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M. Strupp, R. Kalla, J. Claassen, et al.

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A randomized trial of 4-aminopyridine in EA2 and related familial episodic ataxias



M. Strupp, MD
R. Kalla, MD
J. Claassen, MD
C. Adrion, MPH
U. Mansmann, PhD
T. Klopstock, MD
T. Freilinger, MD
H. Neugebauer, MD
R. Spiegel, PhD
M. Dichgans, MD
F. Lehmann-Horn,
MD, PhD
K. Jurkat-Rott, MD
T. Brandt, MD, FRCP
J.C. Jen, MD, PhD
K. Jahn, MD

Address correspondence and reprint requests to Dr. Michael Strupp, Department of Neurology and IFB^{LMU}, University of Munich, Campus Grosshadern, Marchioninstr. 15, 81377 Munich, Germany
michael.strupp@med.uni-muenchen.de

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ABSTRACT

Objective: The therapeutic effects of 4-aminopyridine (4AP) were investigated in a randomized, double-blind, crossover trial in 10 subjects with familial episodic ataxia with nystagmus.

Methods: After randomization, placebo or 4AP (5 mg 3 times daily) was administered for 2 3-month-long treatment periods separated by a 1-month-long washout period. The primary outcome measure was the number of ataxia attacks per month; the secondary outcome measures were the attack duration and patient-reported quality of life (Vestibular Disorders Activities of Daily Living Scale [VDADL]). Nonparametric tests and a random-effects model were used for statistical analysis.

Results: The diagnosis of episodic ataxia type 2 (EA2) was genetically confirmed in 7 subjects. Patients receiving placebo had a median monthly attack frequency of 6.50, whereas patients taking 4AP had a frequency of 1.65 ($p = 0.03$). Median monthly attack duration decreased from 13.65 hours with placebo to 4.45 hours with 4AP ($p = 0.08$). The VDADL score decreased from 6.00 to 1.50 ($p = 0.02$). 4AP was well-tolerated.

Conclusions: This controlled trial on EA2 and familial episodic ataxia with nystagmus demonstrated that 4AP decreases attack frequency and improves quality of life.

Level of evidence: This crossover study provides Class II evidence that 4AP decreases attack frequency and improves the patient-reported quality of life in patients with episodic ataxia and related familial ataxias. *Neurology*® 2011;77:269–275

GLOSSARY

4AP = 4-aminopyridine; **EA** = episodic ataxia; **EA2** = episodic ataxia type 2; **IQR** = interquartile range; **MS** = multiple sclerosis; **VDADL** = Vestibular Disorders Activities of Daily Living Scale.

Episodic ataxia type 2 (EA2) is a rare autosomal dominant hereditary disorder caused by heterozygous mutations of the gene *CACNA1A* on chromosome 19p13.¹ The carbonic anhydrase inhibitor acetazolamide has been the drug of first choice for the preventive treatment of episodic ataxia (EA) and especially EA2 (doses of 250–1,000 mg/day),^{2,3} because of the serendipitous discovery of its dramatic impact.⁴ Its efficacy, however, has never been proven in a randomized controlled trial.^{5,6} Acetazolamide effectively prevents or attenuates the attacks in approximately 50%–75% of all patients with EA2.⁷ Clinical experience, however, shows that many patients stop this treatment in the long run because they develop adverse effects or are no longer responsive.^{5,6} Furthermore, the adverse effects of acetazolamide (such as nephrocalcinosis, hyperhidrosis, paresthesia, muscle stiffening with easy fatigability, and gastrointestinal disturbances) limit its usage.⁶ In view of the need to identify an alternative treatment option to acetazolamide and on the basis of pilot studies in subjects with downbeat nystagmus⁸ and EA⁹ as well as findings from animal studies,^{10,11} we conducted a prospective randomized, double-blind, placebo-controlled crossover study of 4AP in familial EA with nystagmus (the majority

From the Department of Neurology, Friedrich-Baur-Institute and IFB^{LMU} (M.S., R.K., J.C., T.K., T.F., H.N., R.S., M.D., T.B., K.J.), Institute for Medical Information Sciences, Biometry and Epidemiology (C.A., U.M.), Department of Clinical Neurosciences (T.B.), University of Munich, Germany; Department of Applied Physiology (F.L.-H., K.J.-R.), University of Ulm, Germany; and Department of Neurology (J.C.J.), University of California, Los Angeles.

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of subjects had EA2), in which we assessed its efficacy by determining the frequency and duration of the ataxia attacks as well as patient-reported quality of life as a reflection of disease burden using the Vestibular Disorders Activities of Daily Living (VDADL) scale.¹² We also evaluated how 4AP was tolerated by monitoring adverse events throughout the study.

METHODS Standard protocol approvals, registrations, and patient consents. The study was approved by the local ethics committee and was performed in accordance with the Declaration of Helsinki and its subsequent amendments, as well as with the guidelines of Good Clinical Practice. This clinical trial was not registered because patient enrollment began before July 1, 2005. Written informed consent was obtained from subjects who met the study inclusion criteria. All study participants received written information about possible side effects of 4AP and a standardized protocol with open questions and specific questions about known side effects before they were included in the study. They were instructed to inform the investigator about any side effects of the agent within 24 hours by phone, fax, or e-mail.

Study subject recruitment. Subjects between the ages of 12 and 80 years were recruited from the Neurological Dizziness Unit of the University of Munich and from the genetic database of the Department of Applied Physiology, University of Ulm, Germany (K.J.-R., F.L.-H.). All potential subjects underwent a detailed clinical examination (appendix e-1 on the *Neurology*[®] Web site at www.neurology.org). The inclusion criteria were as follows: 1) a history of childhood onset of recurrent attacks of ataxia induced by exercise, stress, or alcohol that last from hours to 1 day; 2) central ocular motor dysfunction such as saccadic smooth pursuit, impaired gaze-holding function, or downbeat nystagmus; and 3) a positive family history or the presence of a disease-causing mutation in the EA2 gene *CACNA1A*. The exclusion criteria included the following: 1) prolonged QTc time on EKG; 2) structural lesions in the brainstem or cerebellum on T1- or T2-weighted MRI that exceeded a mild atrophy of the cerebellum; 3) inability to comply with the study requirements; 4) history of seizures or known epilepsy; 5) pregnancy or childbearing potential without use of approved birth control methods; and 6) known allergy to pyridine-containing substances.

Genetic testing. Genomic DNA was extracted from whole EDTA blood using the salt precipitation method. Mutation screening was performed by PCR amplification and direct sequencing of exons most frequently showing mutations: 4–6, 11, 13, 16, 17, 22, 23, 25–27, 29–33, 35, and 36 (primers reported in Ophoff et al.). PCR products were loaded on a 2% agarose gel and stained with ethidium bromide; the bands were cut out under ultraviolet light. Bands were then purified using an Amersham Pharmacia kit and cycle-sequenced with 1 pmol of primer using a dye terminator kit (Applied Biosystems). Sequencing was performed on 6% denaturing polyacrylamide gels in an ABI 377 HT automated sequencer. All sequences with base exchanges were verified by reverse sequencing of a new PCR product of the same DNA sample. A total of 96 control samples were found to be nega-

tive for the novel mutations R455X and D1772G, supporting the suspected disease causality.

Study medication dispensing and allocation concealment. The subjects in the study were randomized (by a computer-generated block randomization list) to receive either placebo or 4AP (5 mg 3 times daily). The treatment assignments were performed by providing the appropriate treatment kit to the clinic, which contained the blinded treatments, each in the appropriate order for the patient to whom it was assigned. This assignment was communicated to both the clinic and the research pharmacy of Klinikum Grosshadern for study drug dispensing. 4AP was obtained from Synopharm GmbH (Barsbüttel, Germany). A total of 5 mg of 4AP and placebo was labeled and packaged in capsules that were identical in appearance and taste to those at the research pharmacy of the University Hospital Munich, Campus Grosshadern and provided directly to the study subjects. Procedures for the treatment trial are detailed in appendix e-1.

Side effects/toxicity monitoring. The safety analysis comprised a structured interview and clinical and laboratory examinations as well as EKGs of the subjects for possible adverse events (in alphabetical order: abdominal pain, agitation, anxiety, blurred vision, diarrhea, dizziness, epigastric discomfort or pain, gait instability, insomnia, nausea, palpitations, peripheral or oral paresthesias, postural vertigo, tremor, or seizures^{13–15}). Adverse events were classified as mild, moderate, or severe.

Side effects were assessed by collecting the standardized protocol every 4 weeks after treatment onset. At this time, subjects were also asked if they had any specific side effects or any side effects at all. Treatment was discontinued for the following reasons: the patient did not want to continue, the patient exhibited poor compliance (i.e., failure to take the agent at least 6 times during the treatment period), or the patient developed severe side effects during treatment or signs or symptoms during the course of the disease that were not compatible with EA2. Subjects who failed to return for a follow-up examination after 7 months were excluded from the final analysis.

Patient self-report of ataxia episodes and quality of life: Efficacy outcome variables. The study participants documented ataxia episode frequency and duration using structured forms to submit at each clinic visit (at the end of the 1-month-long baseline period, at each 3-month-long treatment period, and at the 1-month-long washout period). At each visit, the participants also used the 28-item VDADL¹² to determine their functional burden of disease on a 10-point scale (1 = independent to 10 = ceasing to participate in the activity).

The primary efficacy outcome measure was the average number of attacks per month based on the patients' documented reports. Secondary outcome measures were the total duration of the attacks per month and the VDADL score¹² as a measure of the burden of disease. The VDADL score was the median of all individual answers.¹²

Statistical analysis. The sample size was calculated using SampleStat (SPSS) and was based on a mean difference in the number of attacks between treatment and nontreatment with 4AP of 50% and SD of 25%. This calculation yielded a sample size of 10 subjects, assuming a *t* test for 2 dependent groups, 2-tailed, a type I error rate of $\alpha = 0.01$, and power of 85%. Because the frequency data are skewed, the median and the interquartile range (IQR) were used as robust measures to describe location and variability. The IQR included the central 50% of

Table Baseline characteristics of the subjects included in the study

Subject no.	Age, y/sex	Sequence of treatment	Mutation in the CACNA1A gene/family history	Ocular motor findings ^a	Other neurologic deficits	Attacks/mo ^b	Total duration of attacks/mo, h ^b	VDADL score ^b
1	57/M	Placebo/4AP	p.D1772G	a, b	Ataxic stance and broad-based gait	6	12	8
2	41/M	4AP/placebo	p.R455X	a, c, d	Ataxic stance and broad-based gait	30	15	8
3	13/M	4AP/placebo	p.A454T/brother of no. 8	a, c, d	Mild gait ataxia	1	4	6
4	43/M	Placebo/4AP	No mutation/positive family history of ataxia of mother and cousin	a, c, d, e	Myotonic dystrophy	10	10	4
5	54/M	4AP/placebo	No mutation/father of no. 6	a, c, d	Mild gait ataxia	6	19	1
6	17/F	Placebo/4AP	No mutation/daughter of no. 5	a, c, d, e	None	6	12	5
7	44/M	Placebo/4AP	p.C256R	a	Ataxic stance and broad-based gait	15	25	9.5
8	30/M	4AP/placebo	p.A454T/brother of no. 3	a, c, d, f	Mild gait ataxia	10	20	1
9	63/F	4AP/placebo	p.C1417fs (c.4252-4256delTGTCGgt); mother of no. 10	a, c, d, e	Broad-based gait	27	35	10
10	42/F	4AP/placebo	p.C1417fs (c.4252-4256delTGTCGgt); daughter of no. 9	a, c, e	Mild ataxic stance	15	18	8

Abbreviations: 4AP = 4-aminopyridine; VDADL = Vestibular Disorders Activities of Daily Living Scale.

^a Ocular motor findings: a = saccadic pursuit; b = slow and hypometric saccades; c = horizontal gaze-evoked nystagmus; d = disturbed visual suppression of the vestibulo-ocular reflex; e = downbeat nystagmus; f = upbeat nystagmus.

^b Data at baseline.

the data under study. To assess the difference in attack frequency between the 2 treatment groups, a subject-specific approach was used that was based on a Poisson mixed-effects model, with treatment and period effects being fitted as fixed. The use of a mixed model allows the retrieval of cross-subject information and meaningful estimates of the magnitude of the treatment effect. A patient-specific intercept was included as a random effect.

For secondary outcomes (attack duration and VDADL score), nonparametric procedures by the Wilcoxon test were used to compare measurements with and without 4AP. Statistical calculations were performed using the R software package (version 2.7.0; www.r-project.org). All reported statistical tests were 2-sided, and the significance level was set to 5%.

RESULTS Ten subjects who met the criteria for inclusion in the study were willing to participate. The diagnosis was proven to have a genetic cause in 7 of these (table).

Two novel mutations, R455X and D1772G, were absent in 96 control DNA samples. They led to a premature stop or altered a highly conserved amino acid residue, indicating pathogenicity. All 10 subjects (7 men) finished the study after 7 months. The mean age was 40.4 ± 16.3 years (SD; range 13–63 years). The flow diagram for the study is shown in figure 1.

At baseline, the median number of attacks per month was 10.00 (IQR 6.00–15.00). The median total attack duration per month was 16.50 hours (IQR 12.00–19.80). The median VDADL score was

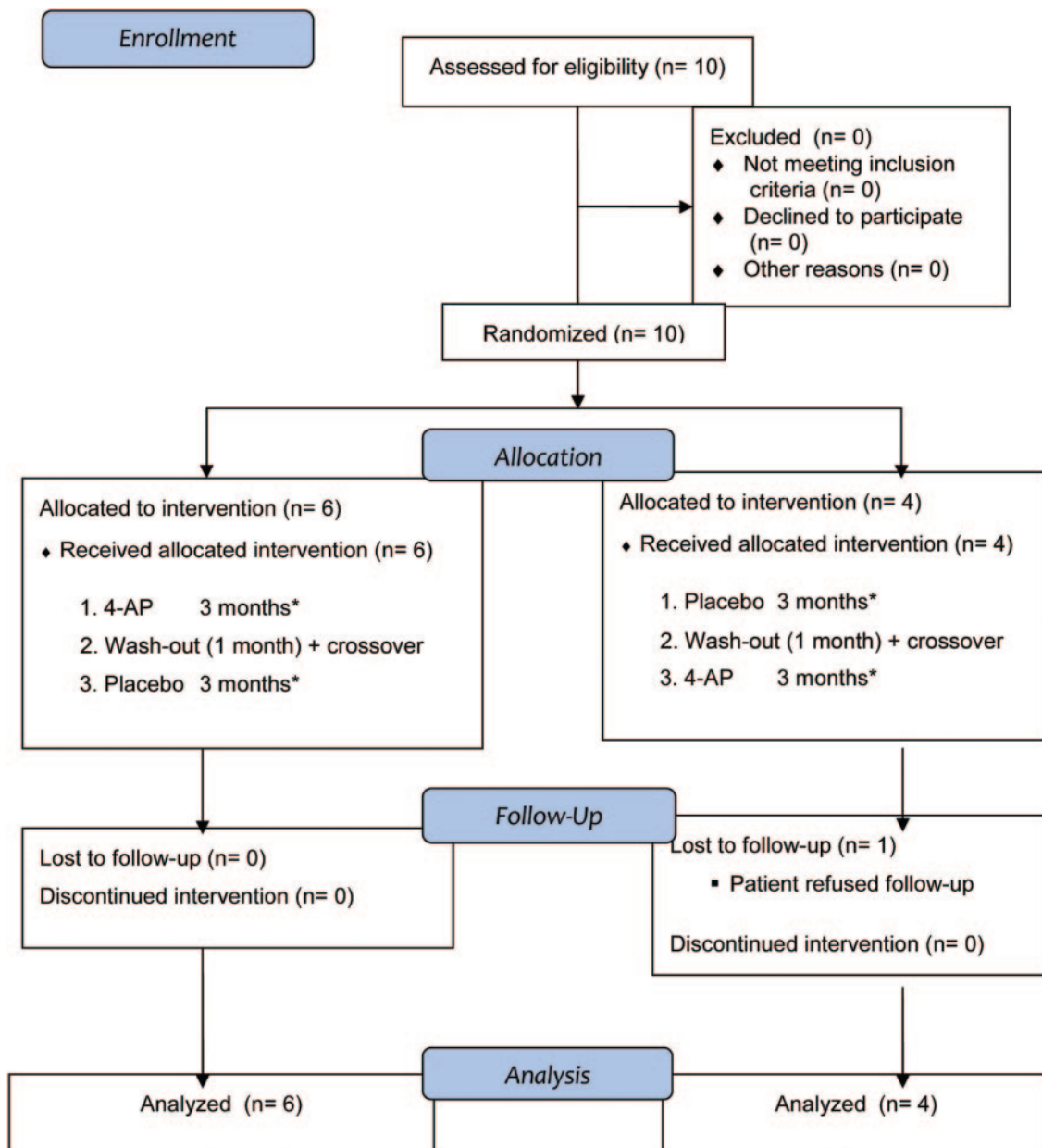
7.00 (IQR 4.25–8.00). Baseline characteristics are summarized in the table.

Subjects receiving placebo had a median of 6.50 (IQR 2.33–13.75) attacks per month. Those receiving 4AP had a median of 1.65 (IQR 1.00–4.78). Statistical analysis with a Poisson random intercept model allowed for quantification of the treatment effect and assessment of the presence of period effects. During treatment, the mean number of attacks per month declined significantly. Administration of 4AP significantly reduced the population mean of attack frequency (reduction from 100% to 34.13%, 95% confidence interval 14.81%–78.65%, $p = 0.03$; figure 2).

For primary outcome measurement, there is no convincing evidence for a period effect ($p = 0.09$; figure e-1). The median cumulative duration of attacks per month decreased from 13.65 (IQR 7.75–16.00) hours during placebo to 4.45 (IQR 2.33–7.50) hours during ingestion of 4AP. The difference between the duration of attacks with and without 4AP was marginally significant ($p = 0.083$, Wilcoxon test; figure e-2).

The administration of 4AP reduced the VDADL score from 6.00 with placebo (IQR 4.25–8.00) to 1.50 (IQR 1.00–4.25). The Wilcoxon signed-rank test revealed a significant decline in the VDADL score ($p = 0.022$; figure 3), indicating a lower burden of disease.

Figure 1 Participant flow



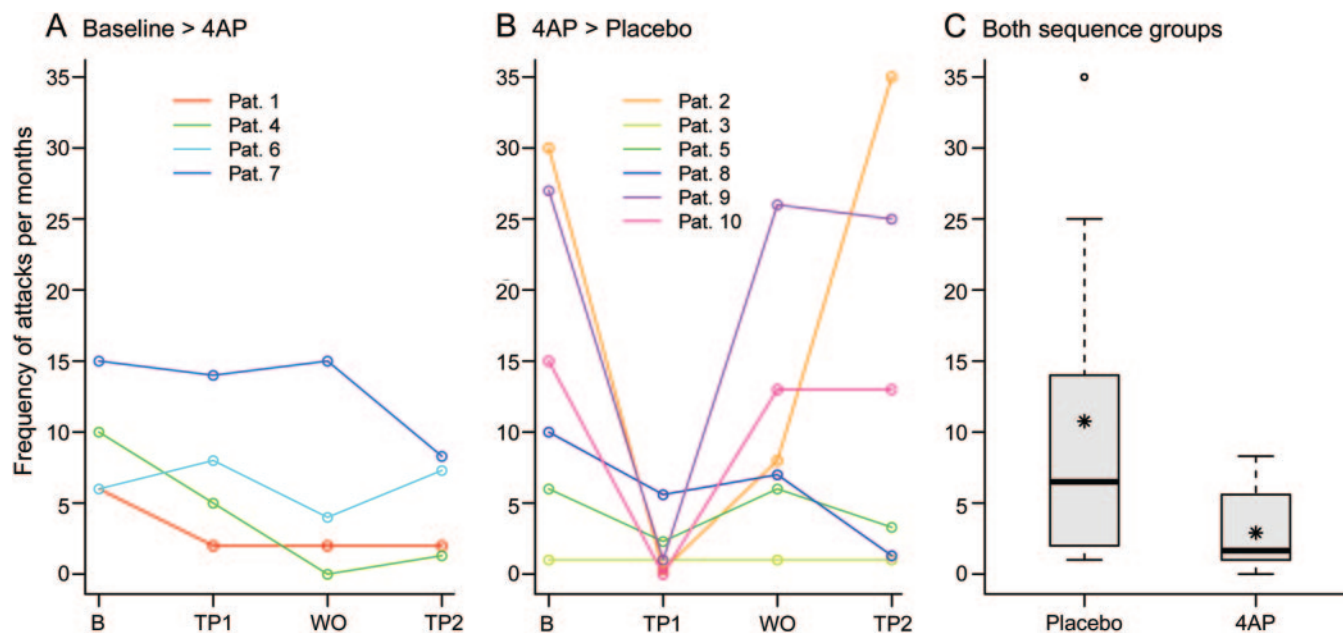
*Physical and neuro-ophthalmologic examinations, patient-reported event diary, and quality of life at the beginning and end of this period. 4AP = 4-aminopyridine.

Only minor adverse events occurred. Patients receiving 4AP reported nausea (n = 2), epigastric discomfort (n = 2), and palpitations (n = 1). One patient receiving placebo treatment reported nausea. Neither 4AP nor placebo had to be interrupted or stopped because of side effects. The follow-up medical reports 2 years after the fourth visit and completion of the treatment trial revealed that 7 of 10 subjects continued to take 4AP; 2 subjects did not continue because of insufficient effect (subjects 1 and 6; table), and one subject did not continue because 4AP was rejected during treatment at a health resort (subject 4; table). Of those still taking 4AP, 2 subjects are completely free of attacks, whereas the

remaining 5 subjects report reduced frequency, duration, and severity of their spells. The dose of 4AP varied between 10 and 15 mg/day. None of these subjects reported side effects.

DISCUSSION A randomized controlled trial had previously established the efficacy of aminopyridines for downbeat nystagmus⁸ and a pilot study for EA2 in humans.⁹ 4AP prevented attacks of ataxia in 2 of 3 patients and markedly reduced it in the third. Cessation of the treatment led to a recurrence within 1–2 days, and subsequent therapy alleviated the symptoms.⁹ These findings in humans were later con-

Figure 2 Number of monthly ataxia attacks (primary outcome)



Number of attacks of ataxia per month (primary efficacy outcome measure) in the 2 treatment sequences (placebo/4-aminopyridine [4AP]; 4AP/placebo). The number was determined by the patient diary. (A, B) Trajectory plots for the 2 sequence groups (1-month baseline period [B], first 3-month treatment period [TP1], 1-month washout phase [WO], and second 3-month treatment period [TP2]). (C) Boxplots for outcome measured during the placebo and 4AP phases (box-and-whisker plot with 25% and 75% percentiles indicating the border of the box, the median [bold line], mean [asterisk], whiskers [extend to the most extreme data point, which is no more than 1.5 times the interquartile range from the box], and outliers). 4AP significantly reduced the number of attacks of ataxia per month ($p = 0.03$). Pat. = patient.

firmed in the tottering mouse model of EA2.¹¹ The present study confirmed and extended the pilot trial to demonstrate that 4AP significantly reduced the attack frequency and improved the quality of life in patients with EA2 and other familial EA with nystagmus not yet genetically defined.

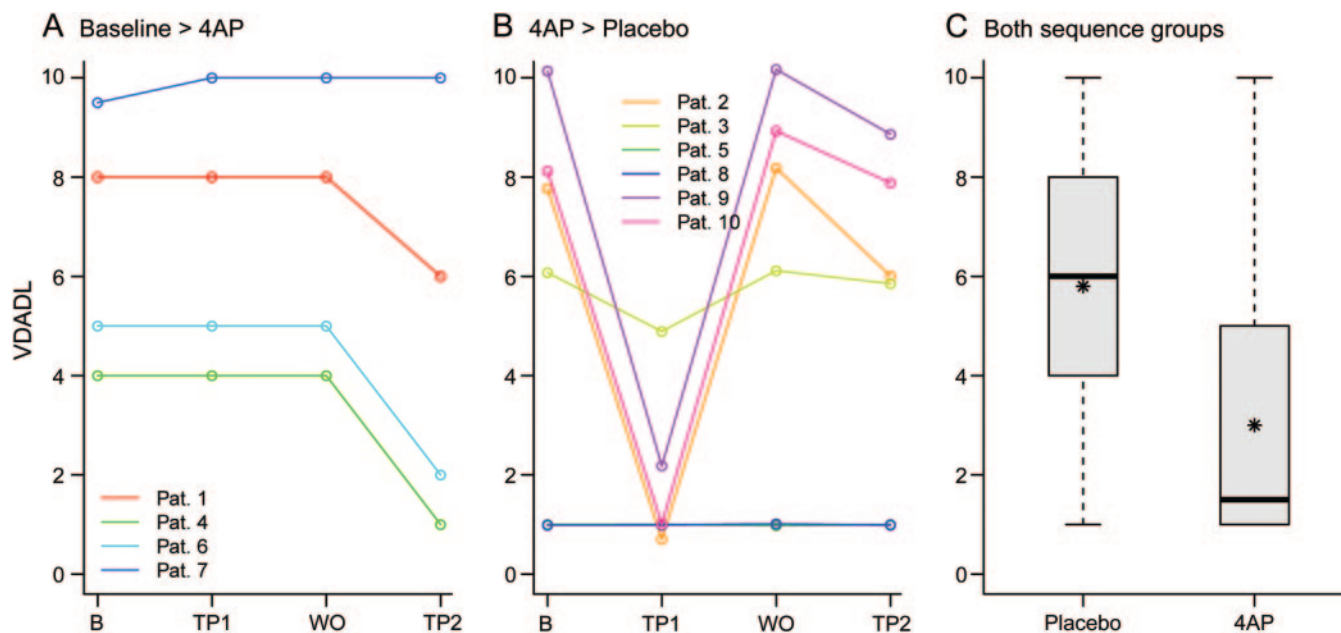
What is the mechanism of action of 4AP in EA2 and related disorders? Ataxia in EA2 is thought to be primarily due to Purkinje cell dysfunction either in neurotransmission^{16–18} or the precision of pacemaking.^{19,20} By inhibiting the potassium currents, aminopyridines increase the duration of the action potential, thereby improving axonal conduction of action potentials and in particular the release of neurotransmitters.²¹ Thus, 4AP and 3,4-diaminopyridine have been used for the symptomatic treatment of Lambert-Eaton myasthenic syndrome,^{14,15} chronic spinal cord injury,²² and multiple sclerosis (MS).¹³ The sustained-release form of 4AP (Fampridine) was recently tested and approved for use in MS.^{23–25} 4AP was shown to reduce triggered attacks in the ataxic calcium channel mouse model tottering.¹¹ In a recent study, 4AP did not influence the rate of activity of Purkinje cells nor did it alter synaptic transmission; however, it restored the precision of pacemaking by blocking K^+ channels and prolonging the action potential and increasing its amplitude of afterpolarization.^{26,27}

4AP was well-tolerated in our study. Side effects were only minor: nausea and epigastric discomfort, each in 2 subjects, and palpitations in one patient. The appearance of only minor side effects in our study can be attributed to the low dosage (5 mg 3 times daily). We observed no cardiac complications, as did recent studies on Fampridine.^{23–25}

The literature reports side effects of aminopyridines such as abdominal pain, agitation, anxiety, blurred vision, diarrhea, dizziness, gait instability, insomnia, palpitations, peripheral or oral paresthesias, postural vertigo, tremor, and seizures in patients treated for Lambert-Eaton myasthenic syndrome, MS, and spinal cord injury.^{13–15} However, in those studies higher doses of up to 40 mg twice daily were often used.

Our study has several limitations. First, although all study participants presented with EA with eye movement abnormalities, they did not all share the same genetic mechanisms. Indeed, although 7 of the 10 subjects were genetically diagnosed with EA2, the remaining 3 subjects did not have a mutation in *CACNA1A*. However, all of these subjects had a family history of EA, suggesting a genetic predisposition in other yet to be identified EA genes. Second, only a few subjects were involved in the study because of the rarity of the disorder. Nevertheless, the beneficial effects of 4AP are significant and welcomed by the pa-

Figure 3 Burden of disease



Vestibular Disorders Activities of Daily Living Scale (VDADL) score as a measure of the burden of disease (secondary outcome). (A, B) Trajectory plots for the 2 sequence groups (1-month baseline period [B], first 3-month treatment period [TP1], 1-month washout phase [WO], and second 3-month treatment period [TP2]). (C) Boxplots for outcome measured during the placebo and the 4-aminopyridine (4AP) phases (box-and-whisker plot with 25% and 75% percentiles indicating the border of the box, the median [bold line], mean [asterisk] and whiskers [extend to the most extreme data point, which is no more than 1.5 times the interquartile range from the box]). There are no outliers. 4AP significantly reduced the VDADL score ($p = 0.022$). Pat. = patient.

tients. Third, the long-term efficacy and side effects of 4AP were not evaluated. A study on the long-term treatment of Lambert-Eaton myasthenic syndrome with aminopyridines reported that the positive effects persisted and that no additional side effects developed.²⁸ We anticipate that a dose-finding study and longer-term trial of 4AP in EA2 and related disorders will be necessary to assess its safety and effects on disease progression. Animal and cell studies have shown neuroprotection.^{29–31}

Our findings demonstrate that 4AP has a prophylactic effect on ataxia attacks in EA2 and related disorders, improves the quality of life, and is well-tolerated. 4AP provides an effective alternative therapeutic approach in the treatment of EA2 and related disorders for those who cannot tolerate or do not respond to acetazolamide.

AUTHOR CONTRIBUTIONS

M.S., R.K., T.K., and K.J. contributed to the study concept and design. M.S. and T.F. acquired data and recruited patients. J.C., T.K., H.N., K.J.-R., and K.J. analyzed data. R.K. analyzed data. M.W., J.C., T.K., T.F. H.N., M.D. F.L.-H., K.J.-R., and K.J. analyzed and interpreted the data. R.K., J.C., C.A., U.M., and K.J. provided statistical analysis. M.S., R.S., and T.B. provided study supervision and coordination. C.A. prepared the figures. M.S., R.K., J.C., C.A., U.M., T.K., T.F., H.N., R.S., M.D. F.L.-H., K.J.-R., T.B., J.C.J., and K.J. drafted/ revised the manuscript for content, including medical writing for content. M.S., R.K., and T.B. obtained funding.

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DISCLOSURE

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M. Strupp, R. Kalla, J. Claassen, et al.

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