Author's response to reviews

Title: Do advertisements for antihypertensive drugs in Australia promote quality prescribing? A cross-sectional study

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Author's response to reviews: see over
Response to reviewers

We thank the referees for their detailed and thoughtful reviews. We will respond to their concerns in turn.

**Referee 1**

The authors conclude that Australian antihypertensive advertisements largely do not promote quality prescribing. This is not sufficiently supported by the study as it is conducted/presented, and therefore both abstract and discussion should be adjusted on this point. The reason for this is that the authors appear to give more (subjective) attention/weight to some key messages (thiazide, lifestyle) than to others (range of drug treatments can be used, choice depends on patient characteristics). They give post-hoc reasons for why the advertisements were not promoting quality prescribing (not defined in their methods and not systematically evaluated).

We did not intend to give more weight to some key messages than others, and did not make any post-hoc adjustments to our analysis. Our reasoning was a priori but perhaps not explained clearly enough in the methods section of our paper. We have added a sentence to our methods section to cover this point: “We regarded advertisements as not fully promoting guideline-concordant care if they did not mention all of the items on the check list.”

The reviewers’ comments have also led us to change the wording of our abstract and conclusion. In our abstract, instead of concluding that the advertisements “do not promote evidence-based cost-effective care”, we now state that the advertisements “provide some but not all of the key messages required for guideline concordant care”.

In our discussion, we previously claimed that “to our question of whether Australian antihypertensive advertisements promote quality prescribing, our results offer a mixed, but largely negative answer”. We have tempered this to “a mixed answer, demonstrating some important missed opportunities for the promotion of quality use of antihypertensives.”

> From the method section, it is unclear how the findings were interpreted. The checklist is not provided, and I wonder whether only frequencies were extracted (yes/no) or whether additional information was systematically extracted (print size)...

> I would like to have the checklist added to the manuscript.

Our checklist was largely designed to extract frequencies and thus consists largely of yes/no questions. We have now included the checklist as an additional file (number 1: checklist.pdf). We have referenced this within the body of the text and described the additional file at the end of the document according to the BMC Public Health instructions to authors.

> Also, it is not clear whether any mention of specific messages/issues was to be interpreted as promoting quality prescribing. This information should be added. It seems that an additional (subjective?) weighing took place where the mention of harms/costs was downgraded because of the small print and the mention of subgroups was interpreted as possibly a negative aspect in the discussion.
The authors’ conclusion appears to be based on the finding that the assessed advertisements did not promote the key messages regarding lifestyle changes or thiazide mono-therapy as first-line treatment. However, key messages also include that “The choice of antihypertensive drug may depend on characteristics of the patient, including other medical conditions or use of other medications.” 41% of the advertisements promoted their drug for a particular subgroup of patients. Unfortunately, the accuracy of this was not assessed but it could be that for these patients thiazide mono-therapy were not first-line treatment. To conclude that such advertisements did not promote quality prescribing seems inaccurate.

Table 1 lists the messages derived from our literature review which we took to indicate the promotion of quality prescribing. These include promotion of appropriate lifestyle modification, assessment and reduction of cardiovascular risk, the range of drug classes available, thiazides as preferable first-line agents, and tailoring of drug choice to the individual patient.

To these issues we added mention of drug costs and drug harms (which we took to be helpful for the promotion of quality prescribing). We have revised our paragraph about this in the hope of greater clarity: “Using these key messages from hypertension management guidelines, we developed a quality checklist to extract data from the advertisements (see additional file 1: checklist.pdf). The checklist was used to measure promotion of lifestyle modification, promotion of thiazides as first line agents, promotion of cardiovascular risk assessment, promotion of use of the drug for specific subgroups of patients, and the mention of alternative antihypertensive classes as treatment options (these issues are all drawn from the quality prescribing messages in table 1). We regarded advertisements as not fully promoting guideline-concordant care if they did not mention all of the items on the check list. We also counted the frequency of mention of drug harms and drug prices, because those factors are included in the NMP definition of quality use of medicines. Finally, we assessed statistical claims, because use of relative rather than absolute measures may have a stronger influence on doctors’ prescribing,[34, 35] and previous research has demonstrated a lack of reporting of absolute measures in pharmaceutical advertisements and brochures,[21, 22]”

We decided to examine “fine print” separately from text in the main body of the advertisement because fine print is less likely to be read. The stratification of our results into these two categories based on font size was pre-planned and not a post-hoc subjective weighing. With the inclusion of the checklist document, this should now be clearer for the reader.

The issue of promotion of use for specific subgroups of patients is quite complex. Discussing results of therapy for specific subgroups of patients may help to tailor the choice of therapy to an individual patient (which was a marker of quality promotion as per table 1). However, in rating the advertisements, we were struck by the fact that many statistical claims were made based on results in high-risk patients, which may not necessarily be able to be extrapolated to lower risk groups. We felt it was important to reflect this complexity in our discussion: “The promotion of medications for specific target groups may help the individualisation of therapy for the patient in an evidence-based manner. However, advertising claims based on data from higher-risk patients may artificially heighten a prescriber’s sense of a drug’s efficacy for patients at lower risk.”

In our original draft paper we included a table with extra detail about subgroups for which the drugs were promoted. We initially left this out after feedback that it represented too much detail. However, we have decided to reinset this as an additional file (number 2: subgroups.pdf). We hope this is helpful in answering the reviewers concern about whether thiazides would have been
contraindicated for the patient groups mentioned. Classical contraindications to thiazides such as severe electrolyte imbalance, hepatic pre-coma, Addison’s disease, gout and paediatric use were not amongst these subgroups. Diabetes is mentioned by some of the advertisements, and we note that there is ongoing debate in the literature about whether thiazides may be a safe choice in diabetes (given the fact that they do tend to cause an increase in fasting glucose levels, but that this does not seem to translate into worse cardiovascular outcomes (see, for example, the ALLHAT trial)). We do not think our paper needs to contain a contribution to this debate, but the inclusion of the additional table will allow interested readers to come to their own conclusions in the light of their own interpretation of current evidence. We have also added the following limitation to our discussion: “We also did not attempt, for those advertisements promoting antihypertensive agents for particular patient subgroups, to determine whether a particular class of antihypertensive would have been the most appropriate choice for that particular subgroup (in fact, such issues are often contested in the literature).”

As for our exploration of the use of statistics, we would not argue that one particular type of risk reduction statistic is always better than another. However, as we discuss, emphasis on relative (rather than absolute) benefit statistics is associated with perceptions of larger benefit. We therefore decided to describe the statistics we found, and believe our interpretation in the discussion is justified: “over-emphasis on relative rather than absolute statistics may create over-optimistic impressions of efficacy and thus encourage over-prescribing”.

Furthermore, in their discussion the authors make clear that only some guidelines promote thiazides as a uniquely preferable first-line choice in the absence of compelling indications. This nuance was not included in the key messages used for this study: Table 1 only states: A range of drug treatments exists (but not that many can be considered first-line choice).

This is another issue of lively and ongoing debate in the literature. Although we did not include this nuance in our table of key messages, we did explicitly mention this as a potential limitation of our study. In response to the reviewer’s concern, we have decided to move most of our commentary on this methodological decision to the methods section: “The guidelines agreed on several key messages for the effective treatment of hypertension and quality use of medicines (table 1). However they were not entirely consistent on one important issue: the choice of first-line drug. Although all guidelines endorse thiazides as a first-line drug class, some listed other classes as equally first-line whilst some promoted thiazides specifically as the first-line class in the absence of compelling indications for another class. This difference between guidelines may arise from different interpretations of the ALLHAT[31] and ANBP2 trials,[35] and from differing emphasis on the importance of cost-effectiveness. Given that the ALLHAT trial had in our opinion a stronger design, and that the National Medicines Policy (NMP) definition of quality use of medicines includes consideration of costs, we regarded the recommendation of thiazides as the first-line class to be correct.”

We retain a brief mention of this issue amongst the limitations described in our discussion: “The guidelines selected for our study varied in their recommendations about first-line drugs so our decision to favour thiazides is open to discussion.”

Also, harms and costs were mentioned in most advertisements. Main outcome measure was defined as: “mention of these issues”. This implies that there was no predefined classification as to where/how this was mentioned. The finding that harms/costs were mentioned in 88/92% of the
advertisements would support a conclusion that advertisements do promote quality prescribing. In comparison, in countries in Europe (where we have a similar Code) costs are seldom mentioned. Therefore, this finding is interesting to report.

Our checklist should now make clear the predefined way in which we looked at the mention of harms and costs. Here is the relevant section of our checklist:

**Harms**

Does the advertisement make any mention of possible harm to health as a consequence of taking the antihypertensive medication(s)? Y/N  
Are these harms only mentioned in the fine print? Y/N  

**Cost**

Does the advertisement make any mention of medication costs? Y/N  
Does the advertisement state the PBS dispensed price for the medication(s)? Y/N  
Does the advertisement give any information on costs or cost-effectiveness beyond stating the PBS dispensed price for the medication(s)? Y/N  
Does the advertisement give cost comparisons between this agent and agents of different classes? Y/N  
Does the advertisement give cost comparisons between this agent and agents from the same class? Y/N

The mention of harms in the fine print of the advertisements and PBS costs are reassuring but unsurprising as they are mandated by the Medicines Australia Code of Conduct. While these are positive, we think that cost comparisons and more prominent mention of harms may be more helpful, as we state in our discussion.

Also, the high percentage of advertisements specifically reminding the reader to consider other than the advertised agents is very interesting (and surprising to me). But it is not clear whether this would be always positive, since the alternative promoted might be less evidence-based. Further assessment on its content is needed.

In fact, most advertisements reminding the reader of alternative agents did so by suggesting they be used additionally (rather than instead of) the advertised drug. We state this in our results.

As for whether a particular drug class is more or less evidence-based than another, we have discussed this above. We think that further assessment of the appropriateness of different classes of drug for different types of patient would be quite fraught due to the fact that these issues are often quite debatable. To quote again the new limitation we have added to our discussion: “We also did not attempt, for those advertisements promoting antihypertensive agents for particular patient subgroups, to determine whether a particular class of antihypertensive would have been the most appropriate choice for that particular subgroup (in fact, such choices are often contested in the literature).”

Finally, the authors refer to studies of 20 to 30 years ago to state that there is observational evidence of associations between doctors’ prescribing and doctors’ exposure to advertisements.[ref.11-15] Given the changes in health care regulation and promotion of evidence-based medicine, it is relevant to refer to more recent studies. For example, in our group, Gieving JP et al (Soc Sci Med 2006) showed that this influence of commercial information has not changed despite efforts of governments and professional organisations...
The authors were unaware of any other similar studies regarding messages in advertisements for antihypertensive medicines. Although a comparison to guidelines may indeed be innovative, comparisons have been made to determine whether print advertisements for antihypertensive drugs were evidence-based. This should at least be mentioned in the discussion. Again, in our group for instance, Greving JP et al conducted such an analysis for antihypertensive drugs (J Hypertension 2007).

We are grateful to the reviewer for drawing these interesting and recent studies to our attention. They are clearly relevant to our paper, and we have now made reference to them. Apart from the latter study, we are unaware of other studies specifically examining antihypertensive advertisements for evidence-based content. We discuss this as follows: “At the time of performing our study, we were unaware of any other similar studies regarding messages in advertisements for antihypertensive medicines. Since then a study of antihypertensive drug advertising in a Dutch journal has been published. This study found 35% of the advertisements contained claims unsupported by evidence.[21]”

Referee 2
While there are no appreciable threats to the internal validity of the study, the main issue seems to be conceptual with the basic assumption for the study question. It seems the basic assumption one must agree with is that advertisements for specific pharmaceutical products should be promoting what is reported in a developed guideline, or a summary of many guidelines. There are guidelines developed by those with vested interests that may not be evidence-based, or may be based on selective evidence. In addition, some guidelines conflict with one another. More importantly for many conditions there is insufficient evidence for a quality guideline. Similarly there are many cost-effectiveness analyses, many performed by those with vested interests and with variation of assumptions frequently those that fund the study find that their product is the most cost-effective option.

I am not sure that this basic assumption, that a regulation that advertisements are not misleading and promote a balanced message means that must provide the content of a guideline or evidence review, is one that many would agree with...

While I make this criticism, I do not think this is a fatal flaw. I think that is the reason for discourse and commentary. The premise of the study is laid out by the authors and the study was well conducted, readers will have to judge for themselves if they agree with the premise.

We agree that the premise on which we base our study is a worthy topic for discussion. We agree that evidence-based guidelines may be imperfect and that their authors may be open to a variety of influences in their interpretation of evidence. In fact, we would not argue that advertisements should necessarily be in accord with guidelines; we argue that they should be in accord with best evidence. In the context of a topic with such an immense literature base as hypertension, we decided to rely on existing guidelines and independent prescribing guides as a source of evidence rather than attempting to distil the voluminous evidence base ourselves. The reviewer has helped us understand that our premise which seems very reasonable to us in our Australian context may be less obvious in other countries. We have provided more explanation of the Australian context for our premise as follows:

“The Medicines Australia Code of Conduct states that all promotional information “must be current, accurate, balanced and must not mislead either directly, by implication, or by
The Australian National Medicines Policy (NMP) states that each partner (including the medicines industry) “accepts that all must be engaged in a cooperative endeavour to bring about better health outcomes for all Australians, focusing especially on people’s access to, and wise use of, medicines.” The NMP definition of “quality use of medicines” includes taking into account “the potential risks and benefits of treatment, dosage, length of treatment, and cost.”[20] We believe evidence-based guidelines are a useful standard for evaluating how well advertisements support, rather than lead away from, wise use of medicine. Thus, the aim of our study was to determine whether print advertisements for antihypertensive medications in Australia promote prescribing for hypertension that is concordant with evidence-based guidelines.”

The reviewer also points out that guidelines may be imperfect and potentially tainted by vested interests. We agree. We now make mention of this in our discussion of our study’s limitations: “We used evidence-based guidelines as a gold standard for evaluating advertisements. The industry may advocate acceptance of lower standards but we believe higher standards for pharmaceutical promotion are required by the Australian NMP.

Guidelines may not be perfect. Sometimes recommendations vary between guidelines. The guidelines selected for our study varied in their recommendations about first-line drugs so our decision to favour thiazides is open to discussion. Guidelines may be biased by vested interests including drug companies.[43]”

Minor essential revision:
1. page 4, last para of the introduction. This paragraph seems best if moved to the methods section as it describes your review of guidelines and development of the quality checklist.

We have moved this paragraph to the methods section as suggested.

In addition, a little more detail about how this review was done (how you selected which guidelines to include, and which publications to include) and any assessment of the content of the final checklist would be helpful. The cynic or critic might say you chose only those guidelines that agree with your point of view. The fact that you provide the actual checklist is essential and shows readers and researchers, who can do their own assessment of face validity. The criteria are used are ones that I think most would agree with.

We have added a little more detail about the types of guidelines we included. We tried to be inclusive in our choice of guidelines, but it could be argued that we did not perform a “systematic” review to identify the guidelines. The guidelines were mostly in agreement on all of the key messages. The main point of discrepancy between some guidelines was on the place of thiazides in therapy. As described above, we have added a further caveat about the thiazide controversy in our methods. Here is our revised paragraph: “In the course of our literature review we identified several major international hypertension guidelines from the World Health Organisation, the US and Europe,[1, 8, 26] as well as several Australian guidelines and prescribing aids[9, 27-29] and other recent publications,[30-34] These were all current and relevant at the time we sampled our advertisements. The guidelines agreed on several key messages for the effective treatment of hypertension and quality use of medicines (table 1). However they were not entirely consistent on one important issue: the choice of first-line drug. Although all guidelines endorse thiazides as a first-line drug class, some listed other classes as equally first-line whilst some promoted thiazides specifically as the first-line class in the absence of compelling indications for another class. This
difference between guidelines may arise from different interpretations of the ALLHAT[31] and ANBP2 trials,[35] and from differing emphasis on the importance of cost-effectiveness. Given that the ALLHAT trial had in our opinion a stronger design, and that the NMP definition of quality use of medicines includes consideration of costs, we regarded the recommendation of thiazides as the first-line class to be correct.”

We agree that the reader will be able to read table 1 and assess its face validity. As we have now included our quality checklist as an additional file, that will also be transparent to the readership.

2. page 5, methods para 2. You report that you included “the largest advertisement for each antihypertensive drug”. Please clarify what you mean by largest, the advertisement that covered the most pages even if those pages were pictures and not text? Or do you mean the advertisement with the most text or claims?

We have now clarified this in the text as follows: “Our analysis included the largest advertisement (by page area) for each antihypertensive drug in each issue.”

In addition, frequently the same advertisement will run in more than one journal. Did you select only unique advertisements, so that no advertisement was rated or counted twice?

We have clarified this at the beginning of the results section as follows: “113 advertisements met our inclusion criteria. These were composed of 27 unique advertisement designs which appeared between 1 and 14 times each.”

3. top of page 6, methods para 3. You report you examined each entire advertisement including contiguous fine print but then state you excluded the fine print form your review. Regulating bodies allow the advertisements to use fine print, and often that is where side effects and other information may be included. E.g. It may be that the fine print is where the advertisement would mention that exercise and a healthy lifestyle should also be promoted. Excluding the fine print may bias your study to underestimate some of the quality content. It might be better to re-review this content and present the data, and then stratify where the content was found, although that is not essential. If no change is made I would say you should provide a rationale for your choice and you need to discuss this as a limitation.

Perhaps our manuscript was unclear as to when and what fine print was excluded from our purview. (Now that we have included our checklist instrument, this may be clearer to the reader.) In fact, we did review all fine print contiguous with the advertisements. For some items (lifestyle factors, range of treatments, and harms) we separately measured whether the items were confined only to the fine print, and stratified accordingly, as Referee 2 suggests.

The only fine print that we ignored for the purposes of our entire study was non-contiguous fine print. By this, we mean an advertisement that had related fine print printed quite separately in the publication, referring to it (for example) with the words: “abridged product information is in the classifieds”. We felt that it was so unlikely that a reader would hunt through the publication to find this information that it was reasonable to exclude it from our study. In fact, only 6 advertisements (of 2 unique designs) in our sample had fine print excluded in this way. This is arguably a limitation but we also feel that it is a realistic reflection of the likely use of the advertisements by the reader.
We have clarified this as follows: “We examined each entire advertisement including contiguous ‘fine print’, but we did not assess further information on other pages of the journals. (Only six advertisements in our sample of 113 referred readers to such non-contiguous fine print.) For some items, we stratified our findings according to whether information was present in the ‘main body’ of the advertisement; for these purposes we excluded the ‘fine print’ and ‘PBS Information’ sections of the advertisement (see additional file 1: checklist.pdf ).”

Discretionary revisions:
1. page 5, Methods. The section begins without much introduction and continues the thought of the last paragraph. I think a brief introductory sentence of paragraph that provides an overview would set up the methods section better. Eg We performed a cross-sectional survey of ..., using a quality checklist that we developed. (Then the details of the checklist development, selection of journals etc as is already reported).

Now that we have moved the paragraph from the discussion to the methods as requested elsewhere, the Methods section begins differently. We provide an overview of our study methods both in the abstract and briefly in the introduction (after stating the case for the premise for our study). With respect, we think that restating this again at the beginning of the Methods may be repetitious. As this is listed as a discretionary revision, we have not changed the manuscript on this point.

2. results para 4. You mention independent rating of advertisements and then adjudication of disagreements. Did you assess interrater reliability? It is not mentioned in the results.

We have added the following comments: “By designing a checklist which was largely ‘yes or no’ in available responses, we tried to minimise subjective interpretative difficulties. Inter-rater reliability was not formally calculated. The few inter-rater differences we found were usually due to oversights, and consensus was easily achieved.”

3. Statistical analysis. This paper is descriptive and provides estimates for the chosen outcomes. That is most appropriate, but you may wish to include a concluding statement that states that. I also assume that some software was used for the database, and for summarizing results. A standard element of ICMJE is to note the software used for analysis.

We have added the following sentence: “Descriptive results in the form of counts and frequencies were calculated using Microsoft Excel.”

Again, we thank the reviewers for their guidance in improving the manuscript, and we hope that it will now be approved for publication.