Netherlands
The Journal of Medicine

SPECIAL ARTICLE

Are claims of advertisements in medical journals supported by RCTs?

L. Heimans[1], A. van Hylckama Vlieg[1], F.W. Dekker[1,2*]

[1]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands,
[2]Center for Innovation in Education, Leiden University Medical Center, Leiden, the Netherlands,
*corresponding author: tel: +31 (0)71-526 52 30, fax: +31 (0)71-526 69 94, e-mail: f.w.dekker@lumc.nl

ABSTRACT

Background: Claims made in advertisements in medical journals might not always be supported by high-quality evidence, and referenced studies may have been sponsored by the pharmaceutical industry itself. We studied to what extent randomised controlled trials (RCTs) support the claims in advertisements in leading medical journals.

Methods: Consecutive unique advertisements were selected from nine different medical journals, and evaluated by 250 medical students using a standardised score form. The quality of RCTs that were referenced in these advertisements was assessed with an instrument based on the Chalmers' score.

Results: 158 RCTs from 94 advertisements were used in the study. In total 55% of the RCTs had a high-quality score, 44% intermediate, and <1% had a low-quality score. Almost 40% of the RCTs had a high-quality score and at the same time supported the claim for which they were cited, while only 17% were also not sponsored by a pharmaceutical company.

Conclusion: RCTs used to support claims in medical advertisements are often not a high-quality and independent source of evidence. This distracts from the credibility of claims in advertisements, even in the high-ranked journals.

KEYWORDS

Advertisements, claims, RCT, support

INTRODUCTION

Pharmaceutical companies make use of advertisements in medical journals to promote their products. To increase credibility, claims made in the advertisements are frequently accompanied by references to sources of evidence. However, these sources may vary in quality and are not always readily accessible. In addition, these studies may have been sponsored by the pharmaceutical industry itself, leading to a potential conflict of interest.

Several studies have assessed the validity of claims in advertisements in medical journals.[1-6] Villanueva *et al.* assessed claims about efficacy, safety, convenience, or cost of antihypertensive and lipid-lowering drugs included in advertisements of six Spanish medical journals. Of the 102 references they were able to trace, 44% did not support the promotional statement and 40% of the references were sponsored by the pharmaceutical industry that made the claim. The authors concluded that doctors should not automatically believe seemingly evidence-based claims made in medical advertisements.[1]

Evaluation of advertisements has been done in various specialities such psychiatry, orthopaedics, cardiology and rheumatology.[1,2,5,6] In 2006, van Winkelen *et al.* assessed advertisements in four leading journals of rheumatology. They selected 84 unique advertisements and 300 references belonging to them. Five percent of these advertisements were supported by high-quality evidence and they concluded, in line with the conclusions made by Villanueva, that few advertisements in journals of rheumatology are entirely evidence-based.[2]

While the results from inventories in specialised journals are not very promising, readers of high-ranking general medical journals might expect that their journals do better in this respect. Leading medical journals are influential and it seems reasonable to believe that they not only publish scientific papers of outstanding quality, but also contain high-level evidence-based advertisements with claims accompanied by valid sources of reference. As there is not much evidence to support this expectation, we studied to what extent randomised trials support the claims of advertisements in leading general medical journals.

MATERIALS AND METHODS

Advertisements were extracted from seven leading medical journals and two specialised journals (*American Journal of Medicine, Annals of Internal Medicine, Archives of Internal Medicine, British Medical Journal, European Heart Journal, Journal of the American Medical Association, Lancet, New England Journal of Medicine*, and *Nephrolopy Dialysis Transplantation*) published between 2003 and 2005. All unique advertisements were included if they made a claim regarding the effect of a drug.

For all claims in the advertisements, references, if any, were checked. Only references to RCTs were included in this study. All publically available RCTs (in digital libraries) were reviewed by a group of 250 medical students following a three-week regular course of 'Scientific Education' in the second year of the medical curriculum at the Leiden University Medical Center. After specific training and small group exercises in critical appraisal, each student independently assessed two RCTs and the advertisements to which the RCTs belonged using a set questionnaire. RCTs were randomly distributed among the students.

The quality of the RCTs was assessed with a modified instrument based on the Chalmers' score.[7] This score measures validity by three subscores: 1) method of treatment assignment (randomisation), 2) control of selection bias after treatment assignment (intention-to-treat principle) and 3) blinding of participants. The score ranges from 0-9 points, with 3 points possible per subscore. The total score is evaluated as low (0-2 points), intermediate (3-5 points) or high (6-9 points).

Truly randomised, blind and the method is described (3 points), the study was stated to involve blind randomisation without a (valid) method (2 points), randomisation without blinding and methods (1 point), randomisation was not mentioned explicitly (0 points).

All patients entered the trial and received assigned treatment (3 points), withdrawals listed and remaining patients analysed by original treatment assignment (2 points), the reports did not mention withdrawals or results had been analysed by received treatment only (1 point), no description of withdrawals and results analysed by received treatment (0 points).

Double-blinded such that patients and caregivers and investigators are all kept unaware of treatment assignment (3 points), only two out of three categories had been blinded or the methods for blinding are not mentioned (2 points), blinding was impossible or it was impossible to judge whether it had been attempted (1 point), could have been conducted as double blinded but had not been (0 points).

The students also evaluated whether the claim in the advertisement was supported by the referenced RCT (i.e., whether the conclusion of the RCT matched with the claim in the advertisement and concerned the same patient population). Furthermore, they recorded whether the RCT was sponsored by the pharmaceutical industry or not.

Analysis

Two to six students assessed each referenced RCT. For each RCT, a final Chalmers' score was calculated, i.e. the mean of the two to six individual scores. In case of a discrepancy of 4 or more points between individual student assessments, a panel of four researchers independently assessed these articles and the new score was discussed in the panel to increase the inter-rater reliability.

The decision whether or not a claim was supported by the referenced RCTs was based on the decision made by the majority of student assessments. In the absence of a majority, the panel reassessed claims and references. The new score was discussed to increase inter-rater reliability. The same protocol was used for the assessment of pharmaceutical sponsorship.

An RCT with a high Chalmers' score that also supported the claim in the advertisement resulted in an evidence-based claim. A claim was classified as not evidence-based when it had a negative Chalmers' score *or* it was not supported by the referenced RCT. A claim was classified as intermediate when the Chalmers' score was intermediate while the RCT supports the claim made in the advertisement. Additionally, the results were related to sponsorship by the pharmaceutical industry.

RESULTS

From the sample of nine medical journals published between 2003 and 2005, 189 unique advertisements were obtained, in which 614 claims were made. Fifty-two claims had no references. From the 562 claims with a reference, 255 references were unusable for our study because they were not RCTs (instead they were reviews, meta-analyses, observational studies or case reports) and 128 were not publically available in digital libraries or untraceable. The remaining references and advertisements were distributed among the students at the Leiden University Medical Center. During the evaluation, 21 RCTs were not rated by the students because of random allocation of the RCTs and because each student rated only two RCTs. In addition, some students stopped active participation in the course completely, did not do their examinations or did not send in their results. In the end, the analysis comprised 158 RCTs from 94 advertisements. The panel had to reassess 40 RCTs.

In total 88 of these RCTs (55.7%) had a high Chalmers' score, 69 (43.7%) had an intermediate score and 1 (0.6%) scored low. Without taking into account the quality of the

RCT, students evaluated 91 RCTs (57.6%) to be supportive for the claims for which they were referenced.

To determine whether the claim was evidence-based, the Chalmers' score was combined with the question whether the RCT supported the claim. In total 62 (39.2%) RCTs with a high Chalmers' score supported the claim in the advertisement, while 29 (18.4%) RCTs with an intermediate Chalmers' score supported the claim. One RCT had a low Chalmers' score, which makes it unsupportive of the claim. This means that 62 claims (39.2%) were supported with high-level evidence. RCTs supporting the claim made in the advertisement were of higher quality than RCTs not supporting the claim (RR for positive Chalmers' score 1.76; 95% CI 1.26 to 2.45).

In total 68 referenced RCTs (43%) were reported to be sponsored by the pharmaceutical industry. Study quality, as measured by Chalmers' score, was not related to being sponsored (RR 1.01; 95% CI 0.76 to 1.33). Of all the RCTs, only 35 (22.2%) had a high Chalmers' score, supported the claim and were not sponsored by the pharmaceutical industry. Only 27 (17.1%) of the high Chalmers' score and supporting RCTs were sponsored (*table 1*).

Table 1. *Chalmers' score combined with the questions whether the RCT supported the claim and whether the RCT was sponsored*

		Supporting the claim in the advertisement	
Chalmers' score	**Sponsored**	**Yes**	**No**
High	Yes	27 (17.1%)	11 (7.0%)
Intermediate		14 (8.9%)	15 (9.5%)
Low		0 (0.0%)	1 (0.6%)
High	No	35 (22.2%)	15 (9.5%)
Intermediate		15 (9.5%)	25 (25.8%)
Low		0 (0.0%)	0 (0.0%)

DISCUSSION

We studied to what extent advertisements in leading medical journals are supported by a high level of evidence. Our results show that almost 40% of the RCTs with a high Chalmers' score supported the claim for which they were cited. Only 17% of the RCTs were of good quality, supporting the claim in the advertisement, and not sponsored by the company itself. In addition 18.4% of RCTs with an intermediate Chalmers' score supported their claim, while 42.4% of RCTs did not support the claim for which they were cited.

Our results are in line with the first available study conducted in this specific field by Villanueva *et al.*[1] They reported that 44.1% of the claims in advertisements in Spanish medical journals were not supported by their reference. It should be noted that a direct comparison between the two studies is difficult, because of the different ways of assessing the references and because they used all references and not just RCTs. Furthermore we used three endpoints (evidence-based, not evidence-based or intermediate) where Villanueva *et al.* used two endpoints (not supported and could-be supported). While Villanueva studied only Spanish medical journals, we found that advertisements in the leading medical journals of the world are not much better.

A recent study on the accuracy of psychiatric medication advertisements reported that claims about efficacy are supported by references 53% of the time.[5] They only used advertisements on psychiatric medications in four journals and the methods to assess whether a claim was supported by a reference were also different. They coded the claims into types and after that their accuracy was evaluated. The evaluators were a professor of psychology and two undergraduate students. This study used other methods to assess claims and their proportion of reliable claims is higher, but they conclude that increased regulation of advertisements is warranted.[5]

Another similar study was performed by van Winkelen *et al.*[2] Only 17% of the claims in this study are supported, which seems low compared with the results in our study. Again the direct comparison is difficult because van Winkelen *et al.* used another classification of the endpoints (well supported, poorly supported and misleading). Furthermore, van Winkelen *et al.* not only used RCTs, but also systematic reviews and other types of studies extracted from journals regarding the subspeciality of rheumatology.

Of all the studies used, 68 (43%) were sponsored by the pharmaceutical industry. The majority of these studies (55.8%) had a high Chalmers' score. The study by van Winkelen *et al.* reported that 97% of the RCTs they used were sponsored by the pharmaceutical industry and that almost 70% of them had a high Chalmers' score and none of them had a low Chalmers' score. Even if an RCT is valid and supports a claim, the fact that it is sponsored by the industry leads to a potential conflict of interest.[8-12] Furthermore, our results are in line with the findings of Tricoci *et al.*[13] who reported that a large proportion (48%) of the practice guidelines of the ACC and the AHA were based on low levels of evidence, such as expert opinion. Although there is no industry funding for guideline development, recommendations based on expert opinion are prone to conflicts of interest. Clinical experts are likely to receive fees and honoraria from the pharmaceutical industry. They conclude that clinicians need to be careful considering recommendations not supported by solid evidence.

A study by Cooper *et al.*[8] determined that 58% of the studies cited in advertisements were sponsored by the pharmaceutical industry or had an author affiliated

with the manufacturer of the product. These results are not surprising knowing that research trials are very expensive and only pharmaceutical companies are able to finance them. Evidence shows that industry-sponsored studies more often report outcomes that benefit the sponsoring company. In 2003 Lexchin *et al.*[10] published a systematic review discussing sponsorship and research outcome. The article reported that research sponsored by the pharmaceutical industry was more likely to produce results favouring the product made by the industry than research funded by other sources (odds ratio 4.05). Other studies have similar conclusions.[9,11,12] Publication bias could be a partial explanation for this finding. Our study, as well as other studies,[9-11] found that methodological quality was not related to sponsorship and that only the outcomes were influenced.

Shortcomings

Assessing the methodological quality of RCTs, even using the Chalmers' score, has unequivocal subjective elements. We tried to minimise misclassification by doing multiple independent assessments of each RCT. Still discrepancies between assessors may arise. In case of discrepancy of four or more points on the Chalmers' score, the reference was assessed again by one of the researchers. The new score was discussed in a panel of the four researchers to increase the inter-rater reliability.

In this study only RCTs were rated. This means that claims with references to other sorts of studies were not assessed. In general, an RCT is the best way to investigate new drugs compared with placebos or older drugs. That is why we aimed to assess whether claims are evidence-based if they have an RCT in their reference. If we had included all the different types of studies, our numbers could have been different.

Not all the claims in the advertisements could be assessed because not all of the references were RCTs. That is why we do not draw numerical conclusions on the level of advertisements. Based on this study we only know more about the extent to which RCTs support claims in advertisements.

Because we failed to get the results from some students and because some RCTs could not be found, we were not able to assess all RCTs. Although our results could have been somewhat more extended we do not feel it influenced the results much, as we were able to draw a significant conclusion from the RCTs we did analyse.

CONCLUSION

Our study aimed to assess to what extent RCTs support claims in advertisements of leading medical journals. Even though an RCT seems a reliable type of study, they are not always of high quality. In our study only 39.2% are of high quality (i.e. has a high Chalmers' score) and at the same time support the claim for which they were cited for. Some RCTs are sponsored by the pharmaceutical industry, leading to a potential conflict of interest. Sponsorship does not affect the methodological quality of studies per se, but there is evidence that sponsorship is associated with a positive study outcome. By and large, only 17% of referenced RCTs are of good quality, supportive, and not sponsored by the company itself. As at least one out of two referenced RCTs are not perfect, our results suggest that physicians should always critically assess the RCTs mentioned in the references of claims before they use them as evidence to prescribe drugs.

ACKNOWLEDGEMENTS

The authors would like to thank J.W. de Jong and F. Lengers for their support in gathering the advertisements. We also wish to acknowledge the work of B. Boesenach, M. Esthuis and F. Smit who helped analysing the data of the study, and of course all the students for scoring the RCTs.

REFERENCES

1. Villanueva P, Piero S, Librero J, Pereiro I. Accuracy of pharmaceutical advertisements in medical journals. Lancet. 2003;361:27-32.
2. van Winkelen P, van Denderen JS, Vossen CY, Huizinga TW, Dekker FW. How evidence based are advertisements in journals regarding the subspecialty of rheumathology? Rheumatol. 2006;45:1154-7.
3. Wilkes MS, Doblin BH, Shapiro MF. Pharmaceutical advertisements in leading medical journals: experts' assessments. Ann Intern Med. 1992;116:912-9.
4. Gutknecht DR. Evidence-based advertising? A survey of four major journals. JABFP. 2001;14:197-200.
5. Spielmans GI, Thielges SA, Dent AL, Greenberg RP. The accuracy of psychiatric medication advertisements in medical journals. J Nerv Ment Dis. 2008;196: 67-73.
6. Bhattacharyya T, Tornetta P 3rd, Healy WL, Einhorn TA. The validity of claims made in orthopedic print advertisements. J Bone Joint Surg Am. 2003;85:1224-8.
7. Chalmers TC, Smith H Jr, Blackburn B, et al. A method for assessing the quality of a randomized controlled trial. Control Clin Trials. 1981;2:31-49.
8. Cooper RJ, Schriger DL. The availability of references and the sponsorship of original research cited in pharmaceutical advertisements. CMAJ. 2005;172:487-91.
9. Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interests in biomedical research: a systematic review. JAMA. 2003;289:454-65.
10. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. BMJ. 2003;326:1167-70.
11. Kjaergard LL, Als-Nielsen B. Association between competing interests and authors' conclusions: epidemiological study of randomised clinical trials published in the BMJ. BMJ. 2002;325:249.
12. Yaphe J, Edman R, Knishkowy B, Herman J. The association between funding by commercial interest and study outcome in randomized controlled drug trials. Fam Pract. 2001;18:565-8.
13. Tricoci P, Allen JM, Kramer JM. Scientific evidence underlying the ACC/AHA clinical practice guidelines. JAMA. 2009;301:831-41.