Randomised controlled trials cited in pharmaceutical advertisements targeting New Zealand health professionals: do they support the advertising claims and what is the risk of bias?

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ABSTRACT

AIMS: To determine whether pharmaceutical advertisement claims targeting health professionals were supported by the randomised controlled trials (RCTs) cited in the advertisements, and to assess the risk of bias in those trials.

METHODS: Pharmaceutical advertisements were obtained from New Zealand Doctor and Pharmacy Today for the period July 2013 to June 2014. All claims made regarding efficacy, safety, and indications were identified and RCTs cited to substantiate these claims were examined. A claim was defined as supported by an RCT if the conclusions drawn in the paper were consistent with the claim. The quality of the RCT was assessed separately, using the Cochrane Risk of Bias Assessment Tool.

RESULTS: In 25 (19%) of the 133 instances in which an RCT was cited, the published paper did not support the promotional claim. Moreover, there were only 10 (8%) instances in which the claim was supported by an RCT with a low risk of bias. Of the 78 cited RCTs, only 14% had a low risk of bias, while 49% had an unclear risk and 37% had a high risk.

CONCLUSIONS: A high proportion of advertisements failed to meet New Zealand regulatory requirements that claims “are valid and have been substantiated.”

Pharmaceutical advertisements are commonly found in publications aimed at health professionals and provide a significant source of income for the journals. While some commentators have argued that advertisements have an educational value in informing prescribers about currently available products, others have expressed concern about the accuracy of therapeutic claims and negative influences on prescribing practices.

In parallel with an increasing focus on evidence-based medicine, there has been an increasing move to cite randomised controlled trials (RCTs) in advertisements. However, while RCTs are the gold standard for testing the effectiveness of treatments, they are not immune to bias. For example, researchers in the Netherlands recently used a modified instrument, based on the Chalmers’ score, to assess the quality of RCTs cited in pharmaceutical advertisements and found that only 55% had a high quality score.

Poor quality pharmaceutical advertisements are a matter of concern, as exposure to such advertising material can sometimes lead to inappropriate prescribing and higher costs to the healthcare system. In New Zealand, therapeutic product advertising is governed by the Medicines...
Act 1981, the Medicines Regulations 1984, and the Misuse of Drugs Regulations 1977, as well as self-regulation through the Advertising Standards Authority (ASA) and industry codes of practice. The Therapeutic Products Advertising Code states that advertising directed to healthcare practitioners “must contain truthful and balanced representations and claims that are valid and have been substantiated”, and “must not encourage, or be likely to encourage, inappropriate or excessive use”. Information about how well pharmaceutical advertisements in New Zealand comply with these regulations is very limited. A narrative account of misleading advertising in four publications read by New Zealand doctors was published in 2002, but there have been no subsequent systematic investigations.

The aims of the present study were to determine whether pharmaceutical advertising claims in two publications that target New Zealand health professionals were supported by the RCTs they cited, and to assess the risk of bias in those trials.

Methods

Unique pharmaceutical advertisements for medicines and medical devices, in the period July 2013 to June 2014, were obtained from two publications targeting New Zealand health professionals: Pharmacy Today (hospital and community pharmacists) and New Zealand Doctor (general practitioners and other health sector workers). Advertisements were considered unique if they differed in product, claim, or cited studies. Each advertisement was assessed for claims regarding efficacy, safety, and indications. Any material cited to substantiate claims was classified in terms of type. All advertisements which included a claim and cited at least one RCT were included in the study.

Full-text copies of the cited RCTs were accessed digitally via Medline. Some articles could not be found immediately on Medline as insufficient information was provided in the citation, thus a general search was performed in Google in order to obtain the name of the article and other relevant information. Eight articles, which could not be found or accessed via Medline, were sourced using the Interloans Service of the University of Otago Medical Library.

Claims were classified as supported or unsupported. A claim was defined as supported if the findings of the cited RCT were consistent with the advertising claim, irrespective of the quality of the study. Claims were classified as unsupported if the subject of the claim was not examined in the RCT, the claim exaggerated the benefits of the drug, the study population was different to that for which claims were made, or the claim was contradicted by the findings of the RCT.

The risk of bias in each RCT was assessed using the Cochrane Risk of Bias Assessment Tool, a standardised instrument which systematically evaluates potential bias in six domains (sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias) and provides an overall summary assessment (low risk of bias, unclear risk of bias, and high-risk of bias) for each study. Both the published paper and any available protocols or trial registration data (if links to protocols, and/or trial registration numbers, were provided by the journal) were examined. The funding source (pharmaceutical industry, non-industry) was also noted.

To standardise the application of the assessment tool, three RCTs which were cited in pharmaceutical advertisements before July 2013 (and therefore were not included in this study) were independently assessed by both investigators. Findings were compared and any inconsistencies were resolved through discussion. The primary investigator (AM) subsequently assessed all of the study RCTs and sought an independent opinion from the second investigator when required.

Results

Figure 1 shows the number of pharmaceutical advertisements published in Pharmacy Today and New Zealand Doctor during the study period, the number of unique advertisements, the number of claims with and without references, and the number of claims which cited RCTs. Ninety-seven (33%) claims cited no supporting evidence, 89 (31%) cited material other than RCTs, two (<1%) cited non-English language material (Swedish, French), and only...
102 (35%) cited one or more RCTs. Some claims cited more than one RCT and some RCTs were cited for more than one claim. Therefore, in relation to the 102 claims which cited at least one RCT, there were 133 instances in which an RCT was cited to support a claim and 78 unique RCTs which were cited.

In 25 (19%) of the 133 instances in which an RCT was cited, the published paper did not support the promotional claim in the pharmaceutical advertisement: in 11 instances the subject of the claim was not examined in the cited RCT; in nine, the claim exaggerated the benefits of the drug; in four, the study population was different to that for which claims were made; and in one, the claim was contradicted by the cited RCT.

Of the 78 RCTs cited, 24 (31%) provided trial registration details in the published paper and 12 (15%) provided access to protocols via the journal webpage. The risk of bias for each RCT is shown in Figure 2. In terms of sequence generation, 39 (50%) RCTs had a low risk of bias, 37 (47%) had an unclear risk and 2 (3%) had a high risk (Figure 3). The corresponding figures (low, unclear, high risk) for the other five domains were: allocation concealment, 34 (44%), 39 (50%) and 5 (6%; blinding of participants, personnel and outcome assessors, 36 (46%), 32 (41%) and 10 (13%; incomplete outcome data, 46 (59%), 24 (31%) and 8 (10%; selective outcome reporting 28 (36%), 46 (59%), 4 (5%); and other sources of bias 43 (55%), 29 (37%) and 6 (8%). The overall risk of bias was low in 11 (14%) RCTs, unclear in 38 (49%) and high in 29 (37%).

Of the 133 instances in which an RCT was cited to substantiate an advertising claim, there were only 10 (8%) in which the claim was supported by an RCT with a low risk of bias. In a further 98, the claim was supported by an RCT with an unclear (55 [41%]) or high (43 [32%]) risk of bias.

The risk of bias, according to whether an RCT was sponsored by a pharmaceutical company, is shown in Table 1. Sixty-one (78%) trials were industry funded. A higher proportion of sponsored trials had a high risk of bias (41%) as compared with those which were not sponsored (24%); conversely, the proportion with an unclear risk of bias was higher in the unsponsored trials (59% versus 46%). For both sponsored and unsponsored studies, the proportion of trials with a low risk of bias was low (13% and 18%, respectively).
Figure 2: RCTs (n=78) according to risk of bias, citing publication, sponsorship by pharmaceutical company, and whether a protocol and trial registration information was available. Green, yellow and red circles indicate low, unclear and high risk of bias respectively. (Full list of references available on request from authors)
Discussion

This review of pharmaceutical advertisements published in *New Zealand Doctor* and *Pharmacy Today* between July 2013 and June 2014 found that 33% of advertising claims cited no supporting evidence and only 35% cited at least one RCT. In 108 (81%) of the 133 instances in which an RCT was cited to support a claim, the RCT drew conclusions which were consistent with that claim. However, only 14% of the 78 cited unique RCTs had a low risk bias and 37% had a high risk; in the remaining 49% insufficient information was reported in order to come to a justified decision. Moreover, in only 10 (8%) of 133 instances was the claim supported by an RCT with a low risk of bias. Conversely, there were 43 (32%) instances in which the RCT that apparently supported a claim had a high risk of bias.

This study had several strengths. First, a systematic approach was taken to collect advertisements; all unique advertisements published over the course of a year were examined to ascertain eligibility for inclusion in the study. Second, the 12-month study period enabled the assessment of advertisements for a range of medicines, including those whose use varies by season (such as drugs for hay fever). Third, a validated instrument, the Cochrane Risk of Bias Assessment Tool, was used to assess the risk of bias in each of the RCTs. Fourth, trial registration information and study protocols, if found, were also examined to enable a thorough assessment.

There were also some limitations. First, one researcher assessed all of the RCTs; in ideal circumstances, the second investigator would have independently assessed the same trials. However, an independent assessment of RCTs cited in advertisements published outside the study period was undertaken for training purposes before the study RCTs were reviewed. The investigators also met regularly to discuss progress and to resolve any uncertainties. Second, vague advertising claims were considered supported as long as the advertised drug was reported to be significantly superior to the comparison drug or placebo. However, the fact that the results were statistically significant does not mean that the findings were clinically important.
Our findings are consistent with previous research in that not all pharmaceutical advertising claims cited material to support the claim; not all claims were supported by the documents they cited; few systematic reviews and meta-analyses were cited; and observational studies, product sheets, ‘data on file’, and conference abstracts were commonly cited as supporting evidence.  

Only two other investigations have systematically assessed the quality of the studies cited to support advertising claims aimed at health professionals. A Swiss study found that 32% of claims were based on potentially biased evidence—defined as RCTs with at least three of the following: no evidence of concealment of allocation, open-label studies, loss-to-follow-up >10%, unexplained drop-outs, selective reporting of positive outcomes, no intention-to-treat analysis; abstracts of RCTs which had not undergone peer-review; observational studies; studies in which non-responders and those experiencing side-effects were excluded in the run-in phase; post-hoc analyses; and narrative, rather than systematic, reviews. A Dutch study, like the present investigation, focussed on the quality of RCTs which were cited to support advertising claims. Using a different tool, a modified version of the Chalmers’ score, the researchers found that only 55% of the RCTs had a high quality score, and even fewer (39%) had both a high quality score and provided support for the claim for which they were cited.  

Several findings of this study warrant further discussion. Overall, 49% of the RCTs examined were classified as having an unclear risk of bias because of incomplete reporting of methods. While reporting improved progressively by decade, and recent publications were more likely to describe the methods clearly and to provide trial registration details and protocols, a considerable proportion (40%) of the trials published in the 2010s still provided insufficient information to enable an assessment of the risk of bias. It will be interesting to see whether this situation improves in the wake of the AllTrials campaign, which calls for all past and present clinical trials to be registered and their full methods and summary results to be published.  

RCTs are the optimal design to study treatment effects and a reference to an RCT in an advertisement may lead some readers to assume that the advertising claim is supported by strong evidence. However, as the present study demonstrates, this cannot be confirmed without critically appraising the relevant RCT. While we located all but one of the cited studies (a study of unknown design which was cited alongside RCTs to support two claims), this took considerable effort and involved the use of the library resources at the University of Otago, especially the Interloans Service which provided material that could not be found through Medline. Many practising physicians and pharmacists are unlikely to have the time and resources to locate the original source material cited in pharmaceutical advertisements. A further barrier is language: although New Zealand Doctor and Pharmacy Today are English language publications, two advertisements referred to non-English language (Swedish, French) studies to support their claims.  

Of the 78 RCTs cited to support advertising claims, 78% were sponsored by the pharmaceutical industry and it is possible that the true proportion was even higher, as funding sources may not have been disclosed in earlier publications. In this highly selected sample of RCTs, we found that the cited industry-sponsored trials were more likely to have had a high risk of bias than the RCTs without industry funding. The impact that pharmaceutical industry funding might have on research findings and the prescribing practices of doctors with financial ties to the industry is a matter of increasing concern nationally and internationally. In line with many earlier publications, a recent Cochrane Review found that industry-sponsored trials reported greater benefits, fewer harms, more favourable overall conclusions, and were more likely to draw conclusions which were inconsistent with the actual results of the research than non-industry-sponsored studies. The authors concluded that these differences were not explained by the sources of bias included in standard risk of bias assessment tools (but might be attributable to the choice of comparators, dosage and timing of comparisons, selective analyses, and selective reporting).
and they called for industry sponsorship to be viewed as a factor which increases the risk of bias. Such an approach obviously requires that funding sources are fully reported. There have also been calls in New Zealand for disclosure of industry payments to doctors.24

To conclude, we found that a high proportion of pharmaceutical advertisements failed to meet New Zealand regulatory requirements that claims “are valid and have been substantiated”. About a third of claims had no references, only 35% of claims cited at least one RCT, and a very small proportion of those claims were supported by an RCT with a low risk of bias. We focussed on two publications and therefore cannot comment on the quality of any advertising material in other New Zealand health professional journals. Nonetheless, our findings do suggest a need for greater monitoring of pharmaceutical advertising in New Zealand.

Competing interests:
Alison Ma received a Summer Research Scholarship from the Division of Health Sciences, University of Otago, to undertake this work.

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