Author's response to reviews

Title: Osteopathic Manipulative Treatment for Low Back Pain: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Version: 3 Date: 6 June 2005

Author's response to reviews: see over
June 6, 2005

Elizabeth C. Moylan, Ph.D.
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Dear Dr. Moylan:

We have completed the second round of revisions to our manuscript (MS: 6646212565097155) entitled, "Osteopathic Manipulative Treatment for Low Back Pain: A Systematic Review and Meta-Analysis of Randomized Controlled Trials." The point-by-point responses to the reviewer comments are summarized below. Cited page numbers refer to the newly revised manuscript submitted at this time.

Reviewer 1: Dan Cherkin

Major Compulsory Revisions

Reviewer Comment (1): I do not believe that the assertion that osteopathic and chiropractic manipulation are different is adequately substantiated and, in the absence of more convincing evidence, the distinction between the techniques of these two professions needs to be stated in less definitive terms. There are numerous chiropractic and osteopathic manipulative techniques and the fact that the "AAOS' outpatient osteopathic SOAP Note Form has check boxes for 14 OMT methods" suggests there is substantial variability in the manipulative techniques performed by osteopaths.

Authors' response: The distinction between chiropractic (and physical therapy) and osteopathic manipulative techniques originally had been stated in less definitive terms. For example, in the background section (page 4), we
continue to state, "Nevertheless, because most studies of spinal manipulation involve chiropractic or physical therapy [5], it is unclear if such studies adequately reflect the efficacy of OMT for low back pain." This is clearly not a definitive statement. The remaining statements regarding inter-profession differences were added in response to the reviewers' previous comments that requested additional information about professional differences with respect to manipulation approaches. These additions to the manuscript are based on several cited references (#9-13) that support our view.

The reviewer's beliefs that: (1) there are small inter-profession differences in manipulation approaches (therefore, a meta-analysis involving only OMT may not be warranted); and (2) there is large intra-profession variability in manipulation approaches among osteopaths (therefore, the meta-analysis may not be valid because of heterogeneity) appear incompatible. We believe that inter-profession differences in manipulation are large relative to intra-profession differences in manipulation. Therefore, it is both appropriate and valid to perform meta-analysis of studies that use OMT as the only manipulation approach.

Reviewer Comment (2): The assertion that it is acceptable to meta-analyze data from a small number of heterogenous studies because others have done it is not a very convincing argument for its use. Its use is either appropriate or inappropriate. In addition, given the small number of studies in each strata (country, type of control, and duration of follow-up), it is hard to believe that any statistically meaningful conclusions can be reached about intra-strata differences.

Authors' Response: The issues of statistical/clinical heterogeneity have been addressed in our previous revision. The reviewer's comment regarding number of studies and sample size are not relevant because the meta-analyses generally demonstrated statistical significance, even with relatively small numbers of studies. The reviewer's comments would have been more germane had statistically significant findings not been observed. In that case, the issue of small number of studies and sample size would have raised questions regarding statistical power. In reality, statistically meaningful (significant) conclusions were reached in many of the stratified analyses.

Reviewer Comment (3): While OMT may have effect sizes that are equivalent to those of other treatments for back pain, these effect sizes are not very large. This needs to be clarified in the results and conclusions. Clinicians and patients will be interested not only in whether OMT is effective, but also in how effective it is.
Authors' Response: Any classification scheme regarding the magnitude of effect sizes is arbitrary. In fact, Elmer Villanueva (Reviewer 3) has suggested making effect sizes more clinically relevant rather than focusing on the magnitude of the effect. This was done in the discussion section of our previous revision, when we compared effect sizes attributed to OMT with effect sizes attributed to NSAIDs. We believe that this represents a very tangible and easily interpreted presentation of the effectiveness of OMT.

Reviewer Comment (4): The conclusion that the benefits of OMT "appears to persist through the first year of treatment" is based on a single trial with follow-up exceeding 6 months. As a result, it is premature to conclude that the effects of OMT have been proven to persist at least one year and that "additional research is warranted to...determine if OMT benefits extend beyond the first year of treatment". This sentence should be revised to state that "additional research is warranted to...confirm if OMT benefits are long lasting."

Authors' Response: We agree with the reviewer's comment. Revisions to the abstract and conclusion sections will be made to reflect that the effects of OMT last at least three months, and that "additional research is warranted to...confirm if OMT benefits are long lasting." Accordingly, a sentence within the results section (page 13-14) was revised to state, "However, unlike these nonsteroidal anti-inflammatory drugs that were evaluated for only three months, OMT may have a longer lasting effect."

Reviewer Comment (5): In order to reassure readers that the studies included in the meta-analyses are indeed of high quality, the text or tables should provide evidence that few, if any, trials had loss to follow-up rates exceeding 15% and that there were not large differences in the follow-up rates across treatment groups.

Authors' Response: Loss to follow-up is only one aspect of methodological quality. In addition, any proposed standards with respect to attrition (e.g. 15% as indicated by the reviewer) are arbitrary, especially in light of the fact that some studies included in the meta-analysis followed subjects for six months to one year.

A better approach to assessing methodological quality is to examine multiple factors. This is the approach that we took in our previous revision, when we cited a reference (#13) that confirmed the methodological quality of four of the studies included in our meta-analysis, as part of their systematic review. They included eight variables in their quality assessment: (1) similarity of baseline characteristics of subjects or adjusted effects reported; (2) concealment of treatment allocation; (3) blinding of subjects; (4) blinding of
provider or other control for attention bias; (5) blinded or unbiased outcomes assessment; (6) dropouts reported and accounted for in the analysis; (7) missing data reported and accounted for in the analysis; (8) intention-to-treat analysis or no differential co-interventions between groups in studies with full compliance. In addition to taking a multivariate approach to quality, another advantage of using this citation is that it precludes the possibility that we, as authors of the meta-analysis paper, may be biased in interpreting the quality of the studies in our meta-analysis. Although the two remaining studies in our meta-analysis were not eligible for inclusion in the previous systematic review because the Cleary study was too small and the Licciardone study was published after the systematic review's closing date, these are easily addressed. With regard to the Clearly study, sensitivity analyses were performed, in which this study was excluded and the results were essentially unchanged. With regard to the Licciardone study, two subsequent references (#48, 49) were cited to support the methodological quality of this study.

In order to help reassure readers that the studies included in the meta-analyses are of high quality, we will list in the methods section the eight quality indicators, noted above, that were addressed in reference #13.

Reviewer 2: Dave Baxter

Reviewer Comment: I have read these materials carefully and would consider that, with one important exception, the authors have adequately addressed the points raised in the earlier review by Dan Cherkin and myself.

The exception derives from the authors' justification of the 'difference' in osteopathic manipulation: particularly that such manipulation is practised by fully licensed physicians (in the USA), and that such manipulation is broader in the range of techniques used compared to chiropractic.

In the first instance, the current review includes trials completed in the United Kingdom, where osteopaths are not licensed physicians, and indeed have only recently received statutory recognition and regulation (through the General Osteopathic Council). Although the authors have elected not to address this point (included as a discretionary revision in my last report) on the grounds that it is a complex issue which is 'beyond the scope of our study's purpose', I would suggest, given that this represents the central thrust of the authors' argument for the unique status of osteopathic manipulation, this issue needs some comment.
Secondly, whilst the contrast with chiropractic manipulation may indeed be useful, this would hardly differentiate osteopathic manipulation from that performed by physiotherapists. If this is indeed the case, then it is worthy of comment: if not, then the distinction between OMT and physiotherapy-performed manipulation is important.

Major Compulsory Revisions

No others indicated.

Authors' Response: In response to this reviewer's general comments noted above, and to his previous comment that was noted to be "discretionary," we have made two revisions.

First, with respect to professional differences in the United States, we have revised a sentence (pages 4 and 5) to reflect that osteopathic physicians can treat low back pain simultaneously using both conventional primary care approaches and complementary spinal manipulation, unlike chiropractors or physical therapists. We added "physical therapists" to this statement to reflect current practice rights in the United States.

Second, in response to the finding of comparable effect sizes in the United Kingdom and the United States, we added another paragraph to the discussion section (page 15) that addresses the question of whether one needs to be trained as a physician to provide OMT effectively.

Reviewer 3: Elmer Villanueva

Reviewer Comment (1): My first advice (one I'm afraid I will classify as a major compulsory revision) is the adoption of the QOROM recommendations in the reporting of meta-analyses. I worked this out with Fiona Godlee when she was at BMC. This resulted in the very clear statement of authors that the BMC supports QOROM recommendations. At the very least, use of these recommendations will make most of the following redundant:

- The Authors will need to show the exact search strategy.
- The Authors will need to describe the study flow.
- The Authors will need to define the population of interest and interventions clearly.
- The Authors will need to specify the outcomes of interest. Descriptions of "contrasts" result in the difficult situation in which the Authors find
themselves -- that of several hundred possible combinations from a thin
evidence base (six studies). In effect, this places all outcomes on a single
footing; in a sense, death is the same as debility. The Authors will need to
be bold and say "We are most interested in return to function (for
instance) at six weeks as the primary outcome of interest". By assiduously
examining all contrasts, any results are difficult to separate from the "this
pill only works for those born under the sign of Libra" saga.

Authors' Response: A detailed search strategy will be provided in an
Appendix to the manuscript, and this is now clearly indicated in the methods
section (page 5). Otherwise, the manuscript conforms to the remaining
QUOROM elements (originally published in Lancet), as presented in the
Instructions for Authors on the BMC-Musculoskeletal Disorders Web site.
The study flow is already provided in Figure 1. The population of interest and
interventions are already described in the methods section and in Table 1.
The outcome of interest, low back pain, has already been stated in the
methods section and throughout the narrative. The final paragraph of the
discussion section already indicates that other outcomes, such as generic
health status, back functioning, work disability, and patient satisfaction,
were not assessed.

Reviewer Comment (2): My second advice is for the Authors to be very careful
in the excessive use of stratified and sensitivity analysis in the presence of
sparse data. For a particular PICO (patient, intervention, control, outcome)
combination the Authors have, at most, a sample size of six. In most cases, it
is difficult to extract information from such a small sample size. Running
several exploratory analyses on such as small sample size is even less likely
to be justifiably prudent.

Authors' Response: There are substantially fewer PICO combinations than
suggested by the reviewer because there is no stratification on patient (all
patient had low back pain), intervention (all treated patients received OMT),
and outcome (low back pain was the only outcome variable). Therefore, the
acronym "PICO" reduces to the letter "C," because only control interventions
were stratified.

We appreciate the reviewer's caution regarding sample size. Obviously, all
things being equal, larger sample size is preferable to smaller sample size.
Nevertheless, as noted in our response to Reviewer 1 (Dan Cherkin), small
sample size is most problematic when statistically significant findings are not
observed. In the later situation, one would question the statistical power of
the analysis. In our meta-analysis, statistically significant findings were
often observed, even in our stratified analyses. This suggests that: (1) OMT
has a substantial effect (as reflected by the numerator for the effect size
computation); or (2) the intra-study variability is small (as reflected by the denominator for the effect size computation); or (3) both. Thus, the effect of OMT on pain and/or the comparability of studies were sufficient to overcome Reviewer 1 and 3's expectations that significant results would not be observed because of small sample size.

Reviewer Comment (3): My third advice is for the Authors to ensure that, even in the absence of statistical heterogeneity, the more substantive problem of clinical heterogeneity is considered. Statistical heterogeneity only measures the departure of each study's "average" effect from the theoretical "middle" effect (however each of these concepts is defined). Ignoring heterogeneity arising from variations in study designs, one common (and perhaps the most important) source is clinical variation.

Authors' Response: The issue of clinical heterogeneity was addressed in the previous revision before Reviewer 3 (Elmer Villanueva) was asked to comment on the present manuscript, when it was raised by Reviewer 1 (Dan Cherkin). It should be noted that previous meta-analyses have included all forms of spinal manipulation (e.g., chiropractic, osteopathic, physiotherapeutic, etc). Our meta-analysis should have less clinical variation simply because all spinal manipulation was of the osteopathic type. Residual variation was addressed by performed stratified analysis (by country, by control group, and by duration of follow-up). The use of stratification is a universally accepted method for controlling for potential confounding (moderator) variables. It has been used in a recent meta-analysis performed in collaboration with the Cochrane Back Review Group (reference #31).

Reviewer Comment (4): My fourth advice is to temper findings if such findings arise from a small number of studies, in spite of the performance of a meta-analysis. The worst-case scenario is one in which a finding is drawn from the results of a single study. Since no meta-analysis actually occurs, it is misleading that such a finding is the result of the synthesis of six studies.

Authors' Response: We are unclear as to which "worst-case scenario" the reviewer refers. It is clearly stated in the method section (page 9) that, "Meta-analysis was performed only when there were at least three contrasts available for data synthesis." There are five "worst-case scenarios" summarized in Figure 3. The number of contrasts for these scenarios ranges from four to eight. The number of studies included ranges from four to six. There is no "meta-analysis" finding based on a single study.

Reviewer Comment (5): My fifth advice is to make "effect sizes" more clinically relevant by back-transforming Cohen's d scores to their original scales. It is particularly difficult for a clinician to interpret an effect size of 2
(say) in decrease in medication use at six weeks (say). What this means is that medication use decreased by 2 standard deviation units at six weeks. Let me quote a common response to the latter statement: "Huh?". The difficulty is one in which the scale is incomprehensible to the common reader.

Authors' Response: There are two main types of pain measures reported in this field of research: nominal pain scales (older studies) and visual analogue scales (current studies). Neither of these measures is readily interpretable from a clinical perspective. Thus, back transforming to either scale would be less clinically relevant than the present comparison of our effect sizes for OMT with reported effect sizes for NSAIDs.

Reviewer Comment (6): My sixth advice is for the Authors to cease comparing effect sizes of OMT to other treatments like NSAIDs because of the simple fact that no head-to-head comparisons were performed and the cross-comparisons result in a Clayton's comparison (for those not up with Australian advertising folklore, Clayton's Kola-based mixer at one stage had a campaign where, it being alcohol-free, was promoted to adults as "the drink you're having when not having a drink"). In other words, this result is the one you report when you don't have an actual result to report.

Authors' Response: As indicated, for the reasons described above, we believe that the comparison of OMT effects with NSAIDs effects is useful. Readers will understand that the OMT vs. NSAIDs comparison is not a head-to-head comparison performed in our meta-analysis because it is presented in the discussion section (not in the results section), and because the NSAIDs portion of the comparison is clearly explained and referenced (#54).

Further, in response to this particular comment, it should be noted that one of our meta-analyses addressed the OMT+usual low back care vs. usual low back care only comparison. This is explained in the results section (page 11) as follows: "The OMT vs. no treatment control comparisons were observed in trials in which all subjects received usual back care in addition to their allocated treatment (ie, OMT and usual care vs only usual care) [44,47]. For these trials, the all-contrasts model (ie, the only model with sufficient contrasts for data synthesis) demonstrated a highly significant reduction in pain with OMT." This result is presented in Table 4 as effect size, –0.53 (95% confidence interval, –0.76 - –0.30); P < .001.

Although this result does not represent a direct head-to-head comparison of OMT with NSAIDs, it is germane to this issue because NSAIDs constitute a mainstay of usual care for low back pain. Importantly, this result suggests not only that the analgesic effects of OMT are comparable in magnitude to
those of NSAIDs, but also that these analgesic effects are in addition to those achieved by NSAIDs.

Major Compulsory Revisions

No others indicated.

Again, we thank the reviewers for their comments. We believe that the revisions described above are responsive to these comments and have enhanced the quality of our manuscript.

Sincerely,

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On behalf of all the authors