International Tinnitus Journal. 2010;16(1):14-24.

Effects of Betahistine on Patient-Reported Outcomes in Routine Practice in Patients with Vestibular Vertigo and Appraisal of Tolerability: Experience in the OSVaLD Study

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Abstract

This was a 3-month multicentre, open-label post-marketing surveillance study of betahistine (24 mg b.i.d. or 16 mg t.i.d.) in patients with vertigo of peripheral vestibular origin. Study endpoints comprised on-treatment changes in the Dizziness Handicap Index (DHI), Hospital Anxiety and Depression Score (HADS) and the Short-Form (SF)-36v2. Total DHI score improved 37.2 points (of a 100-point scale) following betahistine treatment. Corresponding improvements occurred in all three DHI scale domains (all $p < 0.001$ vs baseline). Betahistine therapy was also accompanied by progressive, significant improvements in both HADS-A and HADS-D scores ($p < 0.001$), and improvements in the distribution profiles of anxiety and depression scores. Significant improvements in the Physical Component Summary and Mental Component Summary scores of the SF-36v2 were recorded during betahistine treatment. Betahistine was generally well tolerated. A total of 76 adverse drug reactions (ADRs) were recorded in 49 patients (2.4%), of which 75 were classified as mild or moderate and 54 were possibly related to betahistine. ADRs led to study drug discontinuation in 17 patients. These data illustrate that treatment with betahistine 48 mg/day in patients with recurrent peripheral vestibular vertigo is associated with improvements in objective measures of health-related quality of life and satisfactory tolerability.

Keywords: betahistine; vertigo, dizziness; anxiety, depression. quality-of-life.

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INTRODUCTION

Betahistine is widely used in the management of vertigo but clinical research into this indication[1-3] has not been accompanied by extensive investigation of its impact on health-related quality of life (HRQoL). In order to obtain a wider perspective on this matter, we undertook an observational study to gather patient-reported outcome information about dizziness, generic HRQoL and symptoms of anxiety and depression in a diverse population of patients suffering from peripheral vestibular vertigo.

The study, known by the acronym OSVaLD (A Three-Month Observational Study in Patients Suffering from Recurrent Peripheral Vestibular Vertigo to Assess the Effect of Betahistine 48 mg/day on Quality of Life and Dizziness Symptoms), was conducted in 13 countries with disparate social and linguistic characteristics.

We used the Dizziness Handicap Index (DHI), the Hospital Anxiety and Depression Score (HADS) and the Short-Form (SF)-36v2 to evaluate the effect of betahistine 48 mg/day (as 24 mg b.i.d. or 16 mg t.i.d., according to local prescribing guidance) on, respectively, dizziness, symptoms of anxiety and depression, and quality of life during 3 months of treatment in the context of routine clinical practice. In addition, the tolerability profile of betahistine was monitored.

Preliminary baseline data from this study have been the subject of a separate publication[4]. We now report the final primary findings from OSVaLD.

METHODS

Overview

This was an international, multicentre, open-label, post-marketing surveillance (PMS) study of betahistine in patients with vertigo of peripheral vestibular origin, undertaken in the context of routine primary care.

Betahistine 48 mg/day (as 24 mg b.i.d. or 16 mg t.i.d., according to the approved product information and the provisions of local national labels) was prescribed either as monotherapy or as adjunctive therapy when current anti-vertigo therapy was not sufficient or not tolerated. Prior and concomitant medications could be used as needed.

Inclusion criteria for the study comprised: history of vertigo attacks of peripheral vestibular origin not exceeding 5 years; baseline total DHI score $\geq$ 40; and prescription of betahistine compatible with local labelling. The only exclusion condition was the presence of contraindications to betahistine, as identified in the relevant summary of product characteristics.

A series of three clinic visits was specified in the study design: (i) a baseline assessment visit; (ii) a follow-up visit 1 month after starting betahistine treatment; and (iii) a final visit 3 months after betahistine treatment or at early termination of betahistine therapy. These visits were to be incorporated into the treating physician's usual pattern of follow-up consultations.

Endpoints and statistical considerations

Efficacy

Three well-established instruments – the DHI, HADS and SF-36v2 – were used to evaluate efficacy. The primary efficacy outcome was the change from baseline in total DHI score at 3 months.

The DHI, HADS and SF-36v2 were assessed for the efficacy population. The efficacy population of this study was defined as all patients allocated to treatment who (a) received a prescription of betahistine at baseline and who had at least one subsequent clinic visit (follow-up, final or endpoint visit) and (b) had a score calculated for at least one of the three specified outcomes scales (DHI total, SF-36v2 [both summary scores] or HADS [both anxiety and depression scales]) at the baseline visit and at least one post-baseline visit.

Details and descriptions of all three scales have been published elsewhere[5-14]. In brief, the DHI consists of 25 questions. For each question, a "Yes" response scored four points, a "No" response scored zero points and a "Sometimes" response scored two points. The total DHI score was the sum of the 25 item scores. Within the total score, individual scores were generated for the three subscales "physical" (seven questions), "emotional" (nine questions) and "functional" (nine questions).

The HADS consists of 14 questions, all of which were scored on a 0–3 scale. Two scores were calculated: the anxiety score (HADS-A) and the depression score (HADS-D). The same categories were applied to both subscale scores: 0–7 points = normal, 8–10 points = mild, 11–14 points = moderate and 15–21 points = severe.

For the DHI and HADS, if at least 50% of items were completed in any given subscale, any missing values were assumed to be equal to the mean of the relevant subscale. If fewer than 50% of items were completed, the subscale and scale scores were not calculated.

The SF-36v2 is an extensively documented instrument that consists of 36 questions. Ten scores from the SF-36v2 were analysed using SF Health Outcomes™ Scoring Software. These 10 scores comprised: two summary scores (Physical Health Component summary [PCS] and Mental Health Component summary [MCS]); and eight domains of HRQoL (Physical Functioning [PF]; Role limitation due to Physical health [RP]; Bodily Pain [BP]; General Health perception [GH]; Vitality [VT]; Social Functioning [SF]; Role limitation due to Emotional problems [RE]; and Mental Health [MH]).

Analysis of SF-36v2 data was based on norm-based scoring results to facilitate interpretation.[12,13] To this end, data were scored on a 0–100 scale in relation to the norms for the 1998 U.S. general population. All scores < 50 were interpreted as below the U.S. general population norm; scores ≥ 50 were interpreted as above the U.S. general population norm.

Missing data on the SF-36v2 Health Surveys was dealt with by substituting a person-specific estimate derived from the mean response to the answered items in the same scale when a respondent had answered at least one-half of the items on that scale; if fewer than half the items were completed the score was considered as missing.

Each of the efficacy parameters (DHI total score, HADS total score, SF-36v2 scores and scores on the different subscales) were summarized by descriptive statistics by visit, including last visit on-treatment. Changes from baseline for all efficacy parameters were presented by descriptive statistics, including 95% confidence intervals and one-sample t-test.

Subgroup analyses were performed to explore potential relations between a specific subgroup (gender, disease type, betahistine dosage, country, betahistine treatment at baseline) and the major efficacy variables. Pearson correlation analyses were undertaken to explore the associations between the different efficacy variables. Coefficients ≥ 0.60 (regardless of sign) were considered meaningful.

Safety outcomes

Safety assessment was based on the safety population, which included all patients allocated to treatment who received a prescription of betahistine at baseline and who had at least one subsequent clinic visit.

Reports of adverse drug reactions (ADRs) that started during the study were obtained during the follow-up and final visits, and coded according to the Medical Dictionary of Regulatory Activities (MedDRA) classification version 9.0. These events were also described according to their severity and their relationship to the study drug as judged by the investigator.

Statistical considerations

The primary efficacy criterion was the change from baseline in DHI total score during 3 months of treatment with betahistine 48 mg/day. Based on previous observations on the use of the DHI to evaluate drug therapy in patients with recurrent vestibular vertigo and published evidence that a difference in the total DHI score of 14 points is indicative of a clinically meaningful effect[2,5], and allowing for 25% premature departure from the study, a recruitment target was set of 200 patients per country.

The statistical analyses of the efficacy data were descriptive, and usually limited to mean ± standard deviation (SD). No adjustments were made for multiplicity.

Study organization

General

The study investigators were general practitioners and specialists based at 389 centres located in the following 13 countries: Brazil (3 centres), Canada (16 centres), Croatia (12 centres), Hungary (52 centres), India (23 centres), Latvia (42 centres), Lithuania (45 centres), Malaysia (17 centres), Poland (39 centres), Romania (88 centres), Russia (24 centres), Slovenia (11 centres) and Spain (17 centres). Details of participating practitioners appear in Appendix 1.

Data management and statistical analysis were the responsibility of FOVEA Group (Rueil Malmaison, France). Data entry was performed using Access version 9.0. Quality control was performed using SAS version 8.2. Statistical analysis was performed using SAS version 8.2 and SF Health Outcomes™ Scoring Software of Quality Metric Incorporated.

Ethics and informed consent

The study protocol was submitted to independent institutional review boards and/or independent ethics committees and/or other relevant committees for approval prior to starting the study, as required by local regulatory provisions. This included the review and approval of informed consent forms.

The study was designed and conducted in accordance with the international principles of Good Clinical Practice and the provisions of the Declaration of Helsinki and later amendments.

Informed consent was obtained from each patient in accordance with local regulatory requirements before they were enrolled in the study. Patients were advised that they were free to withdraw from the study at any time, for any reason and without offering any explanation for their decision, and that any such withdrawal could be made without prejudicing normal standards of clinical care.

RESULTS

A safety population of 2032 patients was recruited, from which an efficacy population of 1898 persons was derived. Demographic data for these populations are presented in Table 1 and affirm that the profiles of both populations are congruent with the previously published preliminary baseline data[4]. A total of 1796 patients from the efficacy population completed the study. Betahistine was introduced in response to a new diagnosis in ≈ 56% of patients and because of inefficacy of existing therapy

Table 1. Demographic features of the efficacy and safety populations

	Efficacy population (n = 1898)	Safety population (n = 2032)
Race, n (%)*		
Asian	220 (11.7)	226 (11.1)
Black	21 (1.1)	21 (1.0)
White	1607 (85.6)	1729 (85.1)
Other	30 (1.6)	33 (1.6)
Age (years) (mean ± SD)	53.8 ± 13.6	53.7 ± 13.6
Age class, n (%)**		
18-29 years	69 (3.8)	71 (3.6)
30-39 years	219 (11.9)	243 (12.3)
40-49 years	396 (21.5)	424 (21.5)
50-59 years	537 (29.2)	579 (29.4)
60-69 years	385 (20.9)	405 (20.6)
70-79 years	184 (10.0)	199 (10.1)
80-89 years	43 (2.3)	44 (2.2)
≥ 90 years	5 (0.3)	5 (0.3)
Height (cm) (mean ± SD)	166 ± 9	166 ± 9
Weight (kg) (mean ± SD)	73.4 ± 13.4	73.2 ± 13.3
BMI (kg/m²) (mean ± SD)	26.5 ± 4.3	26.46 ± 4.23

*Percentages based on 1878 patients in the efficacy population.
**Percentages based on data from 1838 patients in the efficacy population and 1970 in the safety population.

in ≈ 37% of patients. Predominant diagnoses underlying the decision to prescribe betahistine were peripheral vestibular vertigo of unknown pathophysiology (≈38% of cases), benign paroxysmal positional vertigo (BPPV; ≈22% of cases) and Ménière's disease (≈14% of cases).

Betahistine dosages at baseline are summarized in Table 2. In Romania, Slovenia, Lithuania, Hungary, Brazil, Latvia, Canada and Poland, betahistine was almost exclusively prescribed as 24 mg b.i.d.; in Croatia, Russia, Spain and Malaysia, betahistine was prescribed almost exclusively as 16 mg t.i.d. India was unusual in having almost equal proportions of patients prescribed the b.i.d. or t.i.d. regimens at baseline. No major changes in betahistine posology were observed during the study.

Table 2. Betahistine posology at baseline visit

	Efficacy population (n = 1898) n (%)	Safety population (n = 2032) n (%)
Betahistine 16 mg t.i.d.	721 (38.0)	742 (36.5)
Betahistine 24 mg b.i.d.	1124 (59.2)	1226 (60.3)
Missing values	53 (2.8)	64 (3.1)

Efficacy outcomes

DHI

On-treatment trends in mean total DHI score are summarized in Figure 1. The mean DHI total score was 64.0 ± 15.1 at baseline: the mean physical score was 20.4 ± 5, the emotional score 19.3 ± 7.7 and the functional score 24.3 ± 6.7. At the end of the study the total DHI score had improved to 26.8 ± 21.5: the mean physical score was 9.4 ± 6.7, the emotional score 7.1 ± 7.9 and the functional score 10.3 ± 8.7. Changes from baseline in all these indices were statistically significant ($p < 0.001$).

DHI responses were similar in men and women and for both betahistine dosages, and were statistically significant ($p < 0.001$) for all tested subgroups of baseline vertigo pathology. DHI responses were also similar and significant ($p < 0.001$ vs baseline) in patients taking betahistine alone or in combination with other therapies. Changes in mean total DHI in individual countries ranged from reductions of 44.0 ± 17.2 in India, 41.7 ± 21.8 in Latvia and 41.0 ± 20.4 in Romania to a reduction of 22.2 ± 23.3 in Spain. In every country, however, the improvement from baseline was robustly statistically significant ($p < 0.001$).

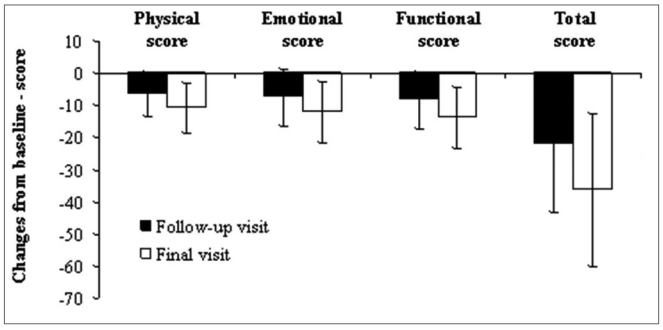


Figure 1. Mean changes from baseline in total DHI score and subscale scores in the efficacy population

HADS

HADS data were available for 1858 patients of the efficacy population. These patients had a mean baseline HADS-A score of 9.9 ± 4.4. Overall, 30.4% of patients (n = 564) had a normal anxiety level, 24.9% of patients (n = 463) had a mild anxiety level, 28.8% (n = 535) had a moderate anxiety level and 15.9% of patients (n = 296) had a severe anxiety level. A smaller proportion of women than men had a normal anxiety level at baseline (27.5% [n = 345] vs 36.3% [n = 217]). The mean HADS-D score was 8.2 ± 4.5; 25.3% of patients (n = 471) had a mild depression level, 20.5% (n = 381) had moderate depression and 9.3% of patients (n = 173) were considered to have severe depression. A larger proportion of women than men had moderate depression (22.4% [n = 281] vs 16.4% [n = 98]).

As illustrated in Figure 2, betahistine therapy was accompanied by progressive, statistically significant improvements in both HADS-A and HADS-D scores ($p < 0.001$). Mean changes from baseline at both visits and for both parameters were numerically larger in women than in men. The overall proportion of patients with a normal anxiety level increased from 30.4% at baseline to 48.9% at the follow-up visit and to 67.3% at the final visit. The proportion of patients with a normal depression level increased from 44.8% at baseline to 61.8% at the follow-up visit and to 74.9% at the final visit. HADS-A and HADS-D scores were significantly improved ($p < 0.001$ vs baseline) in all diagnostic categories.

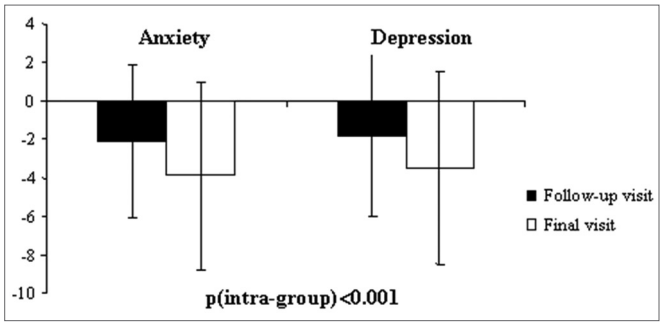


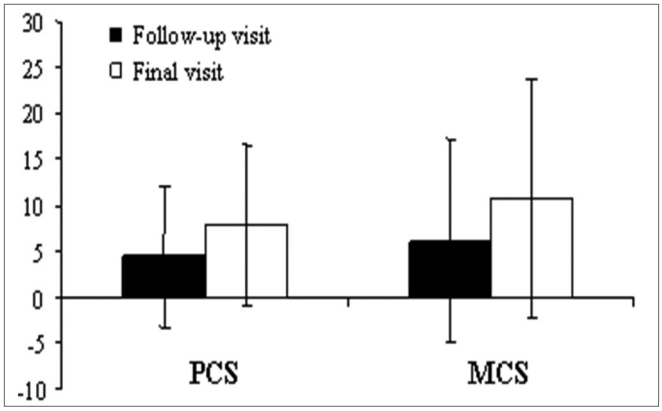
Figure 2. Mean changes from baseline in HADS-A and HADS-D scores in the efficacy population

Significant improvements in both HADS domains were recorded with both betahistine regimens, although the net change in HADS-A was slightly larger in patients receiving betahistine 24 mg b.i.d. (-4.0 ± 4.6 vs -3.4 ± 4.9). Similarly, betahistine 24 mg b.i.d. was associated with a slightly larger improvement in HADS-D than betahistine 16 mg t.i.d. (-3.6 ± 4.9 vs -3.1 ± 4.9).

SF-36v2

At the baseline visit, the mean PCS score was 39.8 ± 7.9; the mean MCS score was 35.6 ± 11.5. In accordance with the norm-based criteria outlined in the Methods section, both these scores were below the U.S. general population norm, indicating a reduced HRQoL status.

Significant improvements in both scores were recorded at the follow-up visit and at the final visit ($p < 0.001$ vs baseline) (Figure 3). As shown in the inset table to Figure 3, changes in PCS and MCS scores over 3 months were slightly greater in women than in men.



SF-36v2 scale (PCS and MCS) (mean ± SD)	Male (n = 605)	Female (n = 1286)
At baseline visit:		
PCS	41.3 ± 8.5	39.1 ± 7.6
MCS	36.8 ± 11.8	35 ± 11.3
At final visit:		
PCS change from baseline (p[intra-group] < 0.001)	7.1 ± 9.2	8.2 ± 8.5
MCS change from baseline (p[intra-group] < 0.001)	10.0 ± 12.7	11.2 ± 12.6

Figure 3. Mean changes from baseline in the Physical Health Component summary (PCS) and the Mental Health Component summary (MCS) of the SF-36v2 in the efficacy population

Significant improvements from baseline in the PCS and MCS domains of the SF-36v2 were recorded for both subgroups of betahistine dosage at the follow-up and final visits (all $p < 0.001$ vs baseline). The net change in PCS from baseline to final visit was numerically slightly greater in patients receiving betahistine 24 mg b.i.d. than in those receiving betahistine 16 mg t.i.d. (8.6 ± 8.8 vs 6.9 ± 8.7). Similarly, consistent benefits were seen in patients assigned to betahistine monotherapy or to combination therapy (all $p < 0.001$ vs baseline) but on-treatment improvements in PCS and MCS scores were numerically slightly larger in patients receiving combination therapy (PCS 8.6 ± 9.1 vs 7.4 ± 8.5; MCS 12.0 ± 12.9 vs 10.1 ± 12.5).

Correlations between DHI, SF-36v2 and HADS scores

A full listing of correlations between DHI, SF-36v2 and HADS scores with a Pearson coefficient ≥ 0.60 (regardless of sign) is presented in Table 3.

Table 3. Correlations between different efficacy indices. A correlation coefficient ≥ 0.6 (regardless of sign) was considered relevant

Scores	Correlation coefficient
At baseline visit	
SF-36v2 scale – MCS & HADS-A	-0.690
SF-36v2 scale – MCS & HADS-D	-0.672
At follow-up visit	
DHI total score & SF-36v2 scale – PCS	-0.640
SF-36v2 scale – MCS & HADS-A	-0.686
SF-36v2 scale – MCS & HADS-D	-0.693
At final visit	
DHI total score & SF-36v2 scale – PCS	-0.740
DHI total score & SF-36v2 scale – MCS	-0.625
DHI total score & HADS-A	0.657
DHI total score & HADS-D	0.614
SF-36v2 scale – PCS & HADS-A	-0.602
SF-36v2 scale – PCS & HADS-D	-0.616
SF-36v2 scale – MCS & HADS-A	-0.754
SF-36v2 scale – MCS & HADS-D	-0.726
ΔSF-36v2 scale – MCS & ΔHADS-A (final visit – baseline)	-0.688
ΔSF-36v2 scale – MCS & ΔHADS-D (final visit – baseline)	-0.651

Body weight

The mean±SD change in weight between baseline and final visits in the efficacy population was 0.2 ± 3.8 kg. No significant difference was observed between patients receiving betahistine 16 mg t.i.d. or betahistine 24 mg b.i.d.

Overall efficacy assessment

Treatment was rated excellent by 36.6% of 1753 patients with recorded data (n = 641) and good by 49.6% of patients (n = 870). No difference was observed between men and women. The investigators' impression of the treatment was excellent for 38.6% of patients (n = 675 of 1747) and good for 50.5% of patients (n = 883). There was good correlation between the opinions of physicians and patients ($r = 0.8$, $p < 0.0001$).

Safety and tolerability

The mean duration of betahistine treatment in the safety population was 94.2 days.

Summary safety findings are shown in Table 4. Forty-nine patients were reported as having experienced at least one ADR (one patient experienced an event at both betahistine dosages). A total of 76 ADRs were reported: seven patients receiving betahistine 16 mg t.i.d. experienced a total of eight ADRs and 26 patients receiving betahistine 24 mg b.i.d. experienced a total of 40 ADRs. The remaining 28 ADRs were recorded in 18 patients whose betahistine posology was unknown.

Table 4. Summary of ADRs in the safety population

	Safety population (n = 2032)	
	Number of patients; n (%)	Number of events
At least one ADR	49 (2.4)	76
At least one serious ADR	1 (0.05)	1
At least one ADR that led to study drug discontinuation	17 (0.8)	24
Death	0 (0)	0

The most frequently reported ADRs were gastrointestinal disorders (33 events in 27 patients, principally abdominal pain upper, nausea or dyspepsia) and nervous system disorders (14 events in 13 patients, principally headaches). The majority of ADRs were characterized as mild (47 events in 33 patients) or moderate (28 events in 19 patients).

Forty-three ADRs in 28 patients were classified as "possibly" and 11 events in 9 patients were classified as "probably" related to use of study medication; the remaining 22 events were regarded as either unlikely (n = 19) or were unknown (n = 3). Thirty-one of the gastrointestinal disorders events were considered possibly

(24 events) or probably (7 events) related to use of study medication, whereas 8 of the nervous system events were considered possibly (n = 7) or probably (n = 1) related.

One ADR was classified as serious. This concerned a cardiac arrhythmia and was also classified as severe. The patient, from Brazil, was receiving betahistine 24 mg b.i.d. Betahistine therapy was discontinued in response to this event.

In all, 24 ADRs led to study drug discontinuation in 17 patients. These ADRs were predominantly gastrointestinal (11 events in 9 patients) or nervous system disorders (6 events in 6 patients). Most of these events were recorded in participants in Brazil (10 events in 7 patients) or Slovenia (9 events in 6 patients). Four of these patients in Brazil were prescribed betahistine 24 mg b.i.d.; betahistine dosage was unrecorded in the other patients who discontinued study medication due to an ADR. No patient discontinued betahistine 16 mg t.i.d. due to an ADR.

One pregnancy with normal outcome was reported in a subject in Latvia. The subject received betahistine 24 mg b.i.d. for 18 days and reported no ADRs.

No death was reported during the study.

DISCUSSION

OSVaLD is the largest study of its kind in patients with vertigo, in terms both of the total number of patients enrolled and their geographic and ethno-cultural diversity. The study is thus a significant development in this area of clinical research. Secondary analyses of results from individual participating countries may be expected to provide insights about the subjective circumstances of vertigo patients in a wider than usual range of national and cultural situations.

Recent exercises in the use of outcomes such as HRQoL to examine the effects of vertigo[15-18] originate from the recognition that diseases of the peripheral vestibular system can have wide-ranging physical and psychological effects on the lives of patients[19,20]. Baseline data from OSVaLD provided corroboration of that premise, with consistent indications of diminished functional capacity and high prevalence of anxiety and depression at baseline[4]. The primary results of OSVaLD, reported here, add to experience with HRQoL instruments in vertigo and provide original data on the response of those indices to therapy delivered in the context of routine clinical care.

The primary efficacy criterion evaluated was the absolute change from baseline in mean total DHI score between the baseline and final (3-month) visits. Substantial improvements were registered in this measure, with a 37-point reduction in the mean total score and double-digit reductions in the three domains (physical, emotional and functional) of the DHI. The improvement in the total DHI score considerably exceeded the numerical threshold for a clinically meaningful response. Improvements in DHI score were statistically robust ($p < 0.001$), were broadly consistent across subgroups defined by gender, betahistine dosage regimen, baseline disease status and other variables, and were compatible with other clinical experience with betahistine (Figure 4)[2,3].

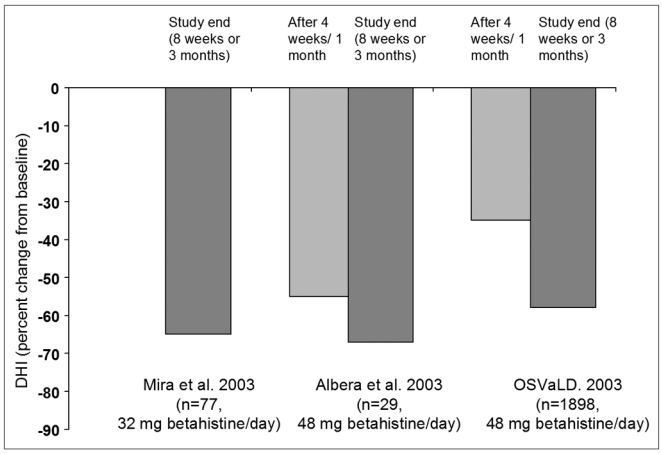


Figure 4. Comparison of DHI improvements in OSVaLD with published data from other clinical trials of betahistine.

Statistically significant ($p < 0.001$) and clinically meaningful improvements were also recorded with the HADS questionnaire, with evidence of improved scores for both anxiety and depression and a substantial improvement in the distribution of both conditions; improvements in the PCS and MCS components of the SF-36v2 were also observed.

Baseline mean HADS-A and HADS-D scores in the OSVaLD cohort were ≈10 and ≈8, respectively. These values are relatively high compared with data from various other types of illness[21-23] and may be indicative of the impact of vertigo on HRQoL. The possible contribution of non-vertigo factors to these scores must be acknowledged, although in the sphere of neurological conditions, differentiating cause and effect can be especially difficult[24,25]. The baseline SF-36v2 data for the OSVaLD population would also appear to support the view that this was a group with a low HRQoL[26]. The effects of betahistine on these indices of HRQoL should be considered in this context of marked baseline HRQoL deficits.

This study is the first of its kind to use both the SF-36v2 and the HADS to evaluate the effect of betahistine on vertigo patients. Additional analysis of the trial database will be needed to establish whether and how the use of multiple instruments provided information beyond what may be obtained from individual questionnaires. An extensive series of correlations has already been identified between responses in the DHI, HADS and SF-36v2 (Table 3). All these correlations were evident for both men and women. Correlations between the DHI and SF-36v2 do-

mains have been reported previously[18], but we believe this to be the first demonstration of correlations between the HADS and DHI in a large-scale vertigo study.

All the correlations identified were compatible with a priori expectations: so, for example, the more the SF-36v2 PCS signified improvement in clinical condition, the more the DHI total score did also. These numerous demonstrations of interrelations between different instruments lend credibility to – but cannot prove – the likelihood of a causal relation between the use of betahistine and the response of the various efficacy measures. This qualification may be especially relevant to depression, which is often the product of multiple influences and likely to be beyond the scope of a single medical intervention. The observed reduction in HADS-assessed depression severity and distribution seen in this study is perhaps the more noteworthy for that reason.

Further perspective on the effects of betahistine in this study may be extracted from reference to the fact that the overall result of the study was replicated in the large subset of patients with an initial diagnosis of BPPV (n = 417). The most recent authoritative examination of this topic affirmed that vertigo symptoms arising from canaliths in the posterior semicircular canal can be relieved via the canalith repositioning manoeuvre (CRM).[27] The five good-quality trials that provided the evidence for this conclusion enrolled a small number of patients (< 300) and follow-up did not exceed 4 weeks. (The authors of this survey concluded that deficiencies in the evidence for the utility of other similar exercises and the usefulness of any such measure in BPPV with a locus in other semicircular canals precluded many firm recommendations.) Studies of the effect of a successful CRM on HRQoL are even smaller in number and scope, apparently being limited to a series of publications by Lopéz-Escámez and co-workers[15,16,18], which reported changes in DHI and SF-36 scores. These investigators reported that the CRM was associated with improvements in HRQoL similar in type and degree to those recorded in the present study. In simple numerical terms, however, the completion of our observational study means that evidence for the HRQoL effects of betahistine now rests on a larger patient population than the equivalent evidence for the CRM, and is based for the most part on a longer follow-up. Experience in OSVaLD does not empower us to comment on the report by Cavaliere et al. that concomitant use of betahistine accelerates responses to repositioning manoeuvres but does not influence longer-term success rates[28].

Safety experience with betahistine in this study was satisfactory, with ADRs affecting < 2.5% of the study population. The predominance of gastrointestinal and nervous system disorders was consistent with previous reported experience with this agent[29].

OSVaLD was an open-label observational study; this is a format with recognized limitations[30], but it was appropriate for an international study in the context of routine care and addressed certain limitations of controlled trials, such as strict limitations on patient eligibility and the use of co-medications. Assessments were conducted in accordance with practitioners' standard clinical practice and the requirements of a PMS study. A 3-month follow-up was chosen as a length of time sufficient to generate useful safety and tolerability data. Issues of differential diagnosis were considered in an earlier report[4]; there is currently no reason to think that our database has been affected by major variations in, or errors of, diagnosis. The original objective of recruiting 200 patients per country was not achieved, but the statistical findings remain robust and the trend of responses was consistent in all countries, suggesting that the efficacy findings are a reliable indication of a true effect. Further it can be demonstrated that the effect seen in OSVaLD on the DHI was similar to that seen in double-blind, placebo controlled clinical studies with betahistine (Figure 4).

CONCLUSION

Our data describe stepwise, sustained and statistically significant improvements in multiple indices of HRQoL in a population of patients from 13 countries treated with betahistine 48 mg/day for recurrent peripheral vestibular vertigo for 3 months. These benefits from betahistine therapy were evident in a range of patient subgroups.

ACKNOWLEDGEMENT

Preparation of this report was assisted by staff of Hughes associates, 3 Collins Street, Oxford OX4 1XS, UK.

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