Reporting of adverse events and statistical details of efficacy estimates in randomized clinical trials of pain in temporomandibular disorders

Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks systematic review

Jennifer S. Gewandter, MPH, PhD; Shannon M. Smith, PhD; Andrew McKeown, BS; Kenessa Edwards, MD; Aastha Narula, BS; Joseph R. Pawlowski, MD; Daniel Rothstein, MD; Paul J. Desjardins, DMD, PhD; Samuel F. Dworkin, DDS, PhD; Robert A. Gross, MD, PhD; Richard Ohrbach, DDS, PhD; Bob A. Rappaport, MD; Barry J. Sessle, MDS, PhD, DSc, FRSC; Dennis C. Turk, PhD; Robert H. Dworkin, PhD

Temporomandibular disorders (TMDs) include musculoskeletal disorders of the masticatory system.[1,2] Results from cross-sectional studies demonstrate that approximately one-third of all people experience acute and chronic painful TMD symptoms at some point in life.[1-3] Treatment approaches vary, including pharmacologic treatments, intraoral appliances, invasive surgeries, self-management techniques (for example, heat, modifying exacerbating behaviors, relaxation, biofeedback), and cognitive behavior therapies.[1,3-5] Determining treatment efficacy requires randomized clinical trials (RCTs), which are considered to provide rigorous evidence for treatment decisions. The quality of evidence provided by RCTs, however, can be affected by a wide array of operational details and statistical methods used to analyze the data. Furthermore, treatment efficacy always should be considered in relation to treatment safety. It is therefore critical that statistical details of efficacy analyses and adverse events (AEs) (that is, harms) data are reported clearly in peer-reviewed publications so

Supplemental material is available online.

ABSTRACT

Background. Statistical methods and adverse events (that is, harms) data affect the accuracy of conclusions about the risk-to-benefit ratio of treatments for temporomandibular disorders (TMDs). The authors reviewed the quality of reporting in TMD clinical trials to highlight practices that are in need of improvement.

Types of Studies Reviewed. The authors included articles published between 1969 and May 31, 2013, in which the investigators reported randomized clinical trials of TMD treatments with pain as a principal outcome variable. Investigators in trials of nonpharmacologic and noninvasive treatments were required to at least mask the participants and assessors; all others were required to be double masked.

Results. Ninety articles qualified for this review: 39 published between 1971 and 2005 (older articles) and 51 published between 2006 and 2013 (newer articles). Specification of primary outcome analyses, methods to accommodate missing data, and adverse event collection methods and rates were generally poor. In some cases, there was apparent improvement from the older to the newer cohort; however, reporting of these methodological details remained inadequate even in the newer articles.

Practical Implications. This review is designed to alert authors, reviewers, editors, and readers of TMD clinical trials to these issues and improve reporting quality in the future.

Key Words. Temporomandibular disorder; clinical trials; multiplicity; missing data; harms reporting; Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks.

JADA 2015:146(4):246-254

http://dx.doi.org/10.1016/j.adaj.2014.12.023

that readers can evaluate the trial's risk-to-benefit conclusions.

Statistical methods such as prespecifying a primary analysis (including the primary outcome variable, statistical test, and time of analysis), adjusting for multiple primary analyses, and using recommended methods to accommodate missing data can minimize bias and type I error rates (that is, concluding there is a treatment effect when one does not exist—false-positive results) of efficacy estimates.[6-16] Descriptions of methods to collect AEs and procedures to analyze AEs, withdrawals due to AEs, and AE results are also necessary to determine whether harms data are adequate and unbiased, as well as to clarify the overall effect of a treatment.[17-22] The Consolidated Standards of Reporting Trials (CONSORT) statement, a minimum set of trial reporting recommendations that has been published in multiple iterations between 1996 and 2010,[23-26] advises detailed reporting statistical details, as well as AE data. Such reporting provides greater transparency about how investigators conducted clinical trials and allows readers to interpret whether the stated trial conclusions are appropriate.

Previous reviews of the medical literature have shown some improvements in RCT reporting after publication of various versions of the CONSORT statement[27-32]; however, more recent reviews of the literature, including analgesic trials, suggest that deficiencies in reporting are still common.[33-41] The goal of this systematic review was to evaluate reporting practices in clinical trials of treatments for TMD from 1969 to 2013 and highlight practices that are in need of improvement.

METHODS

Article selection. In this systematic review, we evaluated reports of RCTs for TMD treatments that were published between the inception of PubMed (1969) and May 31, 2013 (see Appendix 1 for search strategy; available online at the end of this article). Trial investigators could evaluate any type of intervention (that is, noninvasive pharmacologic [for example, oral medication]; invasive [for example, intravenous pharmacologic agents, injections]; and nonpharmacologic, noninvasive [for example, psychological therapies, intraoral appliances]) and were required to have a control group. We excluded articles with only a wait-list control. We required that trials of pharmacologic and invasive treatments be double masked, whereas in nonpharmacologic, noninvasive trials participants and assessors had to be masked (that is, modified double mask; administering research staff could be unmasked). We applied this different standard because it is often impossible to double-mask nonpharmacologic, noninvasive trials completely; thus, these modified double-masked trials likely represent the highest possible rigor for most of these treatments. To be included, articles had to report use of 1 of the following primary or secondary outcome variables: pain intensity, pain relief, pain qualities (for example, allodynia), any composite measure including pain (for example, composite of pain, numbness, and tingling), or amount of opioid or other analgesic sparing. Two authors (J.S.G. and S.M.S.) independently screened all of the identified articles to determine whether they met the inclusion criteria.

Data extraction. We adapted a coding manual (Appendix 2; available online at the end of this article) from previous methods of Gewandter and colleagues[33,34] and Smith and colleagues[39] to evaluate reporting of details that can affect accuracy of treatment effect estimates (for example, identification of primary analyses, methods to adjust for multiple primary analyses, and methods to accommodate missing data), as well as fulfillment of the 10 CONSORT harms reporting recommendations.[25] We coded the method to accommodate missing data as *unsure* if the reported statistical test accommodates missing data only when certain statistical packages are used in specific ways, but insufficient information was provided about what was implemented. We considered a complete case analysis (that is, when authors clearly stated that the analysis omitted cases that did not have complete data for the outcome variable) 1 possible method to accommodate missing data, although statisticians and regulators generally do not recommend this method.[9-11]

To evaluate treatment AE reporting, we included all adverse treatment effects, ranging from tolerability issues to safety concerns, and excluded quantitative sensory testing unless it was specifically identified as AE data. We took a liberal approach, such that we considered reporting a portion of 1 of the CONSORT harms items fulfillment of that item. Each article was coded independently by 2 of the following authors: A.M., K.E., A.N., J.R.P., and D.R. The first authors (J.S.G. or S.M.S.) adjudicated any discrepancies between independent coders' results.

We used descriptive analyses to determine the number and percentage of articles that satisfied each of the reporting criteria. We reported data separately for articles published between 1971 and 2005 (older articles) and those published between 2006 and 2013 (newer articles) because CONSORT reporting guidelines for efficacy and harms-related issues were *both* available by 2004 and therefore better reporting quality was expected after these guidelines had been disseminated. Furthermore, this cutoff provided relatively equal sample sizes for the older and newer sets of articles. Given the large number of comparisons and the descriptive objectives of the analyses, we did not conduct statistical tests, the results of which would be difficult to

ABBREVIATION KEY. **AE:** Adverse event. **CONSORT:** Consolidated Standards of Reporting Trials. **RCT:** Randomized clinical trial. **TMD:** Temporomandibular disorder.