Author's response to reviews

Title: Diagnostic indices for vertiginous diseases

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Version: 2 Date: 18 August 2010

Author's response to reviews: see over
Dear Professor Bereczki,

thank you for considering our manuscript “Diagnostic indices for vertiginous diseases” for publication in BMC Neurology. The reviewers comments were helpful to improve the manuscript. Please find enclosed the revised version, and a point to point answer to the reviewers comments. All changes in the manuscript are printed in red.

Sincerely,

Otmar Bayer

Referee 1

Minor Essential Revisions:

1. Please use terminology or abbreviation consistently throughout the manuscript, such as benign paroxysmal positional vertigo (BPPV).

We changed all occurrences consistently to “benign paroxysmal positional vertigo”.

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München, 14.08.2010
2. Please justify why the short questionnaire is adequate for screening.

Thank you, we mentioned this in the Abstract (under Conclusions) and in the Discussion: “The diagnostic indices were developed as an instrument to preselect patients with vertiginous diseases using a simple screener on the basis of self reporting. Such a screener can never completely replace a medical consultation and a clinical examination of the patient.” However, it may save time and help generalists not specialized in vertigo. Diagnostic (usually more elaborate) questionnaires have become common in assisting the diagnosis of disorders like anxiety, depression, and headache. In epidemiological studies short questionnaires are widely used (e.g. Milde-Busch A et al., "Quality of life in adolescents with headache - Results from a population-based survey", Cephalalgia 2010).

3. It's arguable that the number of the patients in each group is not large enough for statistical analysis to make any conclusive outcomes. Please consider add more patients during revision.

We agree that the small number of patients namely in the MD and VM group is a limitation and mentioned this in the Discussion. However, the statistics used in the selection procedure take the sample sizes into account, potentially leading to less questionnaire items being included (compared to groups with a larger sample size) to avoid overfitting. Still, the AUCs for MD and VM were good. Although, statistics cannot “heal everything”, and it is certainly desirable to have more subjects. Unfortunately the study where these data were collected is over, and meanwhile the dizziness clinic was subjected to major organizational changes. This disables us to just handout some more questionnaires and would be methodologically questionable, since the analyses in this manuscript are based on consecutive patients (see Methods) in a certain diagnostic environment. However, as mentioned in the Discussion (under limitations and under conclusions) we plan to validate the questionnaire in a new study, which will have more subjects.

Referee 2
The authors developed diagnostic indices for four prevalent vertiginous diseases, phobic postural vertigo, benign paroxysmal positional vertigo, Meniere’s disease, and vestibular migraine. Using logistic regression analysis, they built diagnostic scores from preselected seven questions, and suggested cut-off points for each disorder. The screening questionnaire provided by the authors is simple and would be useful especially in epidemiological studies if validated further in a larger number of patients. However, there are several concerns and flaws of this study.

Major compulsory revision:

1. **The authors should provide diagnostic criteria used for each disorder.**

We added the following text to the discussion. “The analyses were based on clinical diagnoses (see Methods) rather than on restrictive inclusion criteria, such as used e. g. in clinical trials. Although the latter approach has the advantage of high diagnostic accuracy, it restricts the study sample to typical patients with clear syndromes, which does not always match with clinical reality. Diagnostic criteria applied in the clinic were: for PPV [BrandtVertigoPPV2003]. BPPV was diagnosed if reproducible by positioning maneuvers, or in case of a distinctive history with other causes ruled out. MD according to the AAO-HNS [AAO-HNS_CHE1995][Stapleton2008] criteria, if hearing loss was not audiologically documented before or in the ENT department, anamnestic hearing loss was accepted. VM patients fulfilled the criteria of definite or probable migrainous vertigo [Neuhauser2001].”


2. **Please specify the number of questionnaire excluded due to missing data.**

What is mean by “missing data”? The authors need to analyze the reasons for missing data and diagnoses of the patients excluded due to missing data since
this issue may be related to inapplicability of the questionnaire to the specific group of patients.

The question of excluded questionnaires is an important issue. We therefore compared the patients which could not be included to those used in our analysis. An overrepresentation of patients with one of the four diagnoses of interest among the excluded patients could give raise to concern that the questionnaire is not suitable to a specific group of patients. However, this comparison (excluded: see table below, included: PPV 53 (40.5 %), BPPV 19 (14.5 %), MD 11 (8.4 %), VM 14 (10.7 %)) yielded no overrepresentation of the four diagnoses of interest among the excluded, except for MD (n. s.; Fisher's exact test for false rejection of H0, that P_MD_excluded = P_MD_included, results in p = 0.43).

Table: Patients not included in the analysis.

<table>
<thead>
<tr>
<th>diagnosis</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPPV</td>
<td>12</td>
<td>16.1</td>
</tr>
<tr>
<td>Vertigo with psychogenic origin</td>
<td>12</td>
<td>16.1</td>
</tr>
<tr>
<td>MD</td>
<td>8</td>
<td>12.9</td>
</tr>
<tr>
<td>Vestibular paroxysmia</td>
<td>3</td>
<td>4.8</td>
</tr>
<tr>
<td>Orthostatic vertigo</td>
<td>3</td>
<td>4.8</td>
</tr>
<tr>
<td>VM</td>
<td>2</td>
<td>3.2</td>
</tr>
<tr>
<td>multifactorial vertigo</td>
<td>2</td>
<td>3.2</td>
</tr>
<tr>
<td>tension-type headache</td>
<td>2</td>
<td>3.2</td>
</tr>
<tr>
<td>cerebellar syndrome</td>
<td>2</td>
<td>3.2</td>
</tr>
<tr>
<td>other vertigo</td>
<td>9</td>
<td>14.5</td>
</tr>
<tr>
<td>vertigo of unclear origin</td>
<td>7</td>
<td>11.3</td>
</tr>
<tr>
<td>total</td>
<td>62</td>
<td>100.0</td>
</tr>
</tbody>
</table>

(This table was already published and is available at http://www.biomedcentral.com/1471-2377/9/29 , Table 5)

Alltogether, 62 (32 %) of the patients eligible could not be included in the analysis. These either did not return the questionnaire (major part), filled out less than 10 % of the questionnaire, or withdrew their consent. Keeping in mind, that the original questionnaire where the items for the diagnostic indices were embedded was 16 pages long, it is likely to obtain better participation in future studies by shortening the questionnaire, i. e. restricting it to the items used for the diagnostic indices.
We amended the discussion to address this issue (“62 (32 %) of the patients ... p = 0.43”).

3. It should be clearly stated that the patients were allowed to check only one answer for each question. This issue is related to the following concerns.

We added “Patients are allowed to check only one answer per question, except for the 2nd and 3rd question.” to the explanatory matter of Table 1. The 2nd and 3rd question listed in Table 1 ask for the presence of symptoms which may result in more than one answer, although usually only one symptom is checked by the patient. Questions about intensity or frequency are restricted to one answer each.

4. In my view, the questionnaires seems inapplicable to the patients with vertigo from more than one cause, i.e. phobic postural vertigo following organic vestibular disorders, vestibular migraine and PPV, and complicated BPPV. The authors should include discussions on this matter.

We added this matter to the Discussion (“This is especially ... or complicated BPPV.”).

5. Page 5, 2nd paragraph: In contrast to the authors’ description, PPV requires only four items for diagnosis in Table 1. Please check on this.

PPV takes into account 5 items, however, 2 of them are grouped under one question “What kind of vertigo do you have?”: The items “rotational vertigo” and “feeling of being in a lift” are both considered in the PPV score.

This misunderstanding is probably prompted by an inconsistency in the Table 1 heading, which we corrected.

6. Page 6, 2nd paragraph: The authors description on the diagnostic indices for VM does not match with the contents in Table 1: “as permanent vertigo” in the Table instead of “appearing in attacks”, and “like on a roundabout” in the Table instead of “like on a boat”

Thank you for pointing us to these errors which we corrected in the text, after rechecking the analysis script which confirmed Table 1 to be right.
8. Page 13, Table: According to the caption, the superscripts in the Item (How often do you have sweating/nausea/vomiting?) for diagnosis of MD are confusing, and delete “0*.98, 1*.98, 2*.98, and 3*.98” in the box.

We have indeed no explanation for the superscripts\(^1\) and deleted them. In contrast, we would like to keep the “0*.98, 1*.98, 2*.98, and 3*.98” to illustrate the log-linear relationship between frequency of sweating/nausea/vomiting and the odds of MD. (We investigated this relationship before, using dummy coding before coming up with ordinal coding, thereby saving degrees of freedom in the logistic model.)

**Minor essential revisions:**

1. Please unify the terminology for the disorders: “Benign paroxysmal vertigo” in the abstract and figure caption and “benign paroxysmal positional vertigo” in the text (Page 3, first line), “Phobic vertigo” in the abstract and Intro, and “phobic postural vertigo” in the figure caption.

Done.

2. Please consider using the word, “persistent” rather than “permanently” when describing occurrence of vertigo.

Thank you, as we aim to test the questionnaire in other languages, we are grateful for such kind of improvements.

3. The 4 figures may be put into one.

We indeed considered to do so before and have put them together into one.

**This manuscript contains numerous grammatical errors.**

1. Page 2, first line of Intro: praxis -> practice
2. Page 2, second line of Intro: delete “about”
3. Page 3, first line of Methods: “condensing of” -> “condensing”
4. Page 3, 9th line of Methods: insert “,” before “orthoptic examination”
5. Page 3, first line of 2nd paragraph of Methods: insert “,” or “;” before “PPV”
6. Page 4, 2nd paragraph: insert “(“ before “defective hearing”

We have rather dropped the “)” after “drop seizures”.
7. Page 4, 3rd paragraph: insert “,” after “mentioned above”
8. Page 4, 3rd paragraph: insert “,” after “the diagnostic score”
9. Page 4, 3rd paragraph: “The effects estimates” should be read as “The effect estimates”.
10. Page 9, 2nd paragraph: “higher” -> “larger”
11. Page 9, 2nd paragraph: “proof” -> “prove”
12. Page 9, 2nd paragraph: “holds” -> “hold”
13. Table 2, caption: “und” -> “and”

Thank you for all your effort helping us towards a manuscript with correct (or at least almost correct) language.