

RESEARCH PAPER

A randomised double-blind, cross-over trial of 4-aminopyridine for downbeat nystagmus—effects on slowphase eye velocity, postural stability, locomotion and symptoms

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ABSTRACT

Objective The effects of 4-aminopyridine (4-AP) on downbeat nystagmus (DBN) were analysed in terms of slow-phase velocity (SPV), stance, locomotion, visual acuity (VA), patient satisfaction and side effects using standardised questionnaires.

Methods Twenty-seven patients with DBN received 5 mg 4-AP four times a day or placebo for 3 days and 10 mg 4-AP four times a day or placebo for 4 days. Recordings were done before the first, 60 min after the first and 60 min after the last drug administration.

Results SPV decreased from 2.42 deg/s at baseline to 1.38 deg/s with 5 mg 4-AP and to 2.03 deg/s with 10 mg 4-AP ($p < 0.05$; post hoc: 5 mg 4-AP: $p = 0.04$). The rate of responders was 57%. Increasing age correlated with a 4-AP-related decrease in SPV ($p < 0.05$). Patients improved in the 'get-up-and-go test' with 4-AP ($p < 0.001$; post hoc: 5 mg: $p = 0.025$; 10 mg: $p < 0.001$). Tandem-walk time (both $p < 0.01$) and tandem-walk error (4-AP: $p = 0.054$; placebo: $p = 0.059$) improved under 4-AP and placebo. Posturography showed that some patients improved with the 5 mg 4-AP dose, particularly older patients. Near VA increased from 0.59 at baseline to 0.66 with 5 mg 4-AP ($p < 0.05$). Patients with idiopathic DBN had the greatest benefit from 4-AP. There were no differences between 4-AP and placebo regarding patient satisfaction and side effects.

Conclusions 4-AP reduced SPV of DBN, improved near VA and some locomotor parameters. 4-AP is a useful medication for DBN syndrome, older patients in particular benefit from the effects of 5 mg 4-AP on nystagmus and postural stability.

INTRODUCTION

Downbeat nystagmus (DBN) is the most frequent form of acquired nystagmus in the primary position.¹ It impairs visual acuity (VA) as a result of vertical oscillopsia^{2–4} and is associated with postural instability.^{5–6} DBN is most often caused by impaired cerebellar function, mainly of the flocculus, for example, due to cerebellar degeneration.^{3–7–9}

In DBN the eyeballs drift slowly upwards followed by a downward correcting saccade.⁴ The upward drift may be due to impaired function of floccular Purkinje cells (PCs)¹⁰ and their

physiological asymmetry.¹¹ Once damaged, the disruption of the system may disinhibit superior vestibular nucleus cells, resulting in spontaneous upward eye drift.¹²

Aminopyridines have been used in Lambert-Eaton myasthenic syndrome and multiple sclerosis.^{13–17} It is known that aminopyridines (4-aminopyridine (4-AP), 3,4 diaminopyridine) reduce the mean peak slowphase velocity of DBN,^{5 10 18–20} and 4-AP prevents attacks in episodic ataxia type 2 (EA 2)^{21 22} and improves interictal cerebellar ataxia²³ and gait²⁴ in EA 2. Their effects on the attacks were also confirmed in an animal model of EA 2, the tottering mouse.^{25 26}

So far, one explanation for its effects on DBN was that 4-AP augments the impaired physiological inhibitory influence on superior vestibular nuclei neurons by increasing the excitability of PCs.²⁷ In the abovementioned animal model of EA 2 it was found that 4-AP facilitates synchrony of firing of the PCs and such action would also enhance the inhibitory influence.²⁵

As several studies had already shown that 4-AP reduces the intensity of DBN, in the current placebo-controlled double-cross-over bi-centre trial we focused on its effects in two different dosages on slow-phase eye velocity, VA, postural stability, locomotion^{28 29} and symptoms.

METHODS

Level of evidence

This cross-over study provides Class II evidence that 4-AP decreases slow-phase velocity (SPV) and improves the results of the get-up-and-go test in patients with DBN.

Patients

Twenty-seven patients with DBN were included; their clinical features are summarised in table 1. The patients were 23–78 years old (mean 64.85 ± 12.01 years; aetiology: 21 idiopathic, six cerebellar degeneration). The mean duration of symptoms attributed to DBN was 8.48 years (± 8.49 range 1–40 years). As in previous studies,³⁰ all patients underwent a complete clinical examination. In one case MRI imaging was not possible, but the aetiology was considered idiopathic because there were

Table 1 Clinical characteristics of the patients with downbeat nystagmus (DBN), categorised by gender, age, neuro-ophthalmological findings, MRI findings, aetiology of downbeat nystagmus, disease duration since diagnosis and response to treatment

Subj.	Age, sex	Sequence of treatment	Aetiology of DBN	Duration of DBN	MRI findings	Neuro-ophthalmological findings (apart from DBN)	Response* (%)
1	70, m	4-AP—placebo	Idiopathic	16	Normal	3, 6	-152.91
2	76, f	4-AP—placebo	Idiopathic	10	Normal	1, 2, 3, left gaze hypermetric saccades	
3	69, m	Placebo—4-AP	Secondary (degeneration)	4	Cerebellar atrophy	1, 2, 4, 3	
4	65, m	4-AP—placebo	Idiopathic	2	Normal	1, 2, 3, 6	48.06
5	78, f	4-AP—placebo	Idiopathic	8	Relatively small flocculus	1, 2, 3, 5, 6, horizontal hypermetric saccades	115.92
6	48, m	4-AP—placebo	Secondary (degeneration)	13	Cerebellar atrophy	2, 5	-14.60
7	62, m	4-AP—placebo	Idiopathic	1	Normal	1, 2, 3, 6	-8.13
8	67, m	4-AP—placebo	Idiopathic	2	Normal	1, 3	165.87
9	69, m	Placebo—4 AP	Idiopathic	1	Normal	2, 3	5.00
10	62, f	4-AP—placebo	Idiopathic	4	Normal	None	177.08
11	60, f	Placebo—4-AP	Idiopathic	12	Normal	2, 3, 5, 6	11.73
12	71, f	Placebo—4-AP	Idiopathic	5	Normal	2, 3, 6	34.10
13	70, m	Placebo—4-AP	Idiopathic	11	Normal	2, 3, 6	-73.35
14	77, m	4-AP—placebo	Idiopathic	2	Normal	1, 2, 3, 4, 5	-57.19
15	65, m	4-AP—placebo	Idiopathic	3	Moderate cerebral atrophy	3	
16	75, f	Placebo—4 AP	Idiopathic	5	White matter lesions bilaterally and in central pons	2, 3, hypometric and slowed saccades	-64.62
17	71, m	4-AP—placebo	Secondary (SCA-6)	5	Normal	5, slowed saccades	-79.87
18	62, m	Placebo—4 AP	Idiopathic	9	Not possible	1, 3, hypoactive optokinetic eye movement	379.00
19	70, f	4-AP—placebo	Idiopathic	26	Marked atrophy of medial temporal lobe	3	
20	42, f	Placebo—4-AP	Idiopathic	9	Normal	UBN on upward gaze	-4.04
21	66, m	Placebo—4-AP	Idiopathic	40	Normal	2, 5	33.06
22	23, f	Placebo—4-AP	Secondary (degeneration)	4	Diffuse cerebral, medullar and cerebellar atrophy	2, 5	19.99
23	74, f	4-AP—placebo	Idiopathic	16	Normal	5, 6	90.30
24	74, f	4-AP—placebo	Idiopathic	5,5	Normal	1, 3, 5, 6, alternating skew deviation during lateral gaze, gaze holding deficit horizontally and downward	28.37
25	51, m	Placebo—4-AP	Secondary (paraneoplastic)	3	High signals in periphery of cerebellum bilaterally	None	-73.71
26	63, m	Placebo—4-AP	Idiopathic	5	No path around foramen magnum, T2 hyperintensity in pons	None	26.88
27	71, m	4-AP—placebo	Secondary (degeneration)	7,5	Various lesions due to multiple sclerosis	Occasionally dysmetric saccades	-98.60

With regard to the response, positive values indicate a better response(*) under 4-AP than under placebo.

Values were calculated as follows: percentage of change of slow phase velocity (SPV) from baseline to the measurement 60 min after first drug administration for 4-AP and placebo.

Afterwards, subtraction of the percentage of change of SPV under placebo from the percentage of change of SPV under 4-AP. 1=pathological head thrust test; 2=gaze-evoked

nystagmus; 3=saccadic smooth pursuit; 4=rebound nystagmus; 5=VOR suppression disturbed; 6=upward vertical OKN not inducible/diminished.

OKN, optokinetic nystagmus; UBN, upbeat nystagmus; VOR, vestibulo-ocular reflex.

no further indications of structural lesions. ECG and laboratory tests (Vitamin B12 and Mg²⁺) showed normal results at baseline.

Patients were randomly assigned (for patient flow see figure 1) to receive four single capsules (morning, noon, afternoon and evening) of 5 mg 4-AP (or placebo) for the first 3 days and 10 mg 4-AP (or placebo) for the following 4 days. This was followed by 6 days with no medication (=wash-out period). The treatment was switched (cross-over) 1 week later. All measurements were done before the first drug administration (=baseline), 60 min after the first drug administration (=5 mg 4-AP or placebo; post1) and 60 min after the last drug administration (=10 mg 4-AP or placebo; post2) because prior studies in patients with multiple sclerosis had shown that 4-AP is rapidly absorbed, with peak serum levels being reached between 20 min

and 60 min after dosing. Serum half-life was reported to lie between 1 h and 3 h.³¹

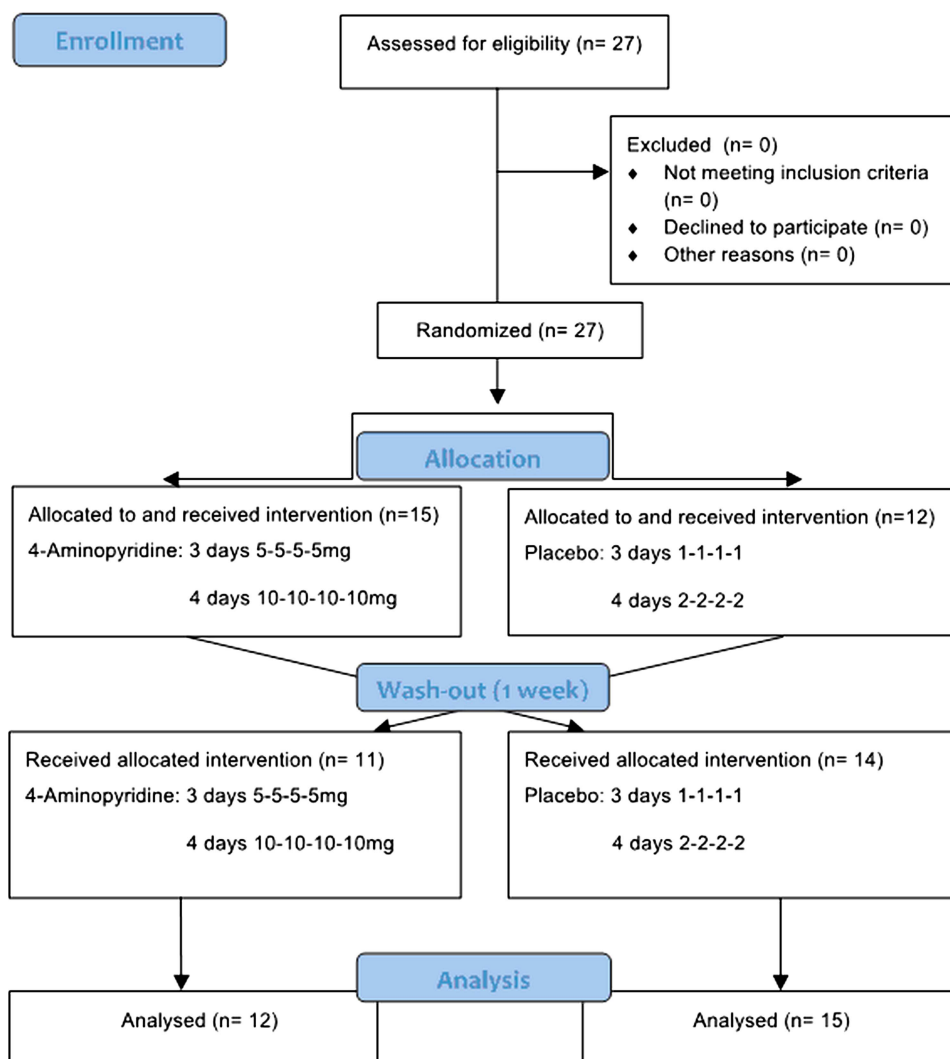
No patient was taking medication that affected the ocular motor or vestibular systems. In no patient was DBN due to medication or metabolic disorders.

Randomisation and masking

Patients were randomised (by a computer-generated block randomisation list) to receive first either placebo or 4-AP and then, after the cross-over and wash-out periods, the opposite. The treatment assignments were carried out by providing the clinic with the appropriate treatment kit, which contained the blinded treatments, each in the appropriate order for the patient to whom it was assigned (for further information see online supplementary material no. 1 and figure 1).

Movement disorders

Figure 1 Participant flow. Access the article online to view this figure in colour.



Recording of eye movements

Patients were seated in an upright position. Based on prior work,^{30 32} a 30-second eye movement recording was carried out with 3-D video-oculography (Munich: GN Otometrics Hortmann Vestlab 100; London: Senso-Motoric Instruments Berlin; sampling rate=50 Hz, resolution 0.1° in horizontal and vertical direction, accuracy=0.6°, range= ±30° in horizontal and vertical directions). The recording order was (1) calibration with targets 8.5° apart, (2) gaze straight ahead with fixation and (3) gaze straight ahead in darkness. Targets were laser-projected at eye level onto a white cardboard screen located 60 cm in front of the patient. A padded head restraint was provided. Darkness recordings were for future studies; for the current clinical trial we only report fixation data.

The data analysis was carried out offline using Matlab (The Mathworks, Natick, Massachusetts, USA). The calibrated data were low-pass filtered (for further information see online supplementary material no. 1).

Visual acuity

VA was measured by a Snellen chart with block letters at a distance of 6 m; near VA was measured with the chart at a distance of 30 cm (optical correction allowed). Measurements were carried out for the left eye and right eye at baseline and after drug/placebo administration. The mean VA of both eyes at each visit was calculated for both distances. Higher values represent better vision.

Locomotor tests

We used the 'timed get-up-and-go test', a validated tool of clinical gait assessment in elderly patients, fallers and Parkinson's disease.³³⁻³⁶ It measures the time (seconds) people take to get up from an armless chair, walk 3 m away from the chair, turn around and walk back towards the chair and sit down.²⁸ Subsequently, the patients performed a tandem walk,²⁹ walking for a distance of 2 m; the task was to step onto previously marked areas on the ground. If the person stepped outside these marked areas, this was considered an error (the number of errors was counted at baseline and subsequent to the administration of the drug/placebo). The time (seconds) to complete the task was measured at baseline and after drug/placebo administration.

Posturographic measurements

Measurements were carried out and postural sway was computed when patients stood upright on firm ground. Total postural-sway values (sway path) for all axes (x,y,z (m/min)) were calculated with eyes open and with eyes closed. The mean values of 30 s on the posturographic measurement device provided an estimation of the mean postural sway (for details see ref³⁷).

Monitoring of satisfaction and side effects

All patients were given questionnaires (adapted for this study³⁸) with Likert-scaled items to describe their satisfaction with the

treatment (drug or placebo). The details of the questionnaire can be found in online supplementary appendix 1.

Statistical data analysis

Data were not normally distributed; hence non-parametric statistical tests were carried out (SPSS V.19, IBM Corporation, Somers, New York, USA). To look for differences between baseline and the two different doses of the drug / placebo, Friedman's test with χ^2 -test statistics was applied. For individual post hoc comparisons, the non-parametric Wilcoxon test statistics were applied with the Bonferroni correction (all two-tailed). The SPV of vertical eye movements was the dependent variable in the eye-movement data. DBN indicated by mean SPV deg/s appears as a positive value on the scale. The time taken (seconds) was the dependent variable in the get-up-and-go test and in the tandem walk. The number of errors represented an additional dependent variable in the tandem-walk task. For posturographic measurements, the average sway values with eyes open/eyes closed represented the dependent variable. In the analysis of VA the dependent variable was the average VA of left eye and right eye for both distances measured. Questionnaire assessment was done by Likert-scaled items (which results in ordinal-scaled data and therefore also requires non-parametric statistical tests). In terms of patient satisfaction with the drug/placebo, higher values indicate higher levels of satisfaction. On the other hand, higher values on the side effects scale mean that more side effects were experienced. A factor analysis was carried out with the aim of determining which patients benefit most and what patient characteristics may be responsible for treatment response. Non-parametric correlations (Spearman's ρ) and a partial correlation to control for covariates were subsequently applied to shed light on those patient characteristics that may indicate a better response to treatment.

RESULTS

Slow phase velocity

Mean SPV decreased from a baseline of $2.42 \text{ deg/s} \pm 2.22$ (mean \pm SD) to $1.38 \text{ deg/s} \pm 1.81$ on 5 mg 4-AP and to $2.03 \text{ deg/s} \pm 2.08$ on 10 mg 4-AP. There was an overall decrease of SPV from baseline in the 4-AP group (Friedman's test with

χ^2 -statistics=6.09, $p < 0.05$, $N=23$) with a significant post hoc difference between baseline and 5 mg 4-AP ($p=0.04$). This decrease was statistically significant even though all outliers were left in the sample (see figure 2). The post hoc analysis between baseline and 10 mg 4-AP did not reveal a significant decrease of SPV ($p > 0.05$).

On placebo, mean SPV was $2.02 \text{ deg/s} \pm 2.21$ at baseline, $1.25 \text{ deg/s} \pm 1.89$ at post1 and $1.76 \text{ deg/s} \pm 2.08$ at post2; there was no significant decrease in terms of SPV (Friedman's test with χ^2 -statistics=2.35, $p=0.31$, $N=23$). Figure 2 presents the data for placebo along with the data for 4-AP.

Regarding the aetiology of DBN, patients with idiopathic DBN ($N=21$) showed an overall significant decrease of SPV on 4-AP (Friedman's test with χ^2 -statistics=9.63, $p=0.008$, $N=19$) with a significant post hoc difference between baseline and 5 mg 4-AP ($p=0.01$). On placebo, there was no significant change of SPV ($p > 0.05$). Patients with secondary DBN ($N=6$) did not show a significant decrease of DBN (all: $p > 0.05$).

Response to treatment

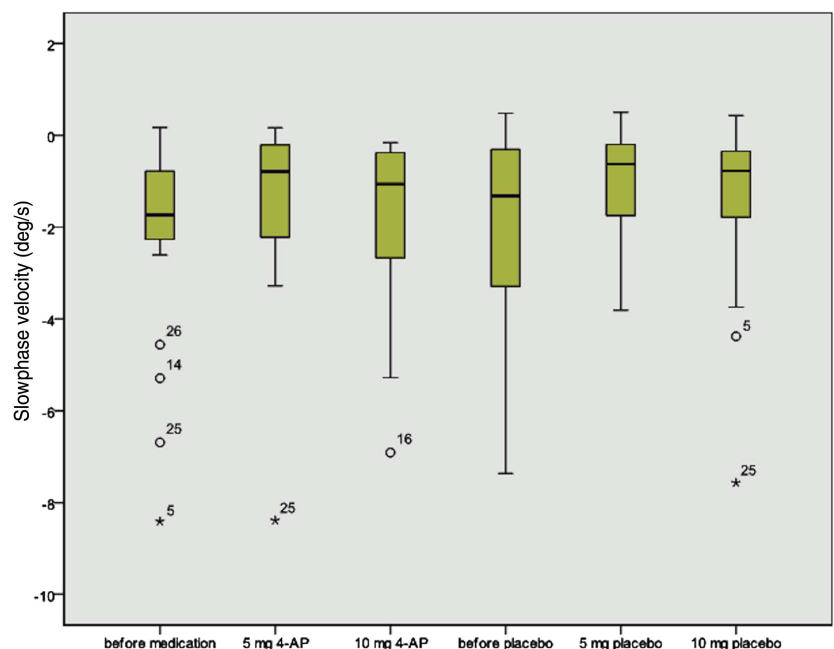
We calculated the percentage of change of SPV from baseline to the measurement 60 min after first drug administration for 4-AP and placebo. Afterwards, we subtracted the percentage of change of SPV under placebo from the percentage of change of SPV under 4-AP. Positive values indicated a better response under 4-AP than under placebo and therefore defined as responder. Of the patients, 57% (13 of 23) were responders (four patients could not be included because of missing values). For an illustration of the change in SPV according to groups of response see figure 3 and table 1.

Visual acuity

Near VA increased from baseline to the two measurements under 4-AP as follows: baseline: 0.59 ± 0.31 ; 5 mg 4-AP: 0.66 ± 0.31 ; 10 mg 4-AP: 0.61 ± 0.29 . On placebo VA changed from a baseline of 0.59 ± 0.31 to 0.63 ± 0.28 and 0.61 ± 0.30 .

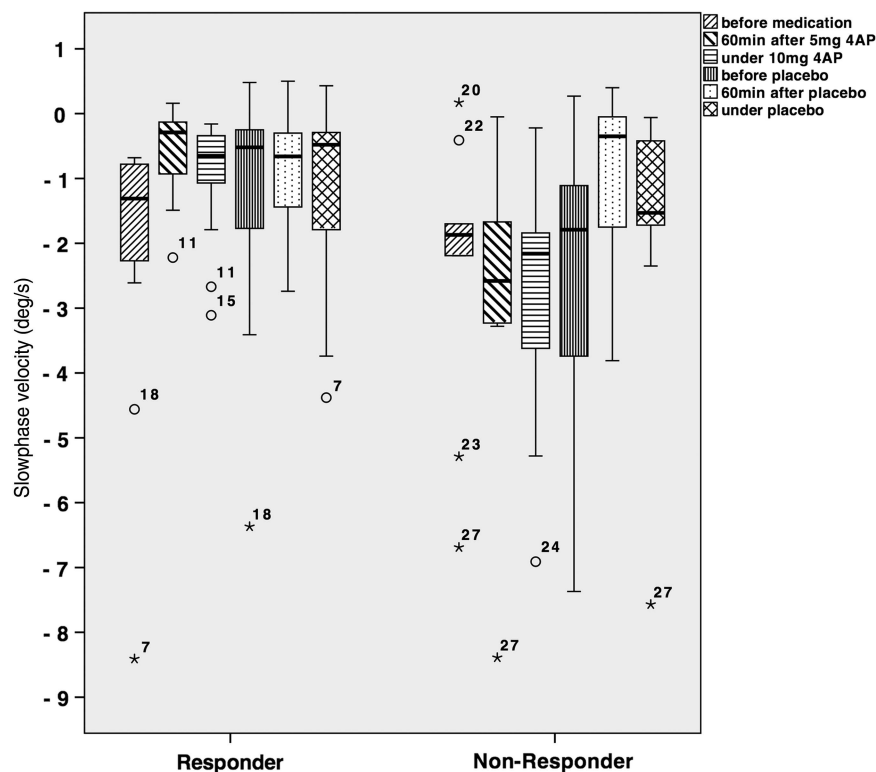
Distant VA increased under 4-AP and placebo as follows: 4-AP: baseline: 0.64 ± 0.26 ; 5 mg: 0.69 ± 0.26 ; 10 mg: 0.74 ± 0.27 ; placebo: baseline: 0.67 ± 0.27 ; 0.72 ± 0.26 and 0.74 ± 0.26 .

Figure 2 Box plots showing the median scores and the box-and-whiskers (25/75 percentiles) including outliers prior to 4-AP/placebo, after 5 mg of 4-AP/placebo and after 10 mg of 4-AP/placebo. The extreme values are represented by the patient numbers in the sample. The differences in terms of mean slowphase velocity (SPV) between baseline and the 5 mg 4-AP condition were significant even when the outliers were included in the dataset. Patient 5 was a 78-year-old woman with a degenerative downbeat nystagmus (DBN) who benefited extremely well from 4-AP in terms of SPV, VA and get-up-and-go test. Patient 25 was a 51-year-old man with paraneoplastic DBN who did not benefit from 4-AP. Access the article online to view this figure in colour.



Movement disorders

Figure 3 Box plots showing the median scores of slowphase velocity (deg/s) and the box-and-whiskers (25/75 percentiles) including outliers prior to 4-AP/placebo, after 5 mg of 4-AP/placebo and after 10 mg of 4-AP/placebo. Subjects were divided into responders and non-responders.



There was an overall increase in near VA from baseline on 4-AP (Friedman's test with χ^2 -statistics=6.98, $p<0.05$, $N=23$) with a significant post hoc difference between baseline and 5 mg 4-AP ($p=0.01$). All changes under placebo were not significant ($p>0.05$). In terms of distant VA, there was also an overall increase from baseline on 4-AP and placebo (Friedman's test with χ^2 -statistics=17.79 and 11.88, both: $p<0.05$, $N=24$) with a significant post hoc difference between baseline and 5 mg 4-AP and between baseline and 10 mg 4-AP (all: $p<0.05$). In the placebo group, there was also a significant post hoc difference between baseline and the first and second measurements after administration (all: $p<0.05$).

Locomotion tasks

The 'get-up-and-go test' revealed a reduction of time (in seconds) from 12.27 ± 13.58 at baseline to 12.15 ± 17.22 on 5 mg 4-AP and 9.4 ± 7.19 on 10 mg 4-AP (Friedman's test with χ^2 -statistics=18.11, $p<0.001$); significant post hoc difference between baseline and 5 mg 4-AP ($p=0.025$) and between baseline and 10 mg 4-AP ($p<0.001$). The placebo condition did not have a significant effect on this task (Friedman's test with χ^2 -statistics=4.625, $p=0.1$). On placebo the time (in seconds) changed from 13.12 ± 15.24 at baseline to 11.44 ± 11.85 and 12.14 ± 16.32 .

With regard to the aetiology of DBN, patients with idiopathic DBN showed an overall improvement on 4-AP (Friedman's test with χ^2 -statistics=12.94, $p=0.002$, $N=18$) with a significant post hoc difference between baseline and 5 mg 4-AP ($p=0.018$) and baseline and 10 mg 4-AP ($p=0.002$). In the group of patients with DBN caused by degeneration, there was only a marginally significant overall improvement on 4-AP (Friedman's test with χ^2 -statistics=5.73, $p=0.057$, $N=5$). On placebo, no significant changes were found.

Tandem-walk time improved in patients administered 4-AP (baseline: $6.62\text{ s}\pm 5.12$; 5 mg: $6.28\text{ s}\pm 4.85$; 10 mg: $5.17\text{ s}\pm 3.55$; Friedman's test with χ^2 -statistics=11.085, $p<0.01$,

$N=22$), and in patients given placebo (baseline: $7.66\text{ s}\pm 5.34$; after 60 min: $6.11\text{ s}\pm 5.54$; after 1 week: $6.22\text{ s}\pm 7.33$; Friedman's test with χ^2 -statistics=11.028, $p<0.01$, $N=22$).

Tandem-walk error improved on 4-AP (baseline: 1.83 ± 2.19 ; 5 mg 4-AP: 1.70 ± 1.84 ; 10 mg 4-AP: 1.22 ± 1.60) and placebo (baseline: 1.63 ± 1.97 ; 5 mg: 1.21 ± 2.02 ; 10 mg: 1.36 ± 1.92) for 4-AP: Friedman's test with χ^2 -statistics=5.85, $p=0.054$, $N=21$, for placebo: Friedman's test with χ^2 -statistics=5.67, $p=0.059$, $N=22$).

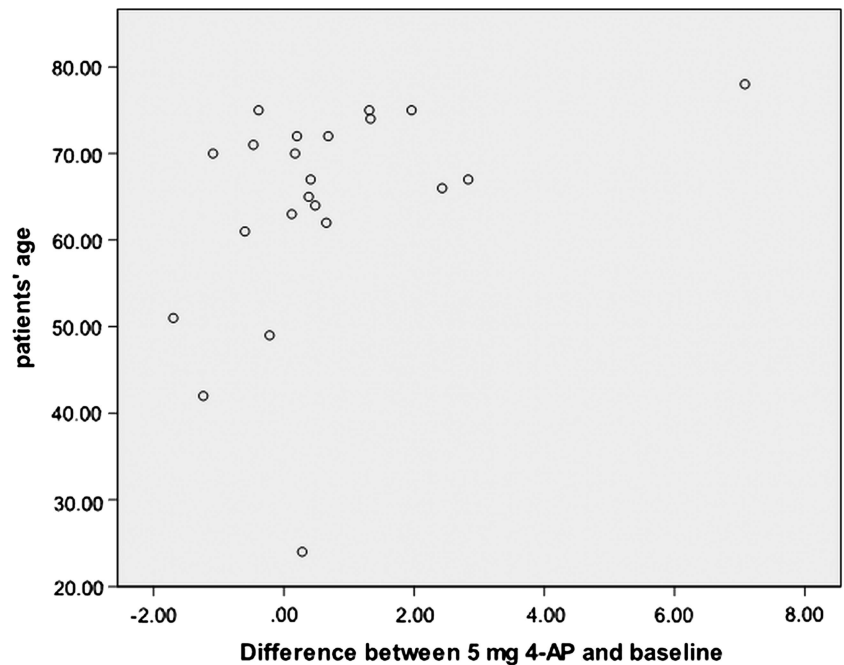
Posturography

In the placebo condition, postural stability remained unchanged with the eyes open (baseline: $1.64\text{ m/min}\pm 0.78$; after 60 min: $1.68\text{ m/min}\pm 0.91$; after 1 week: $1.71\text{ m/min}\pm 0.58$) and eyes closed (baseline: $3.65\text{ m/min}\pm 4.35$; post1: $3.38\text{ m/min}\pm 4.71$; post2: $3.47\text{ m/min}\pm 3.73$). Postural stability with eyes open worsened from $1.51\text{ m/min}\pm 0.82$ at baseline to $1.71\text{ m/min}\pm 0.78$ on 5 mg and $2.05\text{ m/min}\pm 1.36$ on 10 mg 4-AP. Under the condition eyes-closed, it changed from $2.92\text{ m/min}\pm 3.44$ at baseline to $3.14\text{ m/min}\pm 3.34$ on 5 mg 4-AP and $3.60\text{ m/min}\pm 4.01$ on 10 mg 4-AP.

The overall change in postural stability was significant on 4-AP (eyes open: Friedman's test with χ^2 -statistics=7.18, $p<0.05$, $N=22$, eyes closed: Friedman's test with χ^2 -statistics=9.24, $p=0.01$, $N=21$). Post hoc tests revealed that patients were significantly less stable on 10 mg 4-AP (eyes open: $p=0.017$, eyes closed: $p=0.002$), whereas no significant post hoc tests were found after the administration of 5 mg 4-AP (eyes open: $p=0.12$, eyes closed: $p=0.35$).

Postural stability did not generally decrease with 4-AP. The opposite was found for increasing age with the 5 mg 4-AP dose: it caused increasing postural stability when patients had their eyes closed. Using age as a covariate, increasing age correlated significantly with the 4-AP-related decrease in SPV in the 5 mg group (partial correlation=0.54, $p<0.05$, see figure 4).

Figure 4 The association of age (in years) and improvement with 5 mg 4-AP in terms of mean slow-phase velocity (SPV) relative to baseline mean SPV measurements. The positive correlation between both variables was statistically significant.



Side effects and patient satisfaction

Reported side effects were nausea (four patients on active substance, two on placebo, one on both), vomiting (three on active substance), sleep disturbances (three on active substance, one on placebo), sleepiness (one on active substance, one on placebo), paraesthesias (one on active substance, one on placebo), palpitations (one on placebo, one on both), worsened balance (two on active substance) and blurred vision (one on active substance). One patient was removed from the study because of a prolonged QTc time (QT time in electrocardiography corrected for heart rate) on 4-AP; one patient dropped out of the study because symptoms continued on placebo.

In terms of patient satisfaction, patients were able to choose between the options very happy (ie, want to stay on the drug, 3 points), happy (ie, some benefit, 2 points), not at all happy (want to stop, one point). Patient satisfaction was similar for 4-AP (2.23 ± 0.92) and placebo (2.55 ± 0.51) (Wilcoxon signed rank test $p > 0.2$). The frequency of side effects also did not differ between groups (Wilcoxon signed rank test $p > 0.08$). Improvement of DBN, VA and/or postural stability did not have a significant influence on patient satisfaction or on reported side effects (partial correlation: $p > 0.05$).

DISCUSSION

It is well established that aminopyridines decrease the intensity of DBN.^{3 18 20 39 40} Furthermore, 4-AP is evidently more effective than 3,4-diaminopyridine^{31 36–38 41} because it crosses the blood-brain barrier more easily.^{42 43}

In the current study 4-AP significantly reduced the SPV of DBN but only during treatment with 5 mg. Of the patients 57% responded to 4-AP. The SD with 10 mg was higher than with 5 mg which may explain why the difference was not statistically significant. The underlying mechanism of this unexpected dose-effect is so far unclear.

The reduction was less pronounced than that reported in previous studies.^{3 5 18–20 42} However, the variation of SPV was high at baseline and there were also a number of outliers in the dataset. All outliers were, however, left in, in order to represent

all patients, including those with extreme findings. It is worth noting that excluding the outliers would have enhanced the beneficial effects of 4-AP given that the outliers showed poor response to the active drug, which may depend on the aetiology of DBN (see below). Examining the overall response rate, which was higher on 4-AP than on placebo, we can conclude that even though not all patients in our sample responded to the drug, the general finding of previous studies was confirmed. Therefore we also tried to identify those patients who were more likely to respond to the drug, a practical clinical point. It turned out that increasing age predicted better DBN response to 4-AP. Age was also associated with increased postural stability with closed eyes and the 5 mg dose. Further, patients with idiopathic DBN benefited most in terms of SPV (as in a previous study³) and the get-up-and-go test.

Near VA improved significantly on 5 mg 4-AP. The decreased SPV of DBN with 5 mg 4-AP might have led to a better VA. Distant VA improved on 4-AP and placebo. Values of distant VA were generally higher than those of near VA. This can be explained by the age of the patients and the higher incidence of presbyopia⁴⁴ or because convergence usually increases the intensity of DBN. Yee *et al*⁴⁵ reported an enhancement of DBN at convergence in 64% of the tested patients, perhaps giving more chances for the 4-AP to work.

In terms of locomotion, 4-AP significantly improved performance in the 'get-up-and-go test'. The improved performance over baseline levels in the tandem-walk time and the tandem-walk error tests, however, cannot be interpreted as a result of 4-AP, as these improvements were also seen in the placebo condition.

Postural sway increased on 4-AP, whereas no difference was found for placebo. Especially higher doses of 4-AP led to increased postural sway in the eyes-open and eyes-closed conditions, whereas lower doses did not show a significant effect. These findings suggest that there could be a dissociation between the vestibulo-ocular and vestibulospinal systems in their dose responsiveness to 4-AP. All other parameters of locomotion and balance tested did not show any significant correlation to SPV. Regarding postural stability, it should also be mentioned that many patients did not have high postural sway values at

baseline, especially at eyes-open condition. In the group of older patients 5 mg 4-AP improved postural stability perhaps due to the increased sway at baseline especially the eyes-closed condition and therefore worse capacity of postural stability at the beginning. However, this does not necessarily imply that 4-AP is deleterious to postural stability, since increasing age was associated with improved postural stability due to 4-AP (in the 5 mg dose only). These findings, together with the locomotor findings, warrant further investigation.

Only a few side effects were reported in the course of the study, in particular nausea, paraesthesia and sleep disturbances. There were, however, no differences in the total frequency of side effects between 4-AP and placebo; this indicates that overall 4-AP is well tolerated. Patient satisfaction was similar on 4-AP and placebo. Given that 4-AP is a drug for symptomatic but not causative treatment, one would expect to see higher patient satisfaction scores among those patients receiving the drug than among those patients receiving placebo, so why did we not see any relevant differences in terms of patient satisfaction? While 4-AP decreases the amount of DBN, it certainly does not make DBN vanish completely. The fact that DBN just about improves on 5 mg 4-AP (but not on 10 mg 4-AP), while there is a slight (but not statistically significant) improvement in the placebo condition, would suggest that the positive effects of 4-AP might have gone unnoticed for a substantial number of patients. This could be a reason for the absence of statistically significant differences in the patient satisfaction scales. It should be mentioned that the questionnaire was not validated for patients with cerebellar disease. Therefore, longer trials with more detailed and validated questionnaires involving 5 mg 4-AP or 10 mg of the sustained-release form may yield higher scores in terms of patient satisfaction.

From a clinical point of view, this study shows that 4-AP is a promising medication for patients with DBN. It leads to a significant DBN reduction following the 5 mg dose. According to our results, the 5 mg four times a day dose seems to have better effects on the mean SPV data and the VA measurements, it is not generally associated with decreased postural stability and it was associated with improved postural stability in elderly patients. Especially older people who are at risk of stumbling should therefore be tested thoroughly before higher doses of 4-AP are given.

There is a heterogeneous response rate among patients, with some experiencing great benefits, and others worsening, but patients with idiopathic DBN seem to have greater benefit.^{3 20} In regular clinical visits it should be decided on a case-by-case basis if a patient benefits from treatment or not. If eye recording is performed to support this decision it is important that the measurements are done in the same position and at the same time of day at each visit.^{30 32}

In future studies, it will be important to look for patterns that might explain why some patients respond to 4-AP while others do not. One possible starting point for further studies in terms of pathophysiology may be the investigation of a possible dose effect of 4-AP on the brain areas (eg, deep cerebellar or vestibular nuclei) involved in DBN.

From a pharmacological perspective, it may also be worth administering the sustained released form of 4-AP (Ampyra, Biogen Idec, Cambridge, Massachusetts, USA or Fampyra, Europe), since it may have longer-lasting effects and fewer side effects and contraindications. Future studies will be needed to clarify these aspects.

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Patient consent Obtained.

Ethics approval All patients gave their informed consent to participate in our study, which was performed in line with the Helsinki II Declaration and approved by the Ethics Committees of Ludwig-Maximilians University of Munich, Germany and Imperial College London, UK.

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A randomised double-blind, cross-over trial of 4-aminopyridine for downbeat nystagmus —effects on slowphase eye velocity, postural stability, locomotion and symptoms

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