscular and refractory chronic pain disorders in the head and neck region, and the limited understanding of the underlying pathophysiology of pain in TMD as well as the refractory nature of pain in some cases, may explain the clinical interest of physicians in the use of BoT-A in the management of masticatory muscle pain in TMD. The U.S. Food and Drug Administration (FDA) and the European Medicines Agencies (EMA) have not yet approved use of BoT-A to manage masticatory muscle pain in TMD. Nevertheless, it is being used and promoted as an off-label indication [32]. Several studies have been conducted on the effectiveness of BoT-A for the management of masticatory muscle pain in TMD. However, the results have been inconsistent. While some of the studies have reported evidence for its efficacy, others have reported inconclusive findings. Due to this difference in reporting, a systematic review was conducted to determine the effectiveness of BoT-A in the management of masticatory muscle pain in TMD, specifically masticatory myalgia, or masticatory myofascial pain.

Materials and Methodology

The PRISMA guidelines were used as a template for the systematic review. The clinical question, “Is botulinum toxin A more efficacious than placebo treatment for management of pain associated with masticatory myalgia among patients of TMD, in an out-patient setting?” (PICOS) was utilized to guide the review. Observational investigations evaluating the effectiveness of BoT-A for treatment of masticatory muscle pain in TMD, specifically masticatory myalgia or masticatory myofascial pain were included. Publications were limited to English language, humans, and adults (≥ 16 years) only. Publication date limit for the selection of articles was from beginning to June 2016. Publications such as literature reviews and case-reports were excluded from this review. Three reviewers separately identified the pertinent literature by searching MEDLINE via PubMed, The web of science, and Cochrane databases and reference lists of relevant articles for manuscripts meeting the inclusion and exclusion criteria. The databases were searched using relevant keywords and MeSH terms. The search strategy was: (“botulinum toxin”[MeSH]) OR (“botulinum toxin type A”[MeSH]) OR (clostridium botulinum) OR (clostridium botulinum toxin) OR (onabotulinumtoxinA) OR (Abobotulinumtoxin) OR (botulinum) AND (“Myofascial Pain Syndromes”[MeSH]) OR (“myalgia”[MeSH]) OR (“masticatory muscle”[MeSH]) OR (“temporomandibular joint dysfunction syndrome”[MeSH]) OR (“facial pain”[MeSH]).

Overview of the procedure is provided in figure 1. Three reviewers independently read the title and the abstract of all publications that were identified by the search strategy. The reviewers met and developed a final list of publications to be read by consensus. One reviewer read all the papers (SNK); the other two reviewers (HC, YG) equally divided the number of papers so that two reviewers evaluated each paper independently. Articles were reviewed based on the study design, aim of the study, demographics, clinical assessment methodology, botulinum toxin A type and protocol of administration, results, conclusions, adverse events, and limitations. In addition, the randomized controlled trials were assessed using Cochrane collaboration’s tool for assessing risk of bias [33], while rest of the investigations were assessed using Newcastle-Ottawa quality assessment scale for case-control studies [34]. Any disagreements between the reviewers were resolved through discussions and final decisions were reached through consensus.

Results

Three databases (MEDLINE via PubMed, The web of science, and Cochrane databases) and reference lists of relevant articles were systematically searched for articles. A total of 3,198 articles were identified with the search strategy. Three reviewers independently reviewed titles and abstracts of all of the identified manuscripts. The reviewers met and developed a final list of publications to be read by consensus. Three thousand one hundred and eighty five publications were excluded because of at least one of the following reasons: did not assess the effect of BoT-A on masticatory muscle pain associated with TMD, were case-reports or literature reviews, were not in the English language, or were based on animal-models. Thirteen met the inclusion criteria. Of these, 6 were randomized control trials (RCTs), and 7 were non-randomized case-series investigations. The randomized controlled trials included in the present systematic review were prospective human controlled trials, published between 2002 and 2012 [35-40]. Of the six RCTs, two
were crossover studies [35-39] and four were parallel design studies [36-40]. Each investigation evaluated participants using standardized examination protocol except one trial [40]. All of the participants were given diagnosis of either “masticatory myofascial pain” with or without “bruxism” and “functional disc displacement”, or of “chronic facial pain associated with or caused by masticatory hyperactivity, parafunctional movements, and hypermobility disorders”. Furthermore, included participants had chronic symptomatology (3> months) and were refractory to conservative therapy (such as, behavior modification, thermal therapy, physical therapy, and orocutaneous orthotic device therapy). In total, 200 individuals (mostly females) participated, of which 133 underwent botulinum toxin injection therapy. The location and technique of injections varied. Injections were primarily placed in masseter muscles. However, in few studies injections were also placed in temporalis and medial pterygoid muscles. Injections were placed in either a pre-determined area using a specified pattern, such as chessboard or reverse pyramid, or corresponding to the site of maximum pain, or at the “most active site” of the muscle, based on manual palpation or EMG guidance. The total dose of botulinum toxin injected ranged from of 30U-500 per side for masseter muscles, 20U – 35U per side for temporalis muscles, and up to 35U per side for medial pterygoid muscles. In all of the trials, groups receiving BoT-A therapy, had reduction in pain intensity and improvement in range of motion. However, these changes were statistically significant in only two of the six trials. Four of the six investigations reported minor adverse events, such as, discomfort/pain (4), transient facial paralysis (3), headache (7), fatigue (2), influenza like symptoms (2), dry mouth (1), difficulty with swallowing (1) and smiling (4) in association with BoT-A therapy. Overall, 3 of the 6 RCT investigations failed to reject the null hypothesis. However, 2 of these investigations were underpowered (< 50%). The study characteristics are summarized in Table 1. The quality of the RCT was assessed using Newcastle-Ottawa assessment tool. All of the included trials had high risk of performance bias [37]. In this particular investigation, the corresponding group underwent facial manipulation, which would have not made possible for blinding of the participants and researcher. Overall, majority of investigations had low risk of detection, attrition, and reporting bias. Table 2 presents the individual domain risk of bias for each of the included RCT. The non-randomized observational studies selected in this systematic review were case-series, published between 1999 and 2013. Participants were given the diagnosis of “masticatory myofascial pain”, “muscle-centered TMD”, “chronic facial pain”, or “TMD” with or without “bruxism”, “Chronic tension type headache”, and “muscle hyperactivity”. Similar to RCT, all of the participants had chronic symptomatology (3> months) and were refractory to conservative therapy. The location and protocol of injection therapy was variable. Injections were primarily placed in the masseter and the temporalis muscles. However, in some investigations medial pterygoid muscles were also injected. Injections were placed in either a pre-determined area using a specified pattern, such as chessboard or reverse pyramid, or corresponding to the site of maximum pain, or at the site of “maximum muscle thickness”, using manual palpation or EMG guidance. The dosage of injection for each muscle varied from 7.5 U-200 U per side. All of the studies reported reduction in pain symptoms at follow-up. Transient adverse reactions were reported in four of the seven case-series. These consisted of facial muscle weakness and wasting (1), difficulty with speech and swallowing (2), muscle fatigue (35), headaches (3), bruising (1), and facial asymmetry (10). One study was found to be underpowered (< 50%). Six out of seven trials rejected the null hypothesis. However, reduction in pain after undergoing BoT-A injections was found to be statistically significant in all 7 investigations. The study characteristics are categorized and tabulated in Table 3. The quality of non-randomized case-series investigations was evaluated using Newcastle-Ottawa assessment scale for case-control studies. Based on the scale, all of the investigations scored 2 stars on the selection criteria, and 1 star on exposure criteria. No star was awarded to any investigation in comparability category. The results are summarized in Table 4.

Table 1: Assessment of randomized controlled trials using Cochrane collaboration’s tool for assessing risk of bias tool.

| Guarda-Nardini [36] | Ernberg [35] | Kortoglu [38] | Guarda-Nardini [36] | Von Lindern [40] | Nixiort [39] |
|---------------------|-------------|--------------|---------------------|-----------------|------------|
| Random sequence generation | + | + | + | ? | ? |
| Allocation concealment |  | + | + | ? | ? |
| Blinding of participants and personnel | - | + | + | - | ? |
| Blinding of outcome assessment | + | + | + | ? | + |
| Incomplete outcome date | + | + | + | + | - |
| Selective reporting | + | + | + | ? | ? |
| Other bias | ? | ? | - | - | - |

Low risk (+), High risk (-), Unclear risk (?)
Search terms included following keywords and MeSH terms: ("botulinum toxin" [MeSH]) OR ("botulinum toxin type A" [MeSH]) OR (clostridium botulinum) OR (clostridium botulinum toxin) OR (onabotulinumtoxinA) OR (abobotulinumtoxinA) OR (botox) AND ("Myofascial Pain Syndromes" [MeSH]) OR ("myalgia" [MeSH]) OR the ("masticatory muscle" [MeSH]) OR ("temporomandibular joint dysfunction syndrome" [MeSH]) OR ("facial pain" [MeSH]).

Searched in MEDLINE via PubMed, Cochrane, and The web of science and reference lists of relevant articles.

N = 3198

The title and the abstract of all manuscripts were read by three reviewers

Articles excluded
N = 3185
Reviews, case-report, not in English language, investigations did not assess the effect of BOT-A on masticatory muscle pain associated with TMD, animal-based investigations

Articles included
N = 13
One reviewer read all the papers; the other two reviewers equally divided the papers so that each paper was read by two reviewers independently

Figure 1: Overview of the search strategy.
Discussion

A systematic review was conducted to determine the effectiveness of BoT-A in the management of masticatory muscle pain in TMD. Total of 13 articles published on this topic were reviewed. Two out of 6 RCT suggested BoT-A therapy was significantly better in management of masticatory muscle pain in TMD. In contrary, all of the 7 case-series investigations suggested that BoT-A resulted in significant improvement in pain scores and range of motion in patients with masticatory muscle pain. Based on the review of RCT the therapeutic efficacy of the BoT-A therapy in management of masticatory muscle pain in TMD appears to be unequivocal. This inconsistency in the literature may be attributed to multiple methodological variations, such as in the assessment of the subjects and injection protocol, risk of bias, and limitation in the research designs, such as, small sample sizes [35-38], short duration of the follow-up period, inappropriate (low) statistical power [35-39], injecting into the muscle regardless of the site of pain [35-38], or as a one-time intervention [38,39]. These limitations potentially convolute the results. Small sample sizes with short duration follow-up periods, inadequate time of collection of data (<1 hour after injections), or under powered investigations may not allow adequate appreciation of clinically beneficial effects, which may take 5 weeks or even more to be clinically noticeable and last for up to 4-6 months [41]. It has been shown that clinically beneficial effects of BoT-A therapy tend to potentiate with the number of injection cycles [26], however it is not clear if such effects will take place in masticatory muscle pain patients with TMD. In addition, all of the investigations have relied on general sample of masticatory muscle pain patients. Musculoskeletal disorders associated with TMD and other conditions, have multiple underlying pathophysiological mechanisms. Though, they may present clinically with similar characteristics. It may be possible that botulinum toxin may help in disorders associated with specific etiologies (for e.g. muscle pain associated with hypertrophy or hyperactivity) and in general sample of TMD patients these effects may get clouded. Similarly, it has been reported that BoT-A may induce, or in some instances, patients may have pre-existing neutralizing antibodies against BoT-A. Although rare, it may result in clinical ineffectiveness of BoT-A therapy [42,43]. Together, presence of such limitations may have influenced the results in favor of false negative findings. All seven of the case-series investigations found BoT-A therapy to be effective in management of masticatory muscle pain in TMD. However, these results need to be interpreted with caution. Case-series are considered low quality trials in the hierarchy of evidence because of the lack of randomization and blindness, and absence of a control arm. These methodological limitations in research design increase the risk of examiner and subject-associated bias. These risks were also highlighted in the current review by the outcome of Newcastle-Ottawa quality assessment tool. However, it can be argued that due to the acknowledged neuromuscular effects of BoT-A, both subjects and examiners are able to determine the group assignment. Therefore, case-series investigations may be given a consideration when compiling the results. Similarly, among articles reporting effectiveness of BoT-A treatment, some of the investigators failed to apply a standardized clinical examination, or report reliability of examiners to assess the masticatory pain associated with TMD [44-48]. Together, these limitations may have influenced the results in favor of false positive findings. Among the studies investigated, multiple discrepancies in the protocol for BoT-A injection therapy for the management of masticatory muscle pain in TMD were found. The dosage of BoT-A injected varied from 25 units per muscle (one side) to up to 200 units per muscle (one side). Similar differences were observed for the volume and concentration of BoT-A injections. The volume of injected solution varied from .25
milliliters (mL) per muscle to up to 1 mL per muscle, while the concentration of BoT-A also varied from 5 units per 0.1 mL to 40 units per 0.1 mL. The optimal dosage of BoT-A depends on the anatomical characteristics of the individual muscle, such as mass and location, and on the severity of the symptomatology. However, there is no consensus on the therapeutic dosage [49]. Based on our review, BoT-A therapy demonstrated acceptable safety levels. However, these results should be interpreted with caution. The sample sizes of investigations are relatively small and participants were followed for a short period of time. Adverse events associated with BoT-A therapy were transient (hours to weeks) and localized to the areas of injection. Participants reported discomfort at the site of injection, muscle weakness and wasting, difficulty in speech, smiling, and mastication, bruising, and facial asymmetry. Botulinum toxin type A has demonstrated similar safety levels for a variety of other indications [21,22]. Recently, use of BoT-A in the orofacial region has been associated with changes in trabecular bone density [32]. However, the magnitude of risk, generalizability of findings in male gender, and long-term clinical consequence has yet to be determined. Although rare, BoT-A may cause systemic adverse events. There have been reports of influenza-like symptoms, such as nausea, fatigue, upset stomach, and pruritus, as well as respiratory depression. In the present systematic review, a meta-analysis of the published literature was not conducted. This may be considered as a potential limitation. However, in order for the meta-analysis to be conducted, data has to be homogenous and free of any methodological limitations. Unfortunately, the included manuscripts do not fulfill these requirements.

Conclusion
The effectiveness of BoT-A treatment for the management of masticatory muscle pain in TMD has yet to be established. Based on the assessment of randomized controlled trials, the body of literature is equivocal. In contrast, review of case-series investigations suggests therapeutic beneficence of BoT-A therapy in the management of masticatory muscle pain in TMD. Furthermore, results of both randomized controlled trials and case-series investigations are convoluted by the presence of multiple methodological limitations, and heterogeneity in BoT-A injection protocol. Botulinum toxin injection therapy appears to effective in certain patients with masticatory muscle pain disorders. However, there is limited evidence regarding the characterization of participants that would benefit from this therapeutic modality in terms of duration, frequency, quality, and intensity of pain, associated signs and symptoms, with detailed medical history and valid diagnosis. This advocates the need for multi-center investigations with larger sample sizes and longer follow up periods, with adequate characterization of the participants in terms of diagnostic and therapeutic variables.

Conflict of interest
The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

Clinical Implications
Thirteen articles have been published regarding effectiveness of BoT-A in management of muscle pain in TMD. Two out of 6 randomized controlled trials (RCT) and all of the 7 case-series investigations have suggested BoT-A therapy being significantly better in management of masticatory muscle pain in TMD.

Search strategy on PubMed
- TOPIC: (clostridium botulinum)[MeSH Terms] OR ("clostridium"[All Fields] AND "botulinum"[All Fields]) OR ("clostridium botulinum"[All Fields]) OR AbobotulinumtoxinA[All Fields] OR ("botulinum toxins"[MeSH Terms] OR ("botulinum"[All Fields] AND "toxins"[All Fields]) OR ("botulinum toxins"[All Fields] OR ("clostridium"[All Fields] AND "botulinum"[All Fields] AND "toxin"[All Fields]) OR ("Botulinum neurotoxin A"[Supplementary Concept] OR "onabotulinumtoxinA"[All Fields] OR ("onabotulinumtoxinA"[All Fields] OR ("onabotulinumtoxinA"[Supplementary Concept] OR "onabotulinumtoxinA"[All Fields] OR ("botulinum toxins"[MeSH Terms] OR "myalgia"[MeSH] OR "temporomandibular joint dysfunction syndrome"[MeSH] OR "facial pain"[MeSH] AND ("Clinical Trial"[ptyp] OR Clinical Study[ptyp] OR Controlled Clinical Trial[ptyp] OR Randomized Controlled Trial[ptyp]) AND "humans"[MeSH Terms] AND English[lang])

Search strategy on the web of science
- TOPIC: (botulinum toxin) OR TOPIC: (onabotulinumtoxinA) OR (Abobotulinumtoxin) OR TOPIC: (clostridium botulinum toxin A) OR TOPIC: (Botulinum Neurotoxin A) OR TOPIC: (Clostridium Botulinum Toxin Type A) OR TOPIC: (botulinum toxin type a) AND TOPIC: (myofascial pain syndrome) OR TOPIC: (myalgia) OR TOPIC: (temporomandibular joint dysfunction syndrome) OR TOPIC: (facial pain) OR TOPIC: (masticatory muscle)

Search strategy on Cochrane database
- ("clostridium botulinum") OR (Abobotulinumtoxin) OR (botulinum toxins) OR (botulinum toxin A) OR (onabotulinumtoxinA) OR (botulinum) AND ("myofascial pain") OR ("myalgia") OR ("masticatory muscle") OR ("temporomandibular joint dysfunction") OR ("facial pain") (Figure 2 & 3).
Botulinum Toxin Type a for the Management of Masticatory Muscle Pain in Temporomandibular Disorders: A Systematic Review

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Figure 2

Figure 3

PRISMA 2009 Checklist

| Section/topic | # Checklist Item | Reported on page |
|---------------|------------------|-----------------|
| TITLE         | 1 Identify the report as a systematic review, meta-analysis, or both. | 1 |
| ABSTRACT      | 2 Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 3 |
| INTRODUCTION  | 3 Describe the rationale for the review in the context of what is already known. | 4, 5 |
|               | 4 Provide an explicit statement of questions being addressed with reference to participants, interventions, outcomes, and study design (PICO). | 6, 7 |
| METHODS       | 5 Indicate if a review protocol exists and, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including registration number. | 7 |
|               | 6 Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., year range considered, languages, publication status) used as criteria for eligibility, giving rationale. | 7 |
|               | 7 Describe all formation sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies in the searches and data last searched). | 7 |
|               | 8 Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 7 |
|               | 9 Describe the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 8, 7 |
|               | 10 Describe methods of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 7 |
|               | 11 List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 7 |
|               | 12 Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how the information is to be used in any data synthesis. | 7 |
|               | 13 Data the principal summary measure(s) (e.g., risk ratio, difference in means). | 7 |
|               | 14 Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis. | N/A |

RESULTS

| # Checklist Item | Reported on page |
|------------------|-----------------|
| Risk of bias across studies | 15 Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 7 |
| Additional analyses | 16 Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression). If done, indicating which were pre-specified. | N/A |
| Study selection | 17 Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 9, 10 |
| Study characteristics | 18 For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 10, 11 |
| Risk of bias within studies | 19 Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 9-11, 25, 28 |
| Results of individual studies | 20 For all outcomes considered (benefits or harms), present, for each study (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 9-11, 20-27, 20-24 |
| Synthesis of results | 21 Present results of each meta-analysis done, including confidence intervals and measures of consistency. | N/A |
| Risk of bias across studies | 22 Present results of any assessment of risk of bias across studies (see item 15). | 10-12, 25, 28 |
| Additional analyses | 23 Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see item 16]). | N/A |

DISCUSSION

| # Checklist Item | Reported on page |
|------------------|-----------------|
| Summary of evidence | 24 Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 12-14 |
| Limitations | 25 Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified reports, reporting bias). | 13-14 |
| Conclusions | 26 Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 15-16 |

FUNDING

| # Checklist Item | Reported on page |
|------------------|-----------------|
| Funding | 27 Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 15 |

From: Liberati A., Altman D. G., Tetzlaff J., Mulrow C., Gøtzsche P. C., Ioannidis J. P. G., Clarke M., Devereaux P. J., Kleijnen J., and Moher D. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed.1000097. For more information, visit: www.prisma-statement.org.
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