Subject: BMJ - Decision on Manuscript ID BMJ.2014.023605

Body: 25-Jan-2015

Dear Prof. Cohen,

Manuscript ID BMJ.2014.023605 entitled "A Multi-Center, Randomized, Double-Blind, Comparative-Efficacy Study Comparing Epidural Steroid Injections to Gabapentin for Neuropathic Low Back Pain"

Thank you for sending us this paper, which we were pleased to have the chance to consider and enjoyed reading. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it. This is because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript committee meeting, so that we will be in a better position to understand your study and to decide whether The BMJ is the right journal for it.

Many thanks again. We look forward to seeing your revised article within a month and, we hope, to reaching a decision.

** THE REPORT FROM THE MANUSCRIPT COMMITTEE MEETING, REVIEWERS' REPORTS, AND THE BMJ'S GENERAL REQUIREMENTS FOR RESEARCH PAPERS ARE AVAILABLE AT THE END OF THIS LETTER.**

First, however, please read these four important points about sending your revised paper back to us:

1. Deadline: Your revised manuscript should be returned within one month.

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IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Yours sincerely,

Rebecca Burch, MD
Associate Editor, The BMJ
rburch@bmj.com

As well as submitting your revised manuscript, we also require a copy of the manuscript with changes highlighted. Please upload this as a supplemental file with file designation 'Revised Manuscript Marked copy'.

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

INFORMATION ON REVISING THE CONTENT AND FORMAT OF YOUR ARTICLE

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript. Members of the committee were: Elizabeth Loder (Chair), Gary Collins (Statistician), Kristina Fister, Emma Parish, Jose Merino.

Decision: request revisions

Detailed comments from the meeting:
First and foremost, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

* We require trials to be prospectively registered in accordance with ICMJE guidelines. This trial was reported as registered in the same month that treatment began. Please provide exact dates of the start of patient recruitment and trial registration.

*Editors felt that inclusion and exclusion criteria were not clear. The mechanisms for neurogenic claudication and lumbosacral radicular pain are different, so allowing either type of patient may have introduced heterogeneity. How was this handled? What imaging criteria were required?

*There was significant confusion about inconsistencies in “back pain” vs “leg pain” in the title, introduction, inclusion criteria, and outcomes. Which of the two was the target of this study? Why are these two different terms used throughout the paper?

*There is no rationale provided for the target outcome of 1 point difference on the pain scale. Is this clinically meaningful?

*Editors were concerned about the lack of a complete sham/placebo group, rendering the assay sensitivity in doubt.

*Editors did not agree with the conclusion that treatment decisions should be based on patient considerations as this was not evaluated in this study. This study only provides evidence that there is no meaningful difference between the two treatment options.

*We felt that the dichotomy of ESI vs. gabapentin may not reflect real life where patients often try a combination of interventions.

*We do not agree with the reviewer who wanted more extrapolation from statistically non-significant data. We consider results that are statistically non-significant to be negative outcomes.

* We had a number of concerns about the statistical elements and reporting of this trial, all of which are mentioned in the statistical review at the end of this letter (Review 4). We would need to see all of these concerns addressed in entirety prior to reconsidering a revised version of this paper.

IMPORTANT
When you revise and return your manuscript, please take note of all the following points about revising your article. Even if an item, such as a competing interests statement, was present and correct in the original draft of your paper, please check that it has not slipped out during revision.

a. In your response to the reviewers and committee please provide, point by point, your replies to the comments made by the reviewers and the editors, and please explain how you have dealt with them in the paper. It may not be possible to respond in detail to all these points in the paper itself, so please do so in the box provided

b. If your article is accepted it will then be edited, proofed, and - after your approval - published on bmj.com with open access. This open access Online First article will not be a pre-print. It will represent the full, citable, publication of that article. The citation will be year, volume, elocator (a unique identifier for that article): eg BMJ 2008;337:a145 — and this is what will appear immediately in Medline, PubMed, and other bibliographical indexes. We will give this citation in print and online, and you will need to use it when you cite your article.

c. Please write an abridged version of the article for the print and iPad BMJ using the appropriate BMJ pico template for your study's design. Please be reassured that it doesn't take long to complete this. When your BMJ pico is ready please email it to papersadmin@bmjgroup.com.The templates for you to download are at http://resources.bmj.com/bmj/authors/bmj-pico

d. Please include these items in the revised manuscript to comply with BMJ style:

Title: this should include the study design eg "systematic review and meta-analysis”

Abstract
structured abstract including key summary statistics, as explained below (also see http://resources.bmj.com/bmj/authors/types-of-article/research)
for every clinical trial - and for any other registered study - the study registration number and name of register – in the last line of the structured abstract.

Introduction
this should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now

Methods:
for an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials can be found
Results
please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines http://www.equator-network.org/reporting-guidelines/sampl/

summary statistics to clarify your message. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

For a clinical trial:
• Absolute event rates among experimental and control groups
• RRR (relative risk reduction)
• NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000)

For a cohort study:
• Absolute event rates over time (eg 10 years) among exposed and non-exposed groups
• RRR (relative risk reduction)

For a case control study:
• OR (odds ratio) for strength of association between exposure and outcome

For a study of a diagnostic test:
• Sensitivity and specificity
• PPV and NPV (positive and negative predictive values)
one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used
for articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system
Discussion
please write the discussion section of your paper in a structured way, to minimise the risk of careful explanation giving way to polemic.Please follow this structure:
statement of principal findings of the study
strengths and weaknesses of the study
strengths and weaknesses in relation to other studies, discussing important differences in results and what your study adds. Whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses (eg Cochrane reviews)
meaning of the study: possible explanations and implications for clinicians and policymakers and other researchers; how your study could promote better decisions
unanswered questions and future research

Footnotes and statements

What this paper adds/what is already known box (as described at http://resources.bmj.com/bmj/authors/types-of-article/research)

ID of ethics committee approval and name of the ethics committee/IRB; or a

statement that approval was not required (see http://resources.bmj.com/bmj/authors/editorial-policies/guidelines) and a statement that participants gave informed consent before taking part

a statement that any identifiable patients have provided their signed consent to publication. Please submit, as a supplemental file, the signed BMJ patient consent form giving consent to publication in The BMJ of any information about identifiable individual patients. Publication of any personal information about a patient in The BMJ, for example in a case report or clinical photograph, will normally require the signed consent of the patient.

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a data sharing statement declaring what further information and data you are willing to make available, over and above the results reported in the paper. Suggested wording: "Data sharing: technical appendix, statistical code, and dataset [state whether any patient level data have been anonymised] are available at this repository or website OR from the corresponding author at ". If there are no such further data available, please use this wording: "Data sharing: no additional data available". For papers reporting the main results of trials of drugs or devices we require that the authors state, at a minimum, that the relevant anonymised patient level data are available on reasonable request from the authors
The BMJ has partnered with the Dryad Digital Repository datadryad.org to make open deposition easy and to allow direct linkage by doi from the dataset to The BMJ article and back - we encourage authors to use this option
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for studies funded or sponsored by industry (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements)
a statement describing the role of the study sponsor(s), if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication
assurance, in the cover letter, that a clinical trial funded by a pharmaceutical or other commercial company follows the guidelines on good publication practice (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements)
inclusion in the list of contributors the name(s) any professional medical writer(s), specifying in the formal funding statement for the article who paid the writer. Writers and authors must have access to relevant data while writing articles.

Patient centred research
for studies that are relevant to patients we expect authors to report in their articles the

extent of their study's patient-centredness, as highlighted by these questions:
did you involve patients/service users/carers/lay people in the design of this study? Please state whether you did, and give details (Methods section)
was the development and/or selection of outcome measures informed by patients' priorities and experiences? Please give details (Methods section)
were patients/service users/carers/lay people involved in developing plans for participant recruitment and study conduct? If so, please specify how (Methods section)
have you planned to disseminate the results of the study to participants? If so how will this be done? (Describe in brief footnote)
are patients thanked in the contributorship statement or acknowledgements?
for articles reporting randomised controlled trials: did you assess the burden of the intervention on patients' quality of life and health? If so, what evaluation method did you use, and what did you find? (Methods and Results sections)

REFEREES COMMENTS

Reviewer: 1

Recommendation:

Comments:
For authors

There is a need for studies that compare epidural steroids with conservative treatments. This study is timely and well designed. Its results are generalizable and of relevance for a broad specialty spectrum, including primary care as source of referral for interventional practice.

Abstract
Please explain the abbreviation ESI.
It would be useful to have a short explanation of "positive successful outcome".
In the conclusions, I would change the term "small" to "moderate". See also my comments for the results and discussion sections.
The last sentence is obscure for those who read only the abstract. I suggest deleting it.

Methods
In the section Participants & Settings, the sentence "or > 3/10 if greater or equal to back pain" is unclear to me. Please re-write.
At the end of the same section, please specify what psychiatric or medical conditions were considered as exclusion criteria; it is not intuitive which specific conditions "might preclude an optimal response to treatment", and why. At least some examples would help.
On page 9, please specify how "moderate or severe canal stenosis" was defined.

Results and Discussion
It seems to me that the results and discussion present too negatively the effects of epidurals. It is true that some of the outcomes, including the main endpoint, were either not significant of revealed modest effects. However, for some of them the effect was not trivial. For instance 51.6% vs. 33.8% of patients felt globally improved at three months. This seems to me a substantial difference in the frame of chronic pain treatment, where we hardly expect considerable improvements in outcome. Also the effect on worst pain was negligible. While I appreciate the conservative attitude of the authors, I would suggest reconsidering the wording throughout the manuscript.

Additional Questions:
Please enter your name: Michele Curatolo

Job Title: Prof.

Institution: University of Washington

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

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Reviewer: 2

Recommendation:

Comments:
Positive

The authors have performed a very elegant comparative-effectiveness study comparing ESIs to the first-line medication gabapentin for managing neuropathic low back pain. As a pain physician who manages patients with neuropathic low back pain, I think this gives us very informative and important messages in ways that will helpimprove clinical management. The article will be of interest to a wide range of medical doctors surgeons, internists and family doctors, and all of the different types of doctors who practice pain, so this matches the BMJ's mission to publish clinically relevant articles as well.

Radiculopathy is an enormous societal burden throughout all over the world, and the use of ESIs and medications such as gabapentin have both come under scrutiny because of their increasing utilization. This therefore seeks to address an extremely very important question. This study does not measure efficacy, but may be more relevant because there have been over 50 studies comparing anticonvulsants and ESI to placebo, and it's unlikely that the next study will provide a definitive answer. Rather, this is the question that primary care (and pain) doctors would like to be answered.

Based on recent literature, this study may be more clinically relevant because the authors elected to use a "true placebo" (intramuscular injection), which seems more difficult to blind, but unlikely to provide any benefit for patients with both spinal stenosis and herniated disc.

An interesting thing that the authors did was to measure blinding at 2 different stages (those who receive ESI are at risk for "unblinding" early, while those who receive a medication are at risk later because of side effects). Even though there was a trend towards better insight into treatment assignment for the gabapentin group at one month, this provides information on the assessment of "blinding" and how to maintain it successfully. Industry sponsored studies approved by regulatory bodies generally do not assess blinding, and the observation that more people who received gabapentin guessed their treatment group at 1-month compared to gabapentin at 1-day or ESI at 1-month raises the question about whether some of these other studies were actually blinded.

Evaluating the primary outcome at one month by comparing a "Single ESI" to "oral

gabapentin" might not be long enough to find any clinical differences between groups. As the authors suggested in their discussion section, few studies have examined the long-term effectiveness of gabapentin, but those that have indicate that the beneficial effects for neuropathic pain are most pronounced early on during treatment, which is similar with ESIs.

The broad inclusion criteria and 3 types of hospitals in this study increase generalization and are consistent with guidelines on comparative-effectiveness research.

Negative

Several limitations that the authors addressed in their discussion section should be considered.

This study was powered to detect a difference between the 2 groups, but the numbers are probably not sufficient to detect subgroup analyses such as the type ESI done, age, or pathology.

Another limitation that either needs to be noted is that the authors did not note the numbers of patients who underwent surgery. In addition, did soldiers or veterans have any different outcomes than civilians?

Minor

Methods (Participants & Settings)

Did all patients included in the study have leg ≥ low back pain? Were there any patients whose average leg pain score ≥ 4/10 on a NRS pain score but back pain was more severe?

Did all patients have MRI images before the study? The authors wrote in one of their articles that there is difficulty in establishing a cause-effect relationship between pathology and pain itself in that many patients have pathology in the absence of pain, so that ESI might show better effectiveness in patients who had signs and/or symptoms of neuropathic low back pain with concordant MRI imaging.

Was there any reason to exclude subjects with ESI within the past 3 years? Did you exclude those subjects for recall bias or because you already knew how they responded?

Did patients undergo only single level ESI? Did you exclude patients if they had multi-level unilateral symptoms?

Randomization and Interventions

Regarding the allocation ("Allocation was performed in groups of 36 (Walter Reed and Johns Hopkins) or 18 by research nurses,"), would you explain the allocation method more in detail?

I realize that the latest guidelines that have been published online, presented and will probably also be presented at the U.S. Food and Drug Administration meeting this month on ESI state that transforaminal ESI with particulate steroids should not be a first-line treatment. However, the authors should still note why they didn't perform bilateral transforaminal ESI for patients with bilateral pain in lieu of interlaminar ESI since it may be superior in cases with scar tissue.

Epidural Injection

Please explain why you used the volume of 4 ml for interlaminar ESI?

Sham Injections & Maintenance of Blinding

Were subjects in ESI group also shielded from the image screen?

Regarding "sham injection," wasn't there any resistance when 3 ml of LA was injected into muscles or ligaments? Were there any patients who complained about discomfort during the injection? If the patient in sham injection group had had ESI (especially transforaminal approach) even once before, I would guess that a few of them could detect the difference between the true ESI and the sham procedure, though blinding was successful.

Pharmacotherapy

I could guess that some patients who already had taken gabapentin before might detect that their medication was placebo.

Statistical Analysis

Regarding sample size and power analysis of the study. Please suggest a reference or explain why you used "a 1.0-point difference in pain scores between groups and SD of each group of 2.0."

Results

Outcomes

Primary care doctors and pain physicians could wonder how long it took to get to the final dose of gabapentin in the Sham ESI group, and whether the dose of gabapentin was related to the outcome in the binary logistic regression.

Please consider showing the results of factors associated with outcome by logistic regression as a table.

End

Additional Questions:
Please enter your name: Jee Youn Moon

Job Title: Clinical Assistant Professor

Institution: Seoul National University Hospital

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

Reviewer: 3

Recommendation:

Comments:
Overall, this is a well-designed and well-written study. There are minor changes and clarifications that would be helpful in strengthening the study.
1. Please display the mean or median gabapentin dose.
2. The authors should mention an additional heterogeneous characteristic of their inclusion criteria as a limitation: both radicular pain and "neurogenic claudication" were included, two different pathologic processes (defined by symptoms and distinct from radiologic diagnosis of disc herniation vs. stenosis), which many each respond differently to the interventions tested here.
3. What is the rationale for this outcome definition: "Reduction in analgesic medications corresponds to > 20% reduction in opioid use or complete cessation of non-opioid analgesic." Is 20% based on prior literature or arbitrary?
4. "Positive" Composite outcome is based on a weak definition of a positive pain response. This definition of "a change greater than 2) that is below the MCID for leg pain according to some literature (3 points on the NRS scale). It would be worth adding additional categorical "responder" analysis using a more robust definition of clinically significant improvement in pain. The proportion of individuals who experience >50% pain reduction is commonly used in the literature as such a threshold. Using responder analysis may also possibly unmask larger differences between the two study groups.
5. The study would be more informative if outcomes were additionally stratified by primary pathology (stenosis vs. disc herniation) at the spinal level thought to be generating symptoms.
6. The study would also be more informative if results were stratified by bilateral ESI vs. unilateral ESI (TF vs. IL).

Additional Questions:
Please enter your name: Zachary McCormick

Job Title: Physician

Institution: Northwestern University/The Rehabilitation Institute of Chicago

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?:

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Reviewer: 4

Recommendation:

Comments:
I find this a slightly confusing read which is due, in part, to inconsistent reporting, there are also some inconsistencies in outcomes between the registry entry, protocol

and the paper.

Title says low back pain, yet primary outcome is leg pain – which I don't understand.

The trial registry entry states

Primary outcomes as leg pain @ 1 and 3 months
Secondary outcomes as Back @ 1 and 3 months, ODI @ 1 and 3 months and Satisfaction @ 1 and 3 months.

Whilst, the paper states

Primary outcome as leg pain @ 1 month
Secondary outcomes as worse leg pain over the past week, average and worse back pain, ODI, adverse events, complications, reduction in analgesic medications, and global perceived effort. So a number of outcomes seem not to be pre-specified, and specific time points not indicated in the paper - though clearly in Table 2, interest is in 1 and 3 months (sample size is based on outcomes at 1 month). The protocol has leg pain as primary and back (average and worse), OWI, medication usage, satisfaction, side-effects and complications.

Table 2 also introduces another unspecified outcome 'composite outcome'. The authors should clarify the inconsistencies, both within in the paper and also so that they tie together what was pre-specified in the trial registry entry.

Sample size calculation: I can see no rationale of a 1 point difference in pain. The assumptions on which the sample size is based are not referenced, more information on the assumptions that were used to derive the sample size are required, including how/why these values were chosen. Some of the assumptions (though not where these values were obtained from) are reported in the protocol, but should be included in the paper.

In the sample size section the authors also conduct post-hoc power calculation – I'm not quite sure why. This is never a good idea (large body of methodological and applied literature on this) and this calculation should be omitted from the paper.

The description of the randomisation is brief, just stating participants were randomised 1:1 using computer generated randomisation tables. More information required. The abstract states randomisation was stratified by site...this is not mentioned in the methods of the paper. The protocol describes this in more detail, and it should also be summarised in the paper.

Eligibility criteria - registry entry states participants were eligible if they were aged 17 or older. In the paper (and protocol) this is 18 or older.

Abstract reports within arm differences from baseline, ok, but I would like the between arm comparison - which is reported in the paper. The results (in the abstract) on worse leg pain is an unspecified post-hoc outcome (which happens to be 'significant').

Treatment effect was analysed using ANCOVA. Did they adjust for anything apart from the baseline value of the outcome and sex (which was a post-hoc decision due to imbalance in the randomisation). Arguably, if sex was an important prognostic factor that balance was important then this should've been included in the randomisation procedure and/or pre-specified in the analysis plan.

The protocol mentions using Bonferroni corrections for multiple testing – yet there is (as far as I can see) no mention of this.

True ITT would use all patients randomised, there is some loss to follow up in the ESI group, where there follow-up outcomes could've been imputed. The protocol mentions imputation for replacing missing data may be used.

typo in Table 1. '3 to 12 months' - 26/73 is 35.6% (not 25.6%)

Would like CONSORT flow diagram to resemble a recommended CONSORT diagram. E.g. How many received randomised treatment, how many were analysed etc.

In the Discussion, they state as a limitation that it was a small trial – how can it be small if the sample size was achieved?

Additional Questions:
Please enter your name: Gary Collins

Job Title: Associate Professor

Institution: University of Oxford

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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If you have any competing interests (please see BMJ policy) please declare them here:

END

Date Sent: 25-Jan-2015