Author's response to reviews

Title: Study protocol: Brief Intervention for Medication Overuse Headache - A double-blinded cluster randomised parallel controlled trial in primary care

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Version: 2 Date: 21 March 2012

Author’s response to reviews: see over
Dear Editor of BMC Neurology,

Thank you for your response regarding our manuscript. We also accept the apologies regarding the delays to the paper and we certainly understand that there may be many reasons for this, not least to find reviewers. We are happy that this could be done in the end!

We would also like to thank the referees of the paper who have obviously done a conscientious work and have given many helpful and positive comments.

Below is an itemized list of replies and comments to the issues raised by the referees. In the attached revised manuscript, the changes made have been marked in red. In addition, the reference list has been revised to fit with the changes in the text and the “et al’s” have been removed as required according to your instructions, these changes have not been highlighted. In addition, the minor changes to table 2 requested by referee 1 have also been made but not highlighted in red.

We hope that with these changes and based on the positive referee comments, the paper will now be found acceptable for publication in BMC Neurology.

Many greetings,

Christofer Lundqvist, Prof (Health Services Research) and Consultant Neurologist

Corresponding author
Reviewer's report

Title: Study protocol: Brief Intervention for Medication Overuse Headache - A double-blinded cluster randomised parallel controlled trial in primary care

Version: 1 Date: 9 February 2012

Reviewer: Paola Torelli

Reviewer's report:
This is a study protocol to evaluate the efficacy of Brief Intervention (BI) specifically designed for treatment of medication overuse headache (MOH) in primary care.
The study consisted in a double-blinded cluster randomized parallel controlled trial (RCT).
The BI involves the use of tools to the identified headache subjects “at risk” of medication overuse and a very short and simple intervention to give information suggesting to cut down the use of the particular substance to predecided “acceptable” levels. The primary objective of this study is to evaluate the effects of a BI versus business as usual (BAU) in the management of MOH in primary care.
The study is well designed and the article is well written.

Minor Essential Revisions
- Table 2: the X have to be re-aligned accordingly to the text

Done

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests'

Reviewer's report

Title: Study protocol: Brief Intervention for Medication Overuse Headache - A double-blinded cluster randomised parallel controlled trial in primary care

Version: 1 Date: 13 February 2012

Reviewer: Paolo Rossi

Reviewer's report:
Main issues
1. Will the study design adequately test the hypothesis?
Yes, it is but I have few criticisms regarding the patients’ selection and the use of SDS (see comments)
2. Are sufficient details provided to allow replication of the work or comparison with related analyses: if not, what is missing?
The authors provided sufficient details to allow replication of the work and comparison with related analysis
3. Does the manuscript adhere to the relevant standards for reporting and data deposition: if not, in what ways?
Yes the manuscripts adhere to the relevant standards
4. Is the writing acceptable?
The writing is acceptable, the study is well introduced, methods are sound and clearly expressed and the discussion is almost complete.

COMMENTS
• Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

The authors should include the guidelines for treatment of MOH of the EFNS panel (Eur J Neurol 2011)

We have now included the suggested reference

background: To support the sentence “Headache is mostly self-managed” the authors used a paper of 1992 that is too old, whereas they have recently published a paper on the management of chronic headache in primary. Please upgrade the reference

This has been done, we have added our own reference which is more appropriate for our Norwegian population.

It would be interesting to know if the authors had problems to collect funds for this study. MOH is essentially a iatrogenic disorders and there is an interest to avoid the diffusion of the message “too many drugs worsen the headache”

This is a very important point and we completely agree with the reviewer that there is a problem with being unclear about the “too many drugs worsen headache” message. We hope that our study will give results that are clear enough regarding the need for more awareness regarding this statement.

Our study was sponsored by the University and by public sponsorship through research funds and not by pharmaceutical firms and I guess the latter may be hard to come by…

• Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Outcome measures paragraph should be placed before the statistics

This has been changed.

• Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

BACKGROUND

The authors use two US studies to support the notion that “most patients use OTC drugs”; they should include data from other countries because US drug market is too different from that of many European countries.

Agreed. We used the US references not least since even in the US where use of “heavier” prescription drugs tends to be much higher, the OTC use is still the dominating, in contrary to what one may expect from the previous focus in detoxification studies. However, the point is taken and a Swedish and our own studies from the Norwegian population have been added.

Page 6. In introducing MOH the authors report data suggesting that it is an
addictive behavior. This is only a part of the history and essentially based on data from clinical populations of patients. MOH is a largely heterogeneous disorders including patients with very low medical needs and complicated difficult to treat patients. The heterogeneity of MOH does not emerge from this study. The authors seem to favour the hypothesis of an addictive component underlying MOH to support the use of SDS. Indeed, several authors have worked on the identification of clinical subgroups of MOH in order to identify those patients necessitating intensive withdrawal and multi-specialty approach, and those patients that may be treated with a brief educational intervention (i.e simple and complicated MOH). The experience of the authors in one of their previous papers (Grande 2011) seems to go in this direction because an impressive proportion of the MOH patients screened in the general population have reduced their intake of painkillers after a short information that is unlike to happen in addicted patients. Please consider these aspects (heterogeneity of MOH, dependence or pseudodependence ? effectiveness of educational intervention on dependency of the severity of clinical picture) in the background that should be written in a more balanced way.

We agree that MOH is heterogenous and that there are probably different populations, some of which may be dependent while others are not or may exhibit a “dependency-like” behaviour (which is the wording used by us throughout the article). We have previously shown that in a primary population the SDS can be used reliably to identify MOH cases, however, we do not dare suggest that all these are dependent. We would also emphasize that there seems to be a relationship between the SDS score and whether patients succeed in detoxification after simple information or not (Lundqvist et al Pain 2012) which suggests that the SDS measures a behaviour relevant to the ease of detoxification. We will also collect data making it possible to divide the MOH patients into different subgroups (i.e. simple and complicated) in the data handling/analysis and, importantly, we will not exclude MOH patients with low SDS scores from the intervention. The background section has been modified to discuss and hopefully clarify these points further.

METHODS
The authors are requested to specify if there is the possibility that the GPs selected for the study had received in the past any specific training about MOH management. If so, this information should be considered in the findings or used to exclude these physician from the study

As far as we have been able to find out there has been no formal training on handling of MOH among the GPs in this part of Norway. We will ask the participating physicians whether they have had such training or not. Since this is a pragmatic trial where the physicians individual background in this respect today is the starting point, we do not wish to exclude any physicians in advance. This point has been added in methods under “Brief Intervention course”.

The authors have explained in the discussion the reason for choosing an age range of 18-50 years, but they did not mention that accordingly with epidemiological studies on MOH the prevalence of this disease is higher in the age-classes 40-49 and 50-65 and that the mean age of MOH at the diagnosis is often older than 50 years. I think that including the patient in the age class 50-60
years would represent a significant improvement to the protocol.

For prevalence studies we certainly agree that it is important also to clarify the picture for the older patient group suggested. However, since this is not an epidemiological study where the prevalence is central, we regarded the possibly confounding effect of multiple drugs for other conditions, not least hypertension, to be more problematic with regard to detoxification and possible headache prophylactic use. If our BI method is effective, it should then be tried also in an older population.

USE of the SDS questionnaire. The large experience of the authors with this questionnaire indicate that it may be useful to identify MOH patients and dependency-like behavior and to predict the prognosis after educational intervention (a paper from Lundqvist et al published in 2012 should be added to the references). The advantage in the identification of MOH is questionable because MOH may be suspected and diagnosed with ICHD-IIR criteria with few questions. The SDS appears very useful for therapeutic purpose. Anyway the authors relies on the SDS for diagnostic purposes (diagnosis of MOH in screened patients is made by GPs by using this tool). In this way they risk to include in the study only MOH patients with dependency-behaviour. Furthermore it is not clear which is the destiny of those patients positive to the screening questions but presenting a SDS score lower than the cut-off level. They may have MOH as well and may represent another control group (MOH with low dependency receiving advice but not BI) Please clarify these points.

Headache classification. It is not clear who will make (and when) the ICHD-II diagnosis. At the moment of the follow-up by the first author? Please specify this point.

This question is very relevant but we believe that the referee may have misunderstood the design and have now tried to clarify it in the method section. We are not excluding patients under the SDS cut-off, on the contrary they also receive a structured intervention of the same type where we, however, cannot use the individual SDS score to underline our evaluation (“the SDS score shows you are at risk…”). The information to those that have high medication intake but not high SDS will also include information about the relationship between drug intake and headache and information about “safe limits” etc. This way we hope to be able to say something about the success of our scheme in the different groups no matter whether they have high SDS or not. In addition, we do not just use the SDS but also the DSM-IV dependency criteria (tested through the relevant part of the MINI interview) to try to assess dependence also through another instrument.

The above points have been addressed through additions in the manuscript (under Methods, Brief intervention, 1.) and a slight modification of fig 2.

Finally, the ICHD-II diagnosis will be made by the first author at the 3 month follow-up interview.

Two weeks recording of the headache diary is a very short period (for instance menstrual attacks or migrainous state may be responsible for false positives). I have participated in the validation of a basic headache diary in a large
multicentre study (Jensen et al 2011, please add to the references) (added) and we did not find any problem with the compliance with 1-month period of recording. I suggest to the authors to ask for a completion of the diary for 1-month period

In our pilot study of the methods we found that the diary was the largest problem regarding response rate – most participants filled it out once and it may well be that a 1 month diary would have been possible at the first time point – however the response rate went down when the second diary had to be filled in even though this also, as stated, was only for two weeks. Also, we would emphasise that in addition to compliance we considered simply the use of a diary over an extended time possibly to interfere with headache related behaviour and possibly also with headache medication and headache load. 2 weeks was a compromise we chose even though a full month would certainly have been expected to be more accurate. The argument about short term change such as in menstruation related migraine is valid but since these patients all have chronic headache and most of them have headache almost every day, we feel that even a 14 day diary period will have a large chance of catching a clear change in number of headache days.

Ethics.
The authors wrote that participating patients and GPs will give informed, written consent. What kind of informations they will receive? Are the authors able to exclude at this level info about medication overuse and the advantage to withdraw the overused drug?

Yes, the patients receive no information about medication overuse in the consent document. The information to the patients which was agreed to by the ethical committee simply states that the aim of the study is to examine how frequent headache is handled over time by the GPs and to help the GPs in diagnosing the headache and use this as basis for improving their treatment of chronic headache. This is for several reasons: i) for blinding purposes, ii) to avoid causing a changed behaviour in advance of the main party of the study and iii) to avoid the risk of medication overusers not wishing to participate in a study focusing clearly on medication overuse and thus dropping out.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
'I declare that I have no competing interests'