Treatment of Vertigo with a Homeopathic Complex Remedy Compared with Usual Treatments

A meta-analysis of clinical trials

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Summary

The increasing interest in alternative medical practices has led to a number of controlled studies on herbal and homeopathic agents. This paper presents the results of a meta-analysis of four recent clinical trials evaluating the homeopathic preparation Vertigoheel® (VH) compared with usual therapies (betahistine, Ginkgo biloba extract, dimenhydrinate) for vertigo in a total of 1388 patients. Two trials were observational studies and the other two were randomised double-blind controlled trials. The duration of treatment (6–8 weeks) and dosage were comparable in all studies. Treatments were evaluated for the variables "number of vertigo episodes", "intensity of episodes" and "duration of episodes". As the studies differed in the age of patients and in the baseline values of vertigo, the individual reductions of number, intensity and duration of episodes were adjusted on equal age and baseline values (total means). An analysis of variance (with studies as random effects) showed no relevant influence of studies on the adjusted reductions and no relevant interaction between studies and treatment effects. The meta-analysis of all four trials showed equivalent reductions with VH and with control treatment: mean reduction of the number of daily episodes 4.0 for VH and 3.9 for control (standard error 0.11 for both groups); mean reduction of the duration (on a scale 0–4) for VH 1.1 and for the control 1.0 (standard error 0.03 for both groups); mean reduction of the intensity (on a scale 0–4) for VH 1.8 and for the control 1.8 (standard error 0.03 for both groups). In the non-inferiority analysis from all trials, VH was non-inferior in all variables. The results show the applicability of meta-analyses on the data from studies with homeopathic drugs and support the results from the individual studies indicating good efficacy and tolerability of VH in patients with vertigo.

Key words

- Homeopathy
- Vertigo
- Vertigoheel®, efficacy, meta-analysis, tolerability

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Zusammenfassung

Behandlung des Schwindels mit einem homöopathischen Komplexpräparat im Vergleich mit anderen Therapieformen / Eine Meta-Analyse klinischer Studien

Es werden die Ergebnisse einer Meta-Analyse von vier klinischen Studien dargestellt, in denen die Wirksamkeit und Verträglichkeit des homöopathischen Arzneimittels Vertigoheel® (VH) bei der Behandlung des Schwindels mit der von anderen gebräuchlichen Arzneistoffen (Betahistin, Ginkgo biloba Extrakt, Dimenhydrinat) bei insgesamt 1388 Patienten verglichen werden. Zwei dieser Studien waren randomisierte, doppelblinde, kontrollierte Studien, die beiden anderen offene Beobachtungsstudien. Primäre Zielgrößen der Wirksamkeit waren in allen Studien die Verbesserung der Anzahl, Intensität und Dauer der täglichen Schwindelattacken. Die Behandlungsdauer (6–8 Wochen) und Dosierung kann bei allen Studien als vergleichbar angesehen werden. Die Studien unterscheiden sich im Alter der Patienten und der Ausgangslage (Zahl der täglichen Attacken). Um diese Unterschiede auszugleichen, wurden in der Meta-Analyse die individuellen Änderungen von Anzahl, Intensität und Dauer der Attacken auf gleiches Alter und gleiche Ausgangslage (Gesamtmittel) adjustiert. Eine Varianzanalyse (mit den Studien als Zufallsfaktor) ergab für die adjustierten Änderungen keinen bedeutsamen Studieneinfluß und auch keine Wechselwirkung zwischen Studien- und Behandlungseinfluß. Die Ergebnisse der vier Studien konnten somit zusammengefaßt werden. Dabei ergab sich für alle drei Zielgrößen eine äquivalente Besserung unter VH und der jeweiligen Kontrollbehandlung: Reduktion der mittleren Zahl der Episoden bei VH 4,0 und bei der Kontrolle 3,9 (Standardfehler 0,11); Reduktion der mittleren Dauer (Scorewert auf einer Skala von 0–4) bei VH 1,1 und bei der Kontrolle 1,0 (Standardfehler 0,03); Reduktion der mittleren Intensität (Scorewert auf einer Skala von 0–4) bei VH 1,8 und bei der Kontrolle 1,8 (Standardfehler 0,03). Die Hypothese der Nichtunterlegenheit von VH konnte bei allen Studien und in der Meta-Analyse mit einer Wahrscheinlichkeit von 97.5 % angenommen werden. Die Analyse bestätigt somit die Ergebnisse der einzelnen Studien, die eine klinisch relevante Wirksamkeit und Verträglichkeit von VH bei Patienten mit Schwindel gezeigt haben.

1. Introduction

Vertigo is the most common form of dizziness; a feeling of unsteadiness, spinning, whirling, or exaggerated motion when stationary. It is usually accompanied by nausea and loss of balance. Sweating, tinnitus and collapse are commonly associated phenomena. Vertigo may be caused by several factors, including head injury, viral upper respiratory infection or cerebrovascular disease. Other causes include tumours, inflammation of or damage to nerves, or the use of drugs that affect the inner ear, including aminoglycoside antibiotics, acetylsalicylic acid, cisplatin and furosemide. Most cases of vertigo occur with nystagmus, an abnormal, rhythmic, jerking eye movement.

Common pharmacological interventions for vertigo are meclizine, dimenhydrinate, promethazine, scopolamine, atropine and diazepam. These drugs have been associated with side effects, such as drowsiness, malaise, visual problems and dry mouth [1], which may be one reason why alternative medical practices are often used to treat vertigo. The interest in complementary medicine is increasing worldwide [2, 3], but in spite of this growing attention, the possible benefits of treatments are often not assessed in proper controlled studies [4].

Vertigoheel®[1)] (VH) is a homeopathic preparation of diluted plant and mineral extracts (listed in Table 1) and homeopathically attenuated petroleum that has long been available over-the-counter in several countries with an established record of general use in the treatment of vertigo [5]. The recent interest in evaluating alternative medical practices in a more rigorous manner is reflected in a number of controlled studies on the effects of VH since 1998. This situation is in marked contrast to that for many other agents used in complementary medicine.

The presence of a number of studies on VH in patients with the same indications allows for a systematic review and meta-analysis of the data. Meta-analyses are a common tool in the evaluation of treatment effects in clinical studies [6] and have found a large application in recent decades across a wide range of indications [7, 8]. The outcomes of meta-analyses show smaller random errors and increased precision compared with the individual trials.

The current work presents a systematic review and meta-analysis of four studies on VH with different control agents. The studies comprise a total of 1368 patients. In this meta-analysis we focused on studies with active controls and did not consider placebo-controlled trials. The four trials used three different comparator substances, betahistine (CAS 5638-76-6), Ginkgo biloba extract and dimenhydrinate (CAS 523-87-5), which provided a spectrum of controls reflecting the varied approaches to vertigo therapy in everyday clinical practice.

[1)] Manufacturer: Biologische Heilmittel Heel GmbH, Baden-Baden (Germany).

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Table 1: Constituents of Vertigoheel.

Anamirta cocculus (levant nut)
Conium maculatum (poison hemlock)
Ambra grisea (ambergris)
Petroleum rectificatum (attenuated petroleum)

2. Methods

Four trials on VH in vertigo have been published and were used as the basis for this analysis [9–12]. Of these, two were randomised controlled trials (RCTs) [9, 12] and two were observational studies (OSs). For inclusion in the analysis, trials had to meet the criteria of comparing VH with an active treatment, have a minimum duration of 6 weeks, and to have completed before January 2004.

Data on baseline characteristics and on effects of treatment during follow-up were obtained from published sources and from investigators or trial sponsors as needed. Data were checked for completeness and accuracy.

All studies evaluated the effects on the three variables "number of vertigo episodes", "intensity of episodes" and "duration of episodes". The variable "number of episodes" was quantified as numbers per day. Intensity and duration of episodes were quantified on a scale from 0–4. For intensity of episodes, the levels were: 0 = no symptoms; 1 = mild symptoms; 2 = moderate; 3 = moderate-to severe and 4 = severe symptoms. The variable "duration of episodes" was graded as 0 = no vertigo or an episode lasting less than 2 min; 1 = duration 2 to 10 min; 2 = duration 11 to 60 min; 3 = 1–6 h and 4 = vertigo episodes lasting longer than 6 h. These scales were used for all studies evaluated.

For the meta-analysis, the reductions in mean numbers of episodes and intensity and duration scores, respectively, were used as variables, adjusted for age and baseline values. Mean differences between the VH and control treatment groups and their 95 % confidence intervals were calculated for all variables. Randomised controlled trials and OSs were analysed separately, as well as in one overall analysis of all four trials. The homogeneity of the adjusted mean differences between VH and control between the studies was tested using an analysis of variance with the studies as random effects. All analyses were done using SPSS 11.5 for Windows (SPSS Software, Munich, Germany).

As all studies included active comparators, the outcomes in the individual trials were not analysed for superiority. Instead, the overall outcomes were analysed for non-inferiority of VH versus active control. This approach was followed for the meta-analysis. The criterion for asserting non-inferiority was that the 95 % confidence interval for treatment differences between the VH group and the control group remained above the value –1.0 for the variable "number of episodes" and above the value –0.5 for the variables "duration of episodes" and "intensity of episodes". This limit of non-inferiority corresponds to 10 % of the maximal range of each scale. The level of significance of each analysis was 5 %.

No analysis was undertaken on the tolerability or the occurrence of adverse events. However, descriptive data were captured in the respective publications to provide a general description of the tolerability of VH compared with the respective comparator treatments.

3. Results

Four trials were included in the meta-analysis, two RCTs and two OSs. Two studies, one RCT and one OS, used betahistine as comparator. The other RCT used Ginkgo biloba extract and the other OS dimenhydrinate as control.

Table 2: Age and baseline episodes of the four trials included in the meta-analysis.

Study	Treatment group	n	Age mean ± SD	Baseline episodes/day (mean ± SD)		
				Number	Intensity	Duration
Study 1 RCT	VH	53	50.0 ± 16.3	4.5 ± 2.0	2.6 ± 0.5	1.7 ± 1.0
	Betahistine	52	54.8 ± 15.9	4.0 ± 1.8	2.5 ± 0.5	1.5 ± 1.1
	Total	105	50.8 ± 15.3	4.3 ± 1.9	2.6 ± 0.5	1.6 ± 1.1
	Significance p		0.211	0.208	0.324	0.390
Study 2 RCT	VH	79	69,6 ± 6,0	6,4 ± 5,5	2,4 ± 0,5	1,7 ± 1,2
	Ginkgo biloba	75	69,4 ± 5,8	5,6 ± 4,7	2,4 ± 0,6	1,7 ± 1,2
	Total	154	69.5 ± 5.9	6.0 ± 5.2	2.4 ± 0.6	1.7 ± 1.2
	Significance p		0.848	0.367	0.831	0.770
Study 3 OS	VH	205	62.6 ± 16.7	5.1 ± 4.0	2.5 ± 0.6	1.6 ± 1.0
	Betahistine	272	62.3 ± 15.2	6.2 ± 4.7	2.4 ± 0.7	1.4 ± 1.0
	Total	477	62.4 ± 15.9	5.7 ± 4.5	2.5 ± 0.7	1.5 ± 1.0
	Significance p		0.811	0.008	0.340	0.116
Study 4 OS	VH	298	56.9 ± 19.0	4.9 ± 3.5	2.4 ± 0.7	1.4 ± 1.0
	Dimenhydrinate	354	58.2 ± 17.5	5.0 ± 4.2	2.5 ± 0.7	1.4 ± 1.1
	Total	652	57.6 ± 18.2	5.0 ± 3.9	2.4 ± 0.7	1.4 ± 1.1
	Significance p		0.397	0.892	0.581	0.615

VH = Vertigoheel, SD = standard deviation, OS = observational study, RCT = randomised controlled trial, n = number of patients.

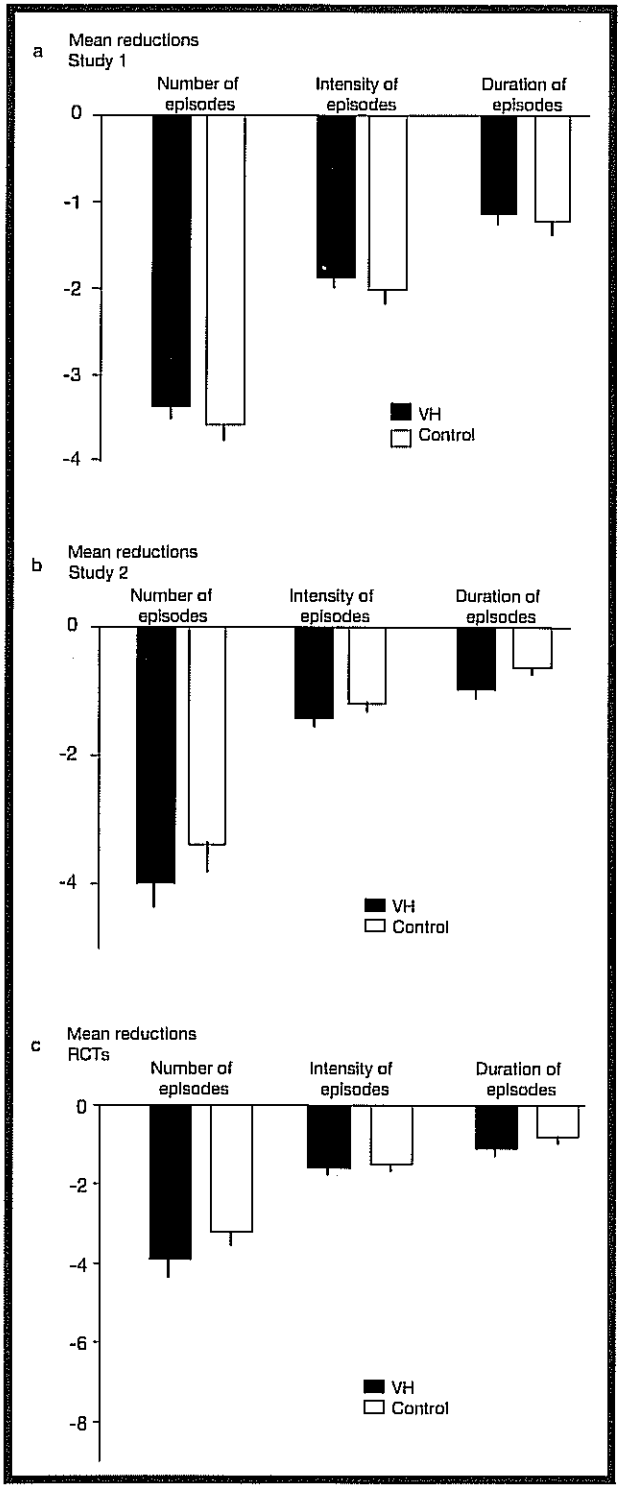

Fig. 1: Reduction in number, intensity and duration or vertigo episodes with Vertigoheel (VH) and control treatments in randomised controlled trials (RTCs) with a) betahistine and b) Ginkgo biloba; c) meta-analysis of both trials. Means and standard errors of the mean are shown, adjusted for age and baseline levels.

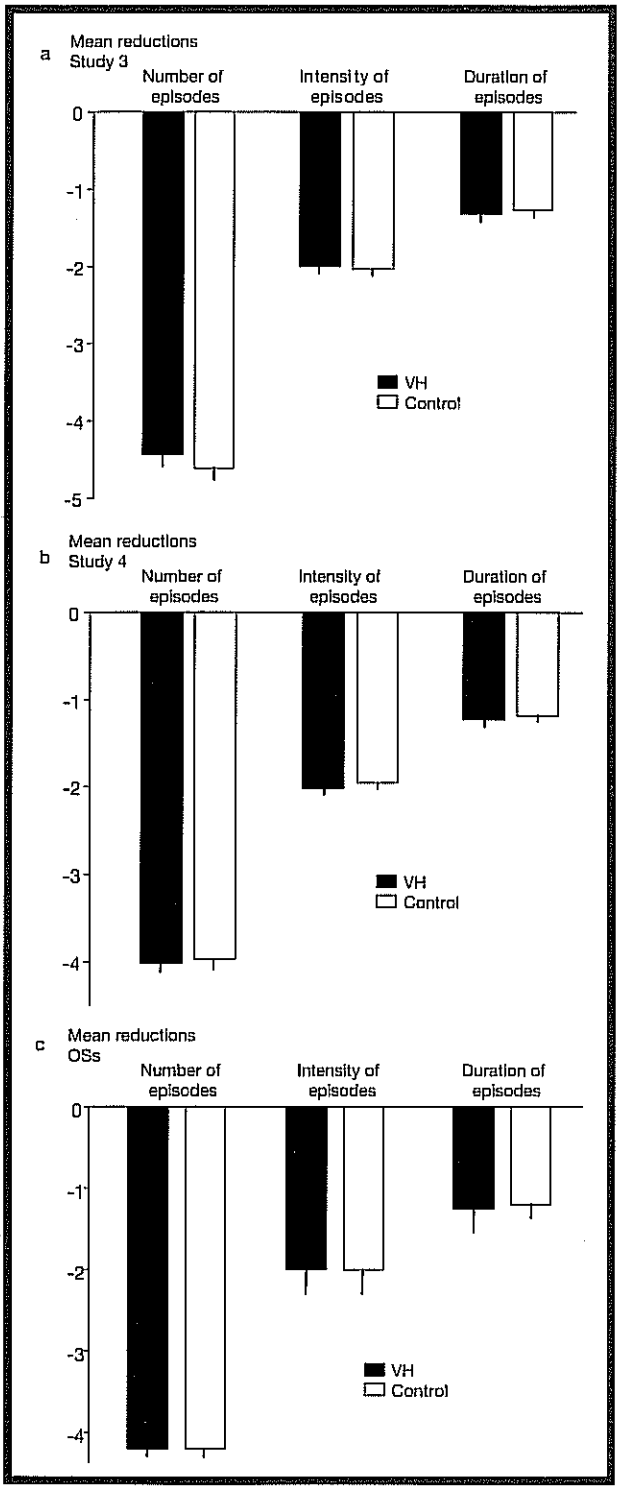

Fig. 2: Reduction in number, intensity and duration or vertigo episodes with Vertigoheel (VH) and control treatments in observational studies (OSs) with a) betahistine and b) dimenhydrinate; c) meta-analysis of both trials. Means and standard errors of the mean are shown, adjusted for age and baseline levels.

A summary of the demographics and baselines of number, intensity and duration of daily vertigo episodes of the trials is given in Table 2. The total number of patients included was 1388; 623 of whom received VH and 753 the control medication. In RCTs a total of 259 patients was enrolled, in OSs 1129. Whereas the 4 studies differed in mean patient age (50 to 70 years) and baseline number of daily vertigo episodes (4.3 to 6.0), there were no significant differences between the treatment groups within the studies. The studies were

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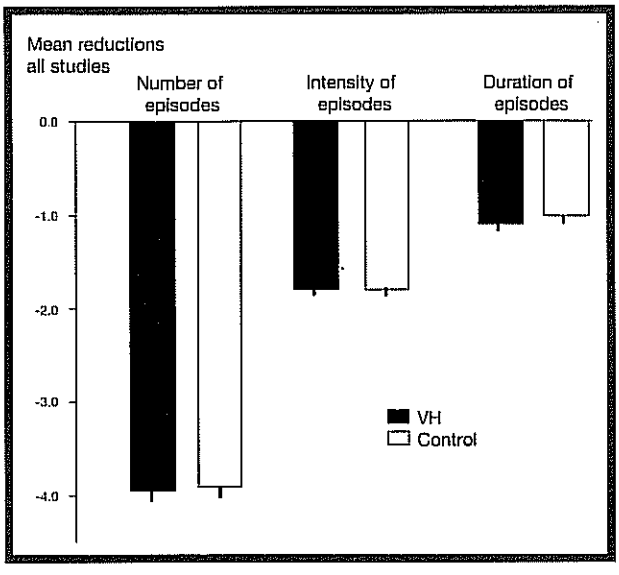

Fig. 3: Meta-analysis of all four studies (VH = Vertigoheel).

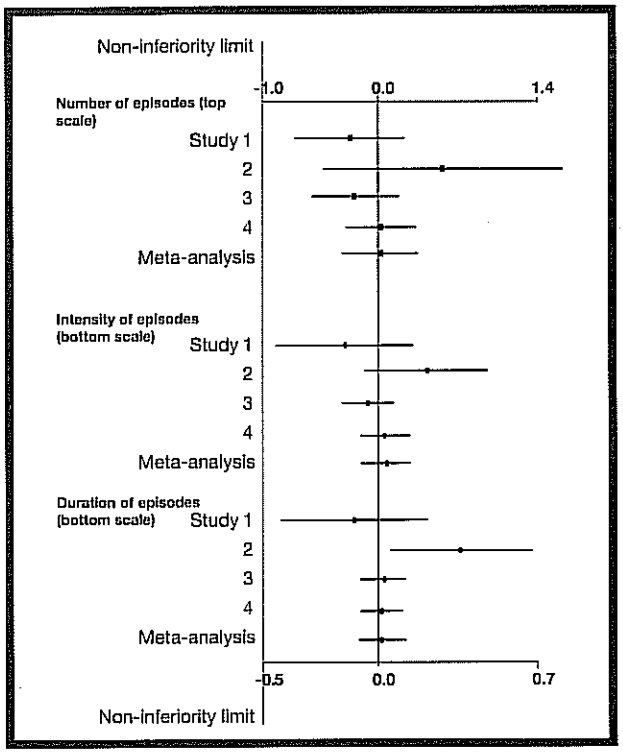

Fig. 4: Non-inferiority analysis of Vertigoheel (VH) versus other treatments for vertigo. Note that the scales are different: for the variable "number of episodes" the top scale is used; for the other variables the bottom scale applies. The dotted line indicates the limit for non-inferiority.

homogenous in intensity and duration scores (2.4 to 2.6 and 1.4 to 1.7, respectively). The mean duration of follow-up ranged from 6 weeks in the RCTs and 8 weeks in the OSs.

All trials provided information on all 3 outcomes included in the analysis. Primary endpoints were the reductions of number, intensity and duration of the daily vertigo episodes between baseline and end of the study. As there were difference in age and baseline values of the episodes between the studies, the individual reductions were adjusted to the mean age and baseline values of the study using an analysis of covariance. The adjusted mean reductions in the VH and control groups are shown in Fig. 1 for the RCTs and in Fig. 2 for the OSs.

The homogeneity of the mean reductions between the studies and a possible interaction between studies and treatment differences were tested using a mixed model with the studies as random and treatments as fixed effects. No significant ($p > 0.01$) differences in mean reductions between the studies and no interactions between studies and treatment differences were found. This analysis verified the methodological soundness of combining the reductions in the individual studies in the meta analysis.

The results of the meta analysis are shown in Fig. 3. On all three endpoints mean reductions were highly similar in both treatment groups: mean reduction of the number of episodes: VH 4.0, control 3.9 (SEM 0.11); mean reduction of duration score: VH 1.1, control 1.0 (SEM 0.03); mean reduction of intensity score: VH 1.8, control 1.8 (SEM 0.03).

To test for non-inferiority, the 95 % confidence intervals for the differences in mean reduction between VH and the control group was calculated. The intervals are shown in Fig. 4. The hypothesis of non-inferiority is accepted (with probability 97.5 %), if the lower limit of the confidence intervals falls within the limits of 10 % of the maximal range of each scale: > -1 in the number of episodes and > -0.5 in the intensity and duration scores, respectively. These conditions were fulfilled both in the meta-analysis and in the analyses of the respective individual studies. Thus, the efficacy of VH in the treatment of vertigo (i.e. reduction of number, intensity and duration of vertigo episodes) can be considered as non-inferior to that of the control medications used in the individual trials.

The tolerability was not included in the meta-analysis but published data from 4 studies describe a generally very favourable tolerability profile for all therapies. The total number of reported treatment-related adverse events in all 4 studies was 10, of which 5 were seen with VH, 2 with Ginkgo biloba, 2 with betahistine and 1 with dimenhydrinate. Treatment-satisfaction scores were generally very good, with the percentage highest satisfaction scores ranging from 80 % (Ginkgo biloba) [12] to more than 90 % (all other therapies).

4. Discussion

This meta-analysis of 4 studies on the efficacy of the homeopathic drug VH compared with common treatments for vertigo shows that the homeopathic remedy is not inferior to the comparator medications measured on the number of vertigo episodes, their duration and intensity.

The approach of meta-analysis of data from multiple trials in patients with the same indication and addressing the same question, in this case the non-inferiority of VH versus other treatments for vertigo, reduces random errors and increases the precision of estimates compared with the individual trials. In the current case, all individual trials reported similar outcomes and the main added value of the meta-analysis was to increase the power of the non-inferiority analysis, where the 95 % confidence intervals of the treatment differences were markedly smaller in the combined analysis compared with individual studies (Fig. 4). The relative treatment effects were similar for all variables, although the most prominent absolute reductions were seen in the number of episodes. The results from the meta-analysis make the individual results seem very unlikely to have been due to a play of chance.

There were many similarities between the included studies which make them suitable for a meta-analysis. All trials studied the same variables using the same means of quantification. All variables were graded on a scale from 0 to 4 except for the variable "number of episodes" which was simply given as numbers of vertigo attacks per day. A difference between the trials lay in the comparator substances used: betahistine, Gingko biloba extract and dimenhydrinate, respectively. Betahistine is commonly used for treatment of vertigo and diseases such as Menier's disease [13]. Ginkgo biloba extract is a widely used alternative medication for vertigo, and benefits compared with placebo have been demonstrated in studies of both vestibular and non-vestibular vertigo [14] Dimenhydrinate is a commonly available over-the-counter combination of two agents, diphenhydramine and chlorotheophylline [15]. This use of different control substances in the analysed trials is not commonly seen as an obstacle to reliable meta-analyses and indeed, some authors expressly recommend the inclusion of differently designed trials in a proper meta-analysis [16]. Further, all studies used comparable doses, as recommended by the respective manufacturers, for VH and the different control agents. Thus, treatment efficacies can be expected to be similar in all 4 studies. This is an important point as the outcomes of meta-analyses can be skewed by the inclusion of very large trials with inappropriately given treatment doses in one of the treatment arms, which reduces the overall reported effect of treatment in this arm. Such effects can be seen, e.g. in analyses of antihypertensive treatments [17]. Moreover, since most of the studies attempted to mirror clinical practice in vertigo therapy, which is characterised by a lack of consensus as to preferred regimen, the variety of comparator substances reflects the current practices. Thus, the results of this meta-analysis should be relevant to a wide spectrum of clinical practices.

The individual non-inferiority analyses consistently indicated non-inferiority of VH over the control therapies, with all left-hand borders of the 95 % confidence intervals comfortably within the limit defining non-inferiority (Fig. 4). Indeed, the border of the confidence interval for the reduction in the duration of episodes with VH versus Ginkgo biloba does not cross the line of unity, indicating superiority of VH on this variable, although it should be noted that none of the studies was designed to prove superiority. This possible superiority of VH on reducing the intensity of vertigo could not be verified in the meta-analysis and must be considered as either a specific advantage over Ginkgo biloba or as a statistical play of chance in the respective study.

The trials included were all non-inferiority trials. Such analyses are commonly carried out when there are ethical obstacles to a placebo-controlled design [18]. In the case of the VH trials, there would be no ethical objections to placebo-controlled design, however, the investigators wanted to capture a situation closer to clinical reality than placebo-controlled trials are able to provide [9–12]. Non-inferiority analyses differ from trials designed to show differences between treatments in that the null hypothesis in equivalence trials is that outcomes between treatment arms are different [18]. One consequence of the design of non-inferiority analyses is a greater dependence on high treatment adherence for a reliable outcome. Non-inferiority analyses in trials with a large number of discontinuations will show results biased towards non-inferiority, as the statistical power to show possible differences is reduced and the overall differences in outcomes shift towards zero [19]. Thus, it is important to have low discontinuation rates and high persistence with the medication. All 4 trials in the current meta-analysis had very high retention rates and in addition the relative short duration of only 6–8 weeks contributed to low numbers of patients dropping out of the studies. Thus, the conclusions from the meta-analysis appear quite robust.

Although no specific analysis of tolerability was carried out, the published data in all 4 trials supported the general good tolerability of complementary medications, specifically VH in this case. Tolerability scores may well vary between RCTs and observational studies as both investigators and patients in RCTs are more likely to look for, adjudicate and report adverse events than patients in studies closer to clinical reality. This is reflected in the numbers of reported adverse events in the studies analysed: the two RCTs, although comprising some 20 % of the total number of patients, reported 90 % of all treatment-related adverse events.

In conclusion, the increased interest in alternative medical practices and the growing number of controlled trials with homeopathic and other complementary medications are opening the way for conducting meta-analyses and systematic reviews of published data. Such analyses will add additional value to the study of non-standard medical practices and, it is hoped, help resolve the issues of sustainability of claims

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made in the individual studies. In the case of the VH trials in the present work, the meta-analysis supports the consistently demonstrated efficacy and tolerability of this homeopathic preparation, effects that seem to be at least as good as for standard therapies.

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