

SP16 Supplementary note on the reasons for retracting the BMJ papers and the subsequent correspondence by Abramson et al and by Malhotra

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In light of the limited and partial correction made by the BMJ on Thursday 15 May 2014, it has become necessary to provide some additional information for the panel's review.

In particular, there has been a failure to make clear the magnitude of the misrepresentation of the rate of side-effects caused by statins in the papers by Abramson et al and Malhotra, which has been repeated in the BMJ by the authors every time that it has been challenged (and, despite assertions to the contrary in the BMJ's editorial and other public statements, was pointed out during the peer review process: see below). As a consequence, confusion about the safety of statin therapy has been increased further among doctors and the public.

Extent of problems explicitly drawn to the Editor's attention during 2013

It has been stated that the extent of the problems with the articles by Abramson et al and by Malhotra was not drawn to the attention of the BMJ before March 2014. For example, on the Today programme on Thursday 15 May, Dr Godlee states "*The extent of the information we were given was much less than Rory is making out*".

This is not correct. At our meeting in December 2013, I went through a set of slides with the Editor that illustrated a number of the problems with both of these papers. I have now added notes to this slide set (see attached) in order to outline the issues that were made with each slide and how they relate to specific problems in the two papers. In summary:

- slides 1-6 dealt with the misleading statements in the Malhotra paper about the relevance of cholesterol and of cholesterol-lowering therapy to coronary artery disease risk and the beneficial effects of statins;
- slides 7-9 dealt with the misleading statements in both papers about the absolute benefit of actually taking statin treatment compared with the effects per mmol/l LDL-reduction (see separate section below dealing with this serious under-estimate of the benefits);
- slide 10 dealt explicitly with the misleading claim in the Abramson et al paper that the excess of muscle pain with statin therapy is 100 times greater in observational studies than reported in clinical trials. It is of note that one of the peer reviewers had advised the BMJ that this comparison was misleading, but the journal still published it. Subsequently, the authors of the Cochrane review on statins in primary prevention (Huffman et al) also drew it to the attention of the BMJ in a letter published in November (prior to my meeting with the Editor), but the BMJ allowed Abramson et al to dismiss this concern and repeat the misleading claim in their response on 20 December. (N.B. This biased comparison is entirely distinct from the misleading claim about 18-20% side-effects based on the Zhang et al paper that has now been partially withdrawn by the BMJ and by the authors.)
- slides 11-13 dealt with the strength of evidence against there being any material effects of statin therapy on memory and cognitive function, based on specific assessment of such outcomes in long-term randomised placebo-controlled trials among elderly individuals (which, with slide 10, contradicted the claim in Abramson et al about "*failure to assess for specific potential adverse events (like myopathy or cognitive changes)*" in the trials.)
- slides 14-17 dealt with the use of observational studies to generate hypotheses about potential effects of statin therapy on outcomes that can then be tested within the large-scale randomised trial databases (and, for the examples considered, not confirmed).

- slide 18 concluded by proposing that, in contrast with the situation when it is not known that a treatment is beneficial, a different threshold for evidence about potential safety concerns was required when it is known reliably that a treatment does reduce adverse outcomes (since, in that case, patients not taking/stopping treatment would cause harm).

Clearly, therefore, the extent of the misleading claims in the papers by Abramson et al and by Malhotra was drawn to the attention of the BMJ more than 6 months before the limited correction it has so far made, not only by me in my meeting with the Editor on 2 December but also by the peer reviewers (see note below) and by the Cochrane collaboration authors. Consequently, it is disingenuous to assert – as was done on behalf of the BMJ on the Today programme – that the problems identified related to “*a single statement in two papers*”.

In order to help the review panel to identify the extent of the problems with these papers, annotated versions of the original papers are attached which highlight sections that contain errors and other misleading information identified during peer review and subsequently.

BMJ editorial/press statements about withdrawal of the 18-20% side-effect claim

With respect to the misrepresentation of the evidence from the paper by Zhang et al, it is stated in the BMJ Editorial of 17 May 2014 that:

“Abramson and colleagues’ article was submitted and peer-reviewed ... The initial submission reported that Zhang and colleagues found that ‘18% of statin treated patients had discontinued therapy because of statin related events’. This was a misreading of Zhang and colleagues’ data that was not picked up by the peer reviewers or editors.”

This point was reiterated in the BMJ’s press release which states:

“This error ... was not picked up by the peer reviewers or editors, explains Dr Godlee”.

However, it has been drawn to my attention that the reason why the peer reviewers did not pick up this error was because neither the claim nor any reference to the paper by Zhang et al was in the draft of the paper that they were asked to review. One of the peer reviewers of the paper has written to say:

“I have retrieved the version I refereed (attached, along with my original report). This did not mention or cite the Zhang study at all, hence I could never have picked up the misreading.”

The reviewer went on to point out that they had also pointed out that the separate claims by Abramson et al about myopathy rates (see note related to slide 10 above) were seriously misleading, but the BMJ allowed these errors to remain in the paper:

“I hopefully made clear in my report that I thought the results relating to myopathy were misleading: indeed I quantified what I thought were the best estimates.” [See reviewers’ comments which confirm that this is the case.]

Clearly this information materially contradicts the BMJ’s recent public statements about both the review process and the extent and timing of the errors that were drawn to its attention.

[Note: It is stated in the BMJ that Malhotra’s paper was peer reviewed but, despite repeated requests, these reviewers’ comments have not been released. Given the problems with the editorial process that have now been identified by making the reviewers’ comments for the Abramson et al paper available, the comments for Malhotra’s paper should be made public.]

Under-estimate of benefits of statin therapy in Abramson et al and Malhotra papers

The peer reviewers and the Cochrane collaboration authors highlighted a number of serious errors with the paper by Abramson et al, and I have provided a detailed note about several other misleading claims in the papers by Abramson et al and Malhotra. One further error that is made in both papers relates to the misrepresentation of the benefits of statin treatment.

This error about the magnitude of the benefits of statin therapy is similar in nature to the misrepresentation of the findings in Zhang et al about the magnitude of the harms (which has now been withdrawn), where both Abramson et al and Malhotra effectively translated “*statin-related events*” into “*side-effects caused by statins*”. With regard to the evidence for efficacy, Abramson et al and Malhotra misleadingly calculate the numbers needed to treat (NNT) to prevent one event based on the per mmol/l reductions reported in the CTT Lancet 2012 paper. For example, in the second paragraph of the second page of the Abramson et al paper, it is stated that:

“140 low risk people must be treated with statin for five years to prevent one major coronary event or stroke...”

and the third bullet of the box also misrepresents the effect of actual treatment:

“In order to prevent one heart attack or stroke, 140 low risk people (<10% five year risk) must receive statins for five years.”

Similarly, Malhotra misrepresents the CTT report, which it references when writing:

“... the number needed to treat (NNT) to prevent one cardiovascular event in one year was 345.... In this group [secondary prevention] the NNT is 83 for mortality”

However, the results per mmol/l reduction in LDL-cholesterol represent the effects observed on average in the randomised trials between patients allocated to take statin therapy (some of whom did not take it for the average of about 5 years) and patients allocated not to take statin therapy (some of whom did). Similarly, the trials of more intensive statin therapy versus the less intensive regimens typically studied in the first set of trials showed that a further 0.5 mmol/l reduction in LDL-cholesterol could be achieved (again despite some non-compliance: see slide 7 and the related note).

As was pointed out at the beginning of the Discussion of the CTT Lancet 2012 paper (and in greater detail in the CTT Lancet 2010 paper): “*Modern statin regimens ... can often reduce LDL cholesterol by more than 1 mmol/L, which would yield even larger absolute reductions in major vascular events*”. For example, the Lancet 2010 paper discusses the potential for reductions in LDL cholesterol of 2-3 mmol/l. Figure 5 in the CTT Lancet 2012 paper (see top section for major vascular events in slide 9) shows that such reductions in LDL cholesterol levels with an effective statin regimen would yield absolute reductions at least twice as big as the risk reductions per mmol/l that were used to calculate “numbers needed to treat”.

Consequently, the failure of both Abramson et al and Malhotra to reflect the necessary caveats about the basis of their estimates of the efficacy of actual treatment with statin therapy, rather than per mmol/ reductions, represents yet another serious error.

Need for complete retraction of the papers by Abramson et al and Malhotra

Instead of dealing properly with all of these problems when they were drawn to its attention, the BMJ allowed the authors to reiterate several of their misleading statements. Moreover, by publishing only a very limited correction and misleading editorial (see above), the BMJ has emboldened the authors of these articles to reiterate yet again their misleading claims

about the magnitude of the rate of side effects. For example, in the Independent on Friday 16 May, Malhotra is quoted with regard to statins as saying:

“The fact that [there is] such a discrepancy between side effects reported in industry sponsored trials and real world experience needs to be seriously examined ...”

The extent of the misrepresentation of the evidence, the misleading statements, and the errors in the papers by Abramson et al and Malhotra invalidates their conclusions. This view was also expressed by Huffman et al in their letter to the BMJ of 27 November and was the view of one of the reviewers of the initial draft paper (even before the claims based on Zhang et al, which have now been withdrawn, were included in the paper following peer review)

Only with complete retraction of the papers by Abramson et al and Malhotra, along with the correspondence in which they repeatedly misrepresent the evidence, will it be likely to be possible to undo some of the damage caused to public confidence by these BMJ reports, and help to minimise the adverse impact on public health of these misleading papers.