Considerations for planning and designing meta-analysis in oral medicine

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Evidence to address a scientific question is generated through the design of research aiming to answer it. Probably the most often sought design in epidemiologic research is a randomized clinical trial that offers the advantage of controlling for confounders, which may influence the trial outcome. In contrast, observational study designs test hypotheses when clinical trials are difficult to implement. The interest in clinical trials has led to an explosion of manuscripts testing interventions in health care, often yielding interesting results albeit in statistically underpowered samples. Thus, the clinician faces the challenge of making sense of multiple studies that produce results of variable strength when attempting to assess the evidence supporting a treatment. Meta-analytic methods represent an alternative to assess the evidence by pooling the results from multiple studies to increase statistical power. This manuscript describes considerations for planning and implementing meta-analysis in oral medicine. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;116:194-202)

Oral medicine offers non-surgical treatment (with the exception of biopsies) for multiple conditions that affect the orofacial region. The myriad of disorders treated by oral medicine experts include oral manifestations of dermatologic disorders, orofacial pain, salivary gland disorders, and oral care of medically complex patients. Although extensive research has been done in some areas, evidence-based treatment of certain disorders remains limited to a small number of clinical studies. A relevant example is the management of burning mouth syndrome, which is supported by less than a handful of interventions tested in clinical trials.[1] Another example, therapy for disorders such as oral lichen planus (OLP), has been traditionally restricted to the topical application of corticosteroids, and few trials have assessed the impact of corticosteroid formulation, potency, and frequency of application on outcomes in OLP subjects.[2] Moreover, the selected primary outcome from a recent Cochrane review was resolution of pain, used as a surrogate marker for clinical improvement. Questions may rise about the concordance of this surrogate with the erosive presentation of OLP, which may not always be symptomatic. Meta-analysis is a critical tool developed by social scientists that applied to clinical medicine is valuable to steer decision-making and formulation of clinical guidelines for the treatment and diagnosis of disease. This manuscript provides a brief illustration of relevant considerations authors should consider when conducting a meta-analysis, and describe some examples of the application of this technique in oral medicine.

DEFINITION

A meta-analysis is the statistical analysis of a large collection of results from individual studies to integrate their findings. This method produces an estimate of the average treatment effect. In addition, an evaluation of the variability across studies is performed to recognize within study and between study differences.[3] These estimates may be useful to generate additional analyses, namely sensitivity analysis and bias assessment, and assist the investigators in evaluating hypothesis regarding the sources of variability. The phases of any meta-analysis should be planned *a priori* and based on specific hypothesis or aims that the investigators would like to explore.[4] This is particularly important to narrow the analysis to the questions of interest, rather than "mining" the data for statistically significant results.

The terms "meta-analysis" and "systematic review" are occasionally used interchangeably in the literature. However, they refer to 2 complementary but different processes. A systematic review is defined as a methodic review of the literature, often accompanied by a scale or grading algorithm that assigns values to the presence or absence of evidence (defined by the publication of

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Statement of Clinical Relevance

This manuscript offers an overview of methodologic considerations in planning systematic reviews and meta-analysis, and provides examples of recent work in oral medicine and lessons learned for future studies.

randomized trials, observational studies, and case reports) that answers the question posed by the systematic review. Systematic reviews minimize bias and errors that can occur with narrative reviews, using a well thought and structured search strategy that will include all the existing literature in a particular topic.[4,5] Systematic reviews may further analyze the data toward a meta-analysis or may be restricted to qualitative grading of the evidence. The decision to pursue additional statistic analysis rests on the investigators after considering the characteristics of the studies reviewed, such as outcome definition and measurement, subject population, study design, presence of bias, and clarity of outcome reporting. Meta-analysts should carefully consider how the data will be pooled, as the simple aggregation of measures is not appropriate. Discussion of network meta-analysis, a method used to compare the results of studies that share a common treatment in similar populations (not in a randomized clinical trial), extends beyond the scope of this manuscript.

RATIONALE

Meta-analysis has the advantage of encompassing large subject numbers, increasing the ability to detect small but clinically important effects. The finding of significant inter-study differences may generate new hypotheses for future research, and analysis of group/subset effects increases precision.[4,5] Supporting arguments for performing a meta-analysis include the increase in power and precision of the calculated estimates, quantification of effect sizes, and the assessment of the consistency of results across trials (Figure 1). The most convincing argument for carrying out a meta-analysis is in the presence of apparently similar clinical studies reporting results with different effect sizes.[6]

PRINCIPLES OF META-ANALYSIS

The underlying basis of a meta-analysis is the integration of summary statistics among studies. Subjects across studies are not directly compared to each other, and details of the design and implementation of the study are evaluated independently.[5] The investigators set the inclusion criteria for studies to be considered. Therefore, they are keenly involved in the assessment of each study prior to performing the analysis. A second principle involves the weighting of studies in the overall analysis, usually following estimates of precision (by the inverse variance method) and study sample size. To illustrate this process, a graphic representation (forest plot) is generated (Figure 1). This principle has been controversial as studies with more subjects often influence the variability of the final effect size, demanding careful scrutiny of study characteristics,
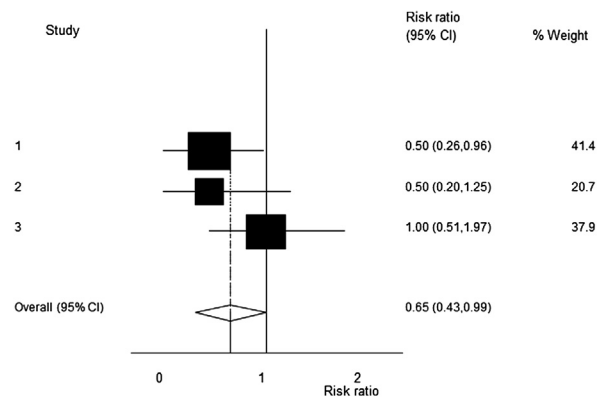

Fig. 1. Example of graphic/forest plot. The black boxes represent the weight of individual studies, and the horizontal lines are the 95% CI of the summary estimate. A risk ratio of less than 1 represents a protective effect. A risk ratio greater than 1 represents increase risk of developing the outcome in the intervention group.

including design, allocation, blinding, implementation, and outcome definition.

META-ANALYSIS OF RANDOMIZED CONTROLLED CLINICAL TRIALS

Randomized controlled trials provide evidence on the efficacy of interventions on separate groups, usually divided into "active" or intervention group and a group treated with a placebo. The randomization scheme should balance the intervention and placebo groups in important known and unknown characteristics that may affect the association between the intervention and outcomes. An advantage of meta-analysis of randomized clinical trials is the presumed low incidence of bias in these studies. In reality, complete avoidance of bias is challenging and many trials in oral medicine include significant bias. Nevertheless, these studies offer summary estimates of effect that can be translated into relative risks (RR) or odds ratio (OR) and are easily interpretable by clinicians who want to see a quantitative difference between groups.[7] The evaluation of study quality and presence of bias is peremptory when performing a meta-analysis. Bias assessment provides an estimate of study quality and allows for sensitivity analysis within groups of studies with greater or lesser quality.

Methods for bias assessment include appraisal of the reporting of the trial, how randomization was done, who was responsible for randomizing subjects, and whether allocation was preestablished, among other items. A widely used scale to assess bias in randomized clinical trials is the JADAD scale, developed and validated in several settings (Figure 2).[8] Additional tools exist to assess the methodologic quality of meta-analysis, (see section on quality evaluation of meta-analysis).[9]

Factor to Evaluate

- Was the study randomized?

- Was the randomization scheme described and appropriate?

- Was the study described as blinded?

- Was the method of double blinding appropriate?

- Was there a description of subject withdrawals?

- Were cointerventions controlled for or avoided?

- Was compliance satisfactory?

- Was the study population homogenous?

- Was the therapeutic time equivalent between groups?

Fig. 2. Items considered in the JADAD scale for quality evaluation of randomized clinical trials. Adapted from Ezzo et al.[8]

META-ANALYSIS OF OBSERVATIONAL STUDIES

Observational studies include cohort and case control designs. The former can occur as prospective or retrospective studies, and focus on follow up of a population that is divided in 2 groups: exposed or not exposed. The outcome is the incidence of subjects who develop the disease during follow up. Retrospective chart reviews are usually considered retrospective cohort designs that explore the association between exposure and occurrence of disease. Case control designs offer a different approach, whereby subjects with the disease are selected and a control group of subjects without the disease is used for comparison. Both cohort and case control designs have their own strengths and are used when randomized clinical trials are difficult to implement or when ethical issues surrounding implementation of a randomized clinical trial are considerable. An example of such case is the controversy surrounding bacterial endocarditis of odontogenic origin and the efficacy of antibiotic prophylaxis. A randomized clinical trial to answer this question would probably be challenged by a Human Subjects Research Committee because of the increased risk to participants who are placed in the "placebo group." In addition, the expense of performing such trial to achieve the required sample size to demonstrate efficacy is prohibitive. Hence, the evidence to address this question is limited to observational and animal studies.

The meta-analysis of observational studies is controversial, and criteria for reporting and evaluating these has only been available in the last 5 years.[9] A critical issue is the lack of valid approaches to the assessment of quality of observational studies. In contrast to randomized clinical trials, no study quality scale has been thoroughly tested and validated for assessment of observational studies. Only one scale, the Newcastle Ottawa Scale has gone through initial face and content validity testing, and further validation is in progress.[10] Observational studies often fail to report clear effect estimates, or grouping of study measures from different studies is not feasible due to inherent differences in methods or inclusion criteria. In this scenario, meta-analysts are left to deal with quantitative comparisons of differences in means or proportions of subjects with the outcome of interest, which yields a mean standard difference estimate. This approach requires additional data abstraction and calculation of standard deviation and medians from each study. Abstraction of this data may be difficult due to lack of reporting or to the requirement of extensive calculations from the information given in the manuscript. Even with this data, the clinical significance of proportional changes in measures requires validation from previous studies with prospective trials. Analysis of diagnostic and prognostic methods can be achieved with meta-analysis, and these techniques require additional considerations beyond the scope of this manuscript.

SELECT META-ANALYSIS IN ORAL MEDICINE

Meta-analysis has been employed in the field of oral medicine since 2001 when human papilloma virus (HPV) was identified as risk factor for oral squamous carcinoma.[11] Since then increased meta-analytic attention to therapeutic areas in oral medicine has occurred (Table I). For example, an evaluation of the evidence on the efficacy of topical corticosteroids in the treatment for OLP failed to identify any randomized clinical trial comparing a corticosteroid to placebo.[2] This meta-analysis also highlighted the absence of studies comparing dosing strategies of topical corticosteroids and reported weak evidence supporting the efficacy of pimecrolimus. In addition, most of the 28 studies reviewed had a high risk of bias. Another study exploring the effectiveness of surgical interventions versus systemic corticosteroid therapy for the periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome reported surgical options as being the choice for long-term resolution of symptoms.[14] PFAPA is one of a handful of immune mediated syndromes that present with recurrent severe aphthous-like oral ulcerations. The treatment for this syndrome is controversial, and although topical/systemic corticosteroid therapy aborts acute symptoms, no conclusive evidence remains regarding long-term resolution. Other interesting reviews explored the efficacy of antiviral therapy for the prevention of primary herpetic gingivostomatitis and recurrent herpes labialis.[13,18] Marginal benefit of antiviral therapy for patients with primary infection was reported, and only 2 studies qualified to be included in the analysis due to reporting and

Table I. Select meta-analysis studies published in oral medicine topics in the last 8 years

Author, year	Outcome	No. of studies included	Total No. of subjects	Interventions or exposures	Conclusion
Zakrzewska, 2005[1]	Effectiveness of interventions for burning mouth syndrome (BMS) Pain relief and global assessment of change	9	470 (BMS)	Antidepressants, anticonvulsants, behavioral, α-lipoic acid, hormone replacement, analgesics	Limited evidence. Few trials with acceptable methodological quality
Zintzaras, 2005[12]	Risk of developing lymphoma in autoimmune disorders	20	8700 cases with Systemic lupus, 95,104 cases with rheumatoid arthritis, 1300 with primary Sjögren syndrome	Non-Hodgkin lymphoma	Association of lymphoma with several autoimmune disorders
Nasser, 2008[13]	Efficacy of systemic acyclovir to treat primary gingivostomatitis Reduction of number of oral lesions, difficulty eating or drinking, pain, fever (primary) reduced hospital admission for children under 6 years of age, quality of life, patient or parental satisfaction (secondary)	2	92 subjects younger than 6 years with primary herpetic gingivostomatitis	Systemic acyclovir	Weak evidence to support the use of systemic acyclovir
Peridis, 2010[14]	Comparison of medical and surgical therapies for PFAPA, effectiveness of tonsillectomy (with/without adenoidectomy), effectiveness of other medical therapies	14	374 (PFAPA)	Antibiotics, cimetidine, corticosteroids, tonsillectomy with/without adenoidectomy	Surgical therapy (tonsillectomy and adenoidectomy is the most effective for long-term resolution of symptoms)
Liu, 2010[15]	Effectiveness of acupuncture to treat trigeminal neuralgia (TGN) Categorical pain relief, functional scale	12	920 (TGN)	Acupuncture (manual or electric)	Weak evidence to support the use of acupuncture in the management of TGN
Thongprasom, 2011[2]	Effectiveness of topical treatment for oral lichen planus (OLP) Oral mucosal pain (primary), degree of erosion, erythema, reticulation (secondary)	28	1205 (OLP)	Topical corticosteroids, cyclosporin, calcineurin inhibitors, aloe vera	No comparison among topical corticosteroids, weak evidence supporting topical cyclosporin, or calcineurin inhibitors
Yang, 2011[16]	Efficacy of non-antiepileptic medications to treat TGN Pain relief, decreased trigeminal neuralgia score (Number of attacks per day and intensity) (primary) Adverse effects in 2 weeks, improvement in pain or TN score at 12 weeks (secondary)	4	139 (TGN)	Carbamazepine, pimozide, proparacaine hydrochloride, tocainide, tizanidine	Insufficient evidence to support benefit from non-antiepileptic medications to treat TGN

Table I. Continued

Author, year	Outcome	No. of studies included	Total No. of subjects	Interventions or exposures	Conclusion
Rigon, 2011[17]	Comparison of effectiveness of arthroscopy to other surgical and nonsurgical treatment of temporomandibular disorders (TMD) Pain relief in muscles and temporomandibular joint (TMJ), change in joint sounds (primary) Functional measurements (opening, excursions) TMJ tenderness on palpation, quality of life and adverse events	7	349 (TMD)	Arthroscopy, open surgery, arthrocentesis, non-surgical treatment	No significant benefit of arthroscopy in pain after 6 months. Moderate improvement in maximum opening with arthroscopy at 12 months when compared to arthrocentesis

methodological issues. In contrast to the acute presentation, analysis of 10 studies supported the benefit of systemic acyclovir and valacyclovir for the prevention of recurrent disease.

Perhaps one of the areas that has received more attention from a meta-analysis perspective is orofacial pain. Multiple studies, mostly published in the last 3 years, have addressed issues such as efficacy of medications for the treatment of trigeminal neuralgia, temporomandibular disorders, and acute and chronic facial pain management.[15-17,19-24] Among these, a paper published in 2010 failed to identify a benefit of systemic corticosteroids in preventing post-herpetic neuralgia, another common complication that oral medicine clinicians manage in the facial area.[19] Select additional manuscripts related to oral medicine deal with the appraisal of therapeutic options for head and neck cancer, the association between autoimmune disease and the occurrence of lymphoma, and the efficacy of treatment of salivary hypofunction.[12,25-29] The report describing the association between autoimmune disease and lymphoma is of importance because it concludes that the risk of developing lymphoma in patients with conditions such as Sjögren syndrome appears to be low, contrary to past belief.[12]

Meta-analysis may offer conclusions that challenge trends in clinical practice due to lack of well-designed studies rather than to evidence of non-efficacy of the intervention. These studies may also offer important information on disease etiology or collate information from other systematic studies.[11] The clinician is alerted to carefully evaluate these manuscripts to understand the relevance of the conclusions and implications to practice. The lesson learned from these and other manuscripts is that key factors to consider when evaluating studies are the presence of bias and the reporting of allocation strategy. They also highlight the broad gap of scientific support for many interventions that are accepted as standard of care and the need for standardization of the methodology and reporting of epidemiologic research.

METHODOLOGIC CONSIDERATIONS

The value of a meta-analysis lies in its strict protocol and reporting criteria. Several issues are relevant to consider during planning and developing the analysis, as they may influence its outcome. The following section will discuss pitfalls and mistakes that can occur in several stages of a meta-analysis. The reader is again reminded that a written protocol must be formulated among the investigators that will serve as a guide to solve any issue that may arise during the implementation of the project. This protocol requires formulation of a specific question to be answered by the analysis, and definition of the desired outcome to be measured.[3]

SOURCES OF DATA

Although the concept of meta-analysis is more than 30 years old, its use has grown dramatically in the last 15 years due to the advent of the internet, the registration of clinical trials in centralized databases, the appearance of electronic search engines, and the systematization of meta-analytic procedures in computer programming. Sources for manuscripts include search engines such as Medline-PubMed/Ovid, ISI Web of Knowledge, EBSCO, Evidence Based Medicine Reviews (EBMR) — Cochrane Database of Systematic Reviews, and the Cochrane Clinical Trial Registry. The National Institute of Dental and Craniofacial Research mandates registration of all federally funded clinical trials in the National Institutes of Health website, and many Institutional Review Boards in the United States and abroad require registration of a clinical trial in this site. Therefore, multiple sources of scientific literature are readily available for potential meta-analysts. Some of these go back as far as 1950, and are usually updated on a monthly or biweekly basis. Even when potential sources are identified, investigators should consult a librarian or informationist for assistance in setting the search terms. Depending on the search engine, this process may take several days or weeks to establish, as combinations of terms, MeSH terms, and keywords is often required in an exhaustive process. This process may take weeks because the validity of the meta-meta-analysis depends on the collection of all published and unpublished evidence, or of a significant sample of all existent evidence. If manuscripts or other evidence (see gray literature below) are missed, this will undermine the strength of the analysis. Authors should also extend their search to additional sources, like data not published in peer reviewed journals, conference abstracts, doctoral thesis, and polling of experts in the field for suggestions of relevant manuscripts (gray literature).[30] The fact that manuscripts with negative results tend not to be submitted or published is termed publication bias, and may amplify an optimistic estimate of effect. This will be discussed in detail in the section describing publication bias. Hand searches of specialty journals published in recent years helps to assure completeness of the search process. Documentation of an attempt by the study team to search the gray literature is imperative in any meta-analysis.

STUDY SELECTION

Selection of studies is based on eligibility criteria and outcomes as defined in the protocol. All manuscripts produced by the search and their abstracts are independently reviewed by at least 2 of the investigators using piloted data abstraction forms, who then note whether to include the study in the final review. The

Funnel plot
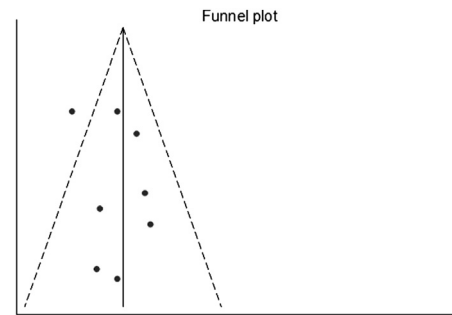
Studies are represented graphically by the dark circles. The base of the funnel represents studies that have high risk of publication bias. Lower risk is represented by aggregation towards the superior portion of the funnel. A study located outside the funnel has a high risk of publication bias. This method is useful to screen studies considered in a meta-analysis

Fig. 3. Hypothetical funnel plot to explore publication bias.

investigators should be blinded to study outcomes to decrease bias as the decision of study inclusion involves study methods and procedures. Obviously, this will not be possible if a specific outcome reporting forms part of the inclusion criteria. Discrepancies between investigators regarding inclusion of studies are resolved by a method stated in the protocol. This may be by consultation with a third investigator, by consensus between the 2 original abstractors, or by an independent review of the complete manuscript. The selection process invariably reduces the number of studies to include in the final analysis. At this point, the investigators proceed to evaluate the quality of the studies and decide if a meta-analysis is feasible, or if differences among studies and quality of studies preclude further evaluation. Besides the scales mentioned previously, study quality assessment is achieved by exploring individual factors associated to the type of study reviewed, including blinding and randomization.

CONSIDERATIONS FOR AGGREGATING DATA

Prior to aggregating data from studies, factors such as differences in patient population, treatment allocation, follow up, and outcome measurement need to be considered. Summary estimates are reported in most studies, and authors may want to request raw or individual patient data if available. This is germane to confirm marginal findings in the analysis, or to calculate stratification of outcomes not performed in the original study. Statistical issues concerning the aggregation of summary estimates deal with accounting for heterogeneity, study quality and choice of measure to report (i.e., RR vs. OR vs. mean standard difference).[31]

STUDY HETEROGENEITY

Heterogeneity among reviewed manuscripts can be initially observed in the initial graphic output and 95% confidence intervals (CIs) (Figure 1). Non-overlap of
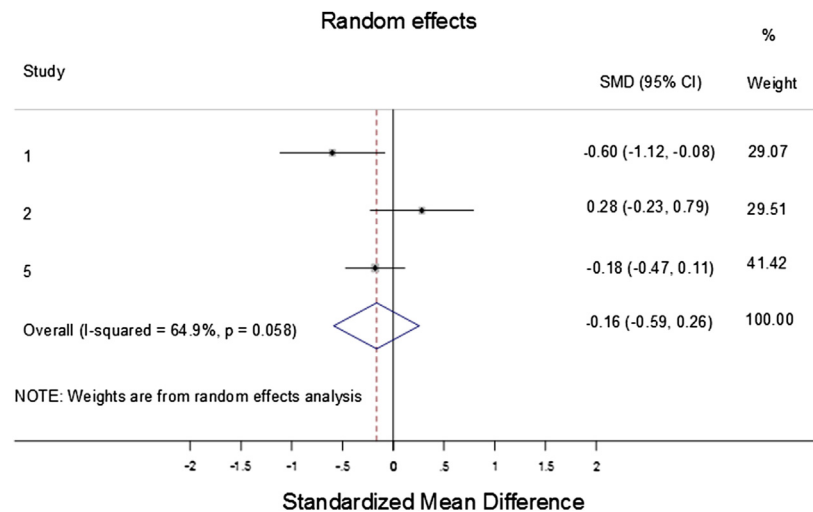
Fig. 4. Forest plot of random effects analysis and heterogeneity estimates.

CIs is a good indicator for heterogeneity. In addition, statistic methods to assess heterogeneity include the calculation of a X^2 test, which has low power with small groups of studies, and the better I^2, that produces a percentage of the heterogeneity attributed to differences between studies. Increased heterogeneity is of concern, and a high percentage (>60% in the I^2 estimate) demands for additional exploration of sources of heterogeneity, such as subgroup and sensitivity analyses. Elucidation of the sources of heterogeneity will require a detailed evaluation of study effects under different circumstances such as diverse subject groups, geographic area, or study drug dosing.

PUBLICATION BIAS

Investigators may be concerned about the over reporting of studies with positive results, as authors are not as eager to submit papers with negative findings. This may "bias" the body of literature toward positive findings, even when the magnitude of these findings may not be so strong.[31] Standard estimation of publication bias is performed by using a funnel plot, (Figure 3) a graphic representation of study precision, provided by measures of variance (1/V) or standard error on the y-axis and effect estimates on the x-axis. The resulting plot will produce an inverted funnel appearance, with smaller studies being spread at the base and larger studies narrowing toward the top.

Study size may have a strong impact on estimation of publication bias. Bias could occur in studies with low quality, or in smaller studies reporting larger treatment effects. The presence of asymmetry in the funnel plot does not necessarily indicate the presence of bias, as additional sources that should be evaluated during study assessment include study heterogeneity, poor choice of effect measure, chance, and methodological issues with subject

selection.[32] Additional statistical methods exist to evaluate publication bias (i.e., metaregression, Begg's and Egger's tests), which are beyond this manuscript.[31,33]

ANALYSIS — FIXED VERSUS RANDOM EFFECTS

Once all study characteristics have been entered in a statistics program, the meta-analysis can be done by fixed or random effects processes. The forest plot (Figures 1 and 4), contains the effect measures from all studies, their weight in the overall analysis, and the summary estimate with its corresponding 95% CI. Often measures of heterogeneity such as the Q statistic, X^2, or the I^2 are also reported within the forest plot.[34] The Q test provides information about the presence of heterogeneity but does not offer a quantitative evaluation of the extent of this heterogeneity. The I^2 offers the advantage of providing a quantitative assessment of the heterogeneity in effect sizes that are due to between study variability. By definition, the fixed effects analysis assumes there is a finite number of studies (the investigators are sure they have captured all published and unpublished material), the differences among studies are due to chance, and the effect of therapy is equivalent across all studies. Random effects meta-analysis is more conservative. The assumptions under this approach are that studies sampled constitute a random sample of all existent studies, and that there is heterogeneity and variability between studies. Random effects analysis assigns less weight to big trials.[34] There is no consensus on which approach is best, and often meta-analysts perform both to explore between study heterogeneity. Both approaches yield similar results when there is no significant heterogeneity and a similar pooled effect, and disparate results when there is marked asymmetry.

PUBLICATION AND QUALITY STANDARDS FOR SYSTEMATIC REVIEWS AND META-ANALYSIS

Substantial advances have been done in the formulation of requirements for reporting and evaluating systematic reviews and meta-analysis. These have resulted from consensus meetings with experts in the field, producing precise elements that must be included in the reporting of meta-analysis.[35−37] These include having access to the study protocol, a detailed description of the search strategy, including sources consulted, assessment of bias and heterogeneity in the studies to be included, and the formulation of pre-specified analysis to follow (stated in the protocol). The most recent standards include the Assessment of Multiple Systematic Reviews (AMSTAR) and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statements, which provide guidelines to reviewers, and authors of meta-analytic manuscripts.[36,37]

CONCLUSIONS

Meta-analysis is a useful statistical approach to summarize the existent evidence on a clinical or scientific question. Rather than being a simple tool, meta-analysis requires meticulous consideration of the study in question, careful formulation of a study protocol to be followed by all investigators, and at least duplicate independent data abstraction. Evaluation of study characteristics and biological significance of pooling estimates from different studies is not a trivial process, and marks the transition from a systematic review to a meta-analysis. The number of published meta-analysis in oral medicine has increased in the last 5 years, albeit limited by the quality of accessible studies, and the availability of funding. In lieu of major clinical trials, oral medicine investigators may benefit from the meta-analysis of small well-designed trials to evaluate the state of the science in our field.

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