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## Unraveling the genetic architecture of migraine: exploring the vascular components

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# CHAPTER 5

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## Effectiveness of acute and preventive migraine treatment in rare migraine syndromes

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*Submitted*

## Abstract

**Background:** Monogenic migraine syndromes offer insights into migraine pathophysiology, but treatment is challenging due to low patient numbers and lack of clinical trials. The Leiden Headache Centre is a national referral centre for these disorders, including Hemiplegic Migraine (HM), Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), and Retinal Vasculopathy with Cerebral Leukoencephalopathy and Systemic manifestations (RVCL-S), providing an opportunity to review treatment effectiveness and side-effects.

**Methods:** Medical records of patients with HM, CADASIL and RVCL-S were reviewed on prescribed acute and preventive medications, treatment effectiveness and side-effects.

**Results:** We included n=78 HM patients (median follow up years (FUY):1 IQR 1-5), n=114 CADASIL patients (FUY:1 IQR 0-3) and n=28 RVCL-S (FUY:8 IQR 5-11) patients. Most effective preventive drugs with the least side-effects for HM were lamotrigine, valproate, topiramate, and acetazolamide. Valproate appeared effective in CADASIL, whereas acetazolamide and propranolol showed efficacy in RVCL-S. Triptans were used by 59% of patients (86/148) with migraine without vascular or other severe lasting side-effects.

**Conclusion:** Preventive treatments aimed at aura symptoms appear to be effective in rare migraine disorders, and triptans appear to be a safe option for acute treatment.

## Introduction

Migraine has a strong genetic component in its pathogenesis and is a hallmark feature of several rare monogenic syndromes.<sup>1</sup> Among these are hemiplegic migraine (HM), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S).

HM is a subtype of migraine with aura that is characterized by motor weakness during the aura phase. There are three known hemiplegic migraine genes: *CACNA1A*, *ATP1A2* and *SCN1A*.<sup>2</sup> Not all patients have a mutation in one of these genes, indicating that there might be undiscovered genes or that hemiplegic migraine might have a multifactorial etiology in some cases, with for instance involvement of co-factor genes such as *PRRT2*.<sup>1</sup> Mean attack frequency is usually lower than in the common types of migraine, but patients with high attack frequency (sometimes including non-hemiplegic migraine attacks) or severe symptomatology still require prophylactic treatment.

CADASIL and RVCL-S are autosomal dominant small vessel diseases. They are caused by heterozygous pathogenic mutations in the *NOTCH3* and *TREX1* gene, respectively.<sup>1</sup> These mutations lead to vasculopathy with cerebral involvement. In both disorders, migraine is part of the phenotype. Migraine prevalence is approximately 40% in RVCL-S and 50% in CADASIL.<sup>3,4</sup>

While these monogenic disorders have contributed greatly to elucidating the pathophysiology of migraine, to date little evidence is available to guide treatment decisions in these patients. Most evidence comes from case reports and series suggesting efficacy of lamotrigine, acetazolamide, verapamil, flunarizine and propranolol.<sup>5-9</sup> A review of migraine treatment in CADASIL indicated that betablockers appeared a poor choice due to unfavorable treatment response.<sup>10</sup>

Receiving adequate acute treatment can also pose challenges for patients diagnosed with rare migraine syndromes. First choice in acute treatment is usually acetaminophen or an NSAID. If common analgesics are not effective, triptans may be prescribed but physicians seem reluctant to start triptans because of presumed vascular side-effects. Migraine with aura was previously thought to be caused by ischemia, but regional cerebral blood flow studies dispelled that notion.<sup>11</sup> Moreover, sumatriptan-induced vasoconstriction occurs only in the dilated vessels, without affecting normal ones.<sup>12</sup> Small retrospective studies in HM and CADASIL patients showed side-effects were

rare and minor.<sup>10,13-15</sup> However, most guidelines still advise against using triptans for patients with hemiplegic migraine or vascular disease.

In this study, we aimed to systematically assess the treatment response and adverse events associated with migraine treatment in patients with HM, CADASIL, and RVCL-S, who were seen at our specialized out-patient clinic.

## Methods

### Participants and procedures

We included patients diagnosed with HM, CADASIL, and RVCL-S, who were referred to the specialized Leiden Headache Centre (national referral centre for rare migraine syndromes) between 2011 and 2021. Only patients with a proven pathogenic *NOTCH3* or *TREX1* mutation were included in the CADASIL and RVCL-S groups. As HM is not always caused by a mutation in *CACNA1A*, *ATP1A2* or *SCN1A*, the HM patients were not required to be proven carriers of a mutation in one of the three established HM genes. A senior neurologist with expertise in hemiplegic migraine (GMT) was always involved in the diagnosis of these patients.

Medical records were reviewed, and data on demographics, migraine, relevant medical history, mutation status and medication use were extracted. Migraine diagnosis was established by an expert neurologist and based on the ICHD-3 criteria (although the criterium for a minimum number of attacks was not taken into account).<sup>16</sup> Distinguishing between migraine with aura and a transient ischemic attack (TIA) in CADASIL patients can be challenging, even more so because aura symptomatology may be atypical in patients with CADASIL.<sup>3</sup> As such, patients were considered migraine patients when migraine aura was the most probable diagnosis. If symptoms were more consistent with a neurovascular event, patients were treated as such. Dosage, treatment duration, adverse events, and decision for (dis)continuation were documented for each prescribed prophylactic migraine drug. Effectiveness was assessed by shared decision making by the expert neurologist(s) and the patient and based on reduction in intensity of the migraine attacks, shorter duration and/or lower frequency, or a combination of these outcomes. Finally, it was documented whether the patient continued using the medication after three months (as this was the predefined minimal period to assess treatment effect). For acute migraine treatments adverse events and effectiveness were documented based on shared decision making of the treating neurologist(s) and the patient.

This study was approved by the Medical Ethics Committee Leiden The Hague Delft. All analyses were performed with SPSS 25.0 (SPSS Inc., IBM, Armonk, NY). Categorical variables were reported as numbers along with their corresponding percentages. When normally distributed, continuous variables were reported as means with standard deviation, and if not normally distributed, as medians with interquartile range.

## Results

### Demographics

In total, 78 HM patients, 115 CADASIL patients, and 28 RVCL-S patients were included in this study. Clinical characteristics are summarized in Table 1. Of the 78 HM patients included, 40% (31/78) was diagnosed with familial HM (FHM), 55% (43/78) with sporadic HM (SHM) and for 5% (4/78) of patients it was unknown whether they had first- or second-degree relatives with HM. Twenty-three HM patients carried a

**Table 1. Patient characteristics**

|                                            | HM<br>(n=78)       | CADASIL<br>(n=114) <sup>a</sup> | RVCL-S<br>(n=28) |
|--------------------------------------------|--------------------|---------------------------------|------------------|
| Age (years)                                | 30 (SD 18)         | 51 (SD 10)                      | 54 (SD 13)       |
| Sex female                                 | 49 (63)            | 65 (57)                         | 18 (64)          |
| Presence of migraine                       | 78 (100)           | 60 (53)                         | 12 (43)          |
| Type of migraine present <sup>b</sup>      |                    |                                 |                  |
| Hemiplegic migraine                        | 78 (100)           | -                               | -                |
| Migraine with aura                         | 20 (27)            | 39 (34)                         | 6 (21)           |
| Migraine without aura                      | 8 (11)             | 18 (16)                         | 11 (39)          |
| Aura without headache                      | 7 (10)             | 23 (20)                         | 5 (18)           |
| Age of migraine onset (years) <sup>c</sup> | 11 (8-16)          | 32 (20-41)                      | 35.0 (20-52)     |
| TIA/CVA                                    | 1 (1) <sup>d</sup> | 60 (53)                         | 4 (14)           |
| Cardiac disease                            | 4 (5)              | 6 (5)                           | 4 (14)           |
| Follow-up duration (months)                | 17 (IQR 6-57)      | 6 (IQR 2-36)                    | 94 (IQR 55-132)  |

TIA: transient ischemic attack; CVA: cerebrovascular accident; CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; RVCL-S: retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations; HM: hemiplegic migraine. Continuous variables are reported as mean (standard deviation) or median (interquartile range), categorical variables as count (percentage). <sup>a</sup> One CADASIL patient had to be excluded due to an uncertain migraine diagnosis. <sup>b</sup> Patients can have multiple migraine diagnoses, <sup>c</sup> CADASIL missing value = 20, Hemiplegic migraine missing value n = 6. <sup>d</sup> One patient (no mutation in *CACNA1A*, *ATP1A2* or *SCN1A*) suffering from linear scleroderma with MRI-proven cerebral ischemia.

**Table 2.** Effectiveness of preventive migraine medication in hemiplegic migraine, CADASIL, and RVCL-S

| Medication                             | Treated, n | Adverse events, n | Effective, n | Discontinued before last follow-up | Reason for discontinuation                                                                                                               |
|----------------------------------------|------------|-------------------|--------------|------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| <b>HM</b>                              |            |                   |              |                                    |                                                                                                                                          |
| Lamotrigine <sup>a</sup> , 2 x 50mg    | 22         | 15/17             | 12/14        | 9/22                               | Ineffective (2/9), side-effects (5/9), ineffective + side-effects (1/9), low attack frequency + pregnancy wish (1/9)                     |
| Valproic acid <sup>b</sup> 3 x 300mg   | 31         | 22/23             | 16/19        | 25/31                              | Ineffective (2/19), side-effects (13/19), low attack frequency (4/19)                                                                    |
| Topiramate <sup>c</sup> 2 x 50mg       | 14         | 7/8               | 5/6          | 13/14                              | Ineffective (2/10), side-effects (5/10), ineffective + side-effects (1/10), low attack frequency (2/10)                                  |
| Acetazolamide <sup>d</sup> , 3 x 250mg | 12         | 10/12             | 7/9          | 10/12                              | Ineffective (2/9), side-effects (2/9), ineffective + side-effects (2/9), low attack frequency (2/9), use of multiple prophylactics (1/9) |
| Verapamil <sup>e</sup> , 3 x 120mg     | 7          | 5/5               | 4/6          | 5/7                                | Ineffective (3/5), side-effects (1/5), ineffective + side-effects (1/5)                                                                  |
| Flunarizine <sup>f</sup> , 1 x 10mg    | 15         | 8/9               | 6/10         | 13/15                              | Ineffective (3/12), side-effects (7/12), ineffective + side-effects (1/12), low attack frequency (1/12)                                  |
| Candesartan <sup>g</sup> , 1 x 16mg    | 11         | 5/5               | 4/8          | 7/11                               | Ineffective (1/5), side-effects (4/5)                                                                                                    |
| Metoprolol <sup>h</sup> , 1x 100mg     | 7          | 1/1               | 3/6          | 6/7                                | Ineffective (3/5), side-effects (1/5), low attack frequency (1/5)                                                                        |
| Propranolol <sup>i</sup> , 1 x 80mg    | 16         | 5/5               | 2/7          | 15/16                              | Ineffective (6/11), side-effects (3/11), ineffective + side-effects (1/11), side-effects + pregnancy wish (1/11)                         |
| Pizotifen, 1 x 1.5mg                   | 6          | 2/2               | 0/3          | 6/6                                | Ineffective (2/4), side-effects (2/4)                                                                                                    |
| <b>CADASIL</b>                         |            |                   |              |                                    |                                                                                                                                          |
| Valproic acid, 3 x 300mg               | 6          | 3/4               | 6/6          | 2/6                                | Side-effects (1/2), attack free (1/2)                                                                                                    |
| Metoprolol, 2 x 100mg                  | 1          |                   | 0/1          | 1/1                                | Ineffective (1/1)                                                                                                                        |
| Propranolol, 1 x 160mg                 | 4          | 2/2               | 4/4          | 3/4                                | Ineffective (1/3), ineffective + side-effects (1/3), pregnancy (1/3)                                                                     |
| <b>RVCL-S</b>                          |            |                   |              |                                    |                                                                                                                                          |
| Topiramate, 2 x 50mg                   | 1          | 1/1               | 1/1          | 0/1                                |                                                                                                                                          |
| Azetazolamide, 3 x 250mg               | 1          | 1/1               | 1/1          | 1/1                                | Side-effects (1/1)                                                                                                                       |
| Propranol 1 x 160mg                    | 1          | 1/1               | 1/1          | 1/1                                | Side-effects (1/1) <sup>j</sup>                                                                                                          |
| Valproic acid, 3 x 300mg               | 2          | 2/2               | 1/1          | 2/2                                | Side-effects (2/2)                                                                                                                       |
| Pizotifen, 1 x 2mg                     | 1          | 0/1               | 1/1          | 1/1                                | No longer available (1/1)                                                                                                                |



|                            |   |     |     |     |                   |
|----------------------------|---|-----|-----|-----|-------------------|
| Metoprolol,<br>1x 200mg    | 1 | 0/1 | 0/1 | 1/1 | Ineffective (1/1) |
| Candesartan,<br>1 x 16mg   | 1 | 0/1 | 0/1 | 1/1 | Ineffective (1/1) |
| Lisinopril,<br>1 x 20mg    | 1 | 0/1 | 0/0 | 1/1 | Ineffective (1/1) |
| Amitriptyline,<br>1 x 40mg | 1 | 1/1 | 0/0 | 1/1 | Ineffective (1/1) |

Medications are ordered based on effectiveness (effective, n (%)). A denominator smaller than the number of patients treated (treated, n) or - indicates missing data. <sup>a</sup>Three patients did not achieve adequate dosage due to discontinuation due to side-effects. <sup>b</sup>Ten patients used less than 900 mg per day, of which two experienced an adequate treatment effect (2 x 300mg and 1 x 300mg, respectively). For the other eight patients no information on effectiveness was available. Of these patients, seven discontinued treatment due to side-effects. <sup>c</sup>Four patients used less than 100 mg per day, of whom one experienced complete remission (1 x 25mg). Two patients did not reach optimal dosage due to side-effects. For the other patients no information on effectiveness was available. <sup>d</sup>Six patients used less than 750 mg per day, of whom two did not achieve adequate dosage due to discontinuation due to side-effects. Two achieved an adequate treatment effect with a dosage of 2 x 250mg. For one patient no information was available on effectiveness and for one effectiveness was unclear as multiple prophylactics were used at the same time. <sup>e</sup>One patient was treated with 1 x 40mg and treatment was discontinued due to side-effects. One patient was treated with a daily dose of 180mg and treatment was effective. Three patients were treated with a daily dose of 240 mg. In one treatment was effective at first. In the end in all these patients treatment was discontinued due to ineffectiveness. <sup>f</sup>Eight patients used 5 mg per day, of whom five discontinued treatment due to side-effects. One patient achieved complete remission. One patient had insufficient effect and for the other patient there was no information on whether there were side-effects or a treatment effect. <sup>g</sup>Four patients did not reach optimal dosage. Two discontinued due to side-effects. One achieved effectiveness with a dosage of 1 x 4mg. For the last patient no information was available on effectiveness or reason for discontinuation. <sup>h</sup>Three patients used less than 100 mg per day, of whom one experienced complete remission (1 x 25mg) but discontinued due to side-effects. One experienced no effectiveness (1 x 50mg) and one had insufficient information to determine effectiveness (1 x 50mg). <sup>i</sup>Three patients used less than 80 mg per day, of whom two discontinued treatment due to side-effects, and one due to ineffectiveness (1 x 40mg). Two patients used 1x 160mg but discontinued treatment due to side-effects. <sup>j</sup>after approximately one year propranolol was tapered off again given the fact that the patient experienced an increase in the severity of already present Raynaud's phenomenon.

pathogenic mutation (*CACNA1A* n = 9, *ATP1A2* n = 14, *SCN1A* n = 0). Two additional HM patients had a variant of unknown significance in *CACNA1A*. There were 60 CADASIL patients with migraine (53%), most experienced migraine with aura attacks (39/60, 65%), 38% (23/60) of the patients had attacks of migraine aura without headache and 30% (18/60) had migraine without aura attacks. Twelve of the 28 RVCL-S patients had migraine (43%), of which most suffered from migraine without aura attacks (11/12, 92%), but 6/12 patients also had attacks of migraine aura without headache (50%) and 5/12 patients had migraine with aura attacks (42%).

Migraine treatment in hemiplegic migraine

Prophylactic treatment

Of the 78 patients with HM, 72 received preventive and/or acute migraine treatment. For one patient it was unclear whether prophylactic medication was started for migraine or for another medical indication. As presence or absence of an effect was also not described, this patient was excluded. Of the included HM patients, 53/78 (68%) were prescribed migraine preventive medication. The preventive drug to be prescribed first was most often valproic acid (n=13) or propranolol (n=11). The treatment responses are summarized in Table 2 and Figure 1. Patients consistently received monotherapy, utilizing one medication at a time, and subsequently used different preventive medications when previous attempts failed.

Valproic acid was prescribed most frequently. Lamotrigine, valproic acid, topiramate and acetazolamide were the most effective medications (effectiveness ranging between 78% and 86%). All medications had a high incidence of side-effects, but these did not always cause patients to discontinue the medication. Severe side-effects (AE grading 3) occurred during use of verapamil and flunarizine. Three patients using verapamil experienced a vasovagal reaction, of whom one fainted. One adolescent on flunarizine gained 25% of his original weight.

Of the HM patients with a proven mutation that were included in this cohort, 16 used preventive medication. When comparing effectiveness between mutation carriers and non-carriers (Supplementary table 1), a few differences are notable. With an effectiveness in 6/6 patients (100%) valproic acid was the most effective prophylactic

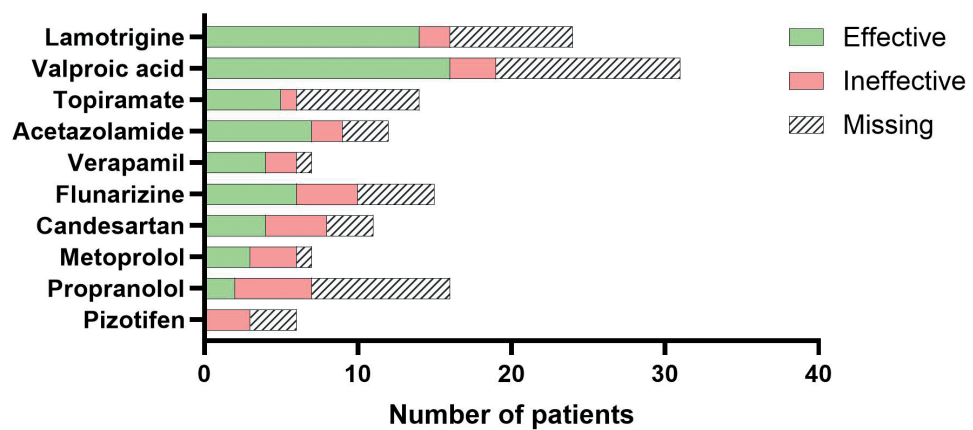


Figure 1. Effectiveness of preventive medication in hemiplegic migraine.

in carriers, where in non-carriers lamotrigine was the most effective treatment (carriers 4/6 (67%) vs. non-carriers 7/7 (100%)).

### ***Acute treatment***

A total of 66 HM patients (85%) used triptans. For 20/66 patients (30%) side-effects were reported. One patient (1.5%) experienced a possible severe side-effect (AE grading 3). Shortly after triptan intake the patient felt unwell and had an aggravation of the HM attack, for which he was temporarily hospitalized. This patient had a good experience with using triptans multiple times before, resulting in shorter duration of the migraine headache. For 52 patients information on effectiveness of triptans was available. Triptans were regarded effective in 26/52 patients (50%), had a varying effect in 8/52 patients (15%) and were not effective in 18/52 patients (35%). Of the 20 patients in whom the effect was described in more detail, 15/20 patients (75%) experienced a decrease in pain severity and 5/20 patients (25%) became pain-free shortly after treatment.

## **Migraine treatment in CADASIL**

### ***Prophylactic treatment***

Of the 60 CADASIL patients with migraine, two patients were excluded because of insufficient information about medication use. Of the remaining 58 CADASIL patients with migraine, 19 received migraine preventive and/or acute treatment. Ten patients were treated with preventive migraine treatments (17%). The preventive most often prescribed first was valproic acid (n=5). The various treatments and treatment responses are summarized in Table 2. All patients used adequate dosages unless described otherwise. Overall, valproic acid was prescribed most frequently (6/10 patients) and was effective at least to some extent in all patients that used it. Although betablockers are not a preferred choice at our clinic, these were used in 5 out of 10 patients, as the general practitioner or a neurologist elsewhere started the medication before referral to our center. Metoprolol was continued in one patient for six months but was not effective and therefore discontinued. Propranolol appeared effective to some extent in four patients, but in two of them treatment was discontinued due to insufficient effect.

### ***Acute treatment***

For two patients it was not clear whether they had used the triptans prescribed to them, and they were, therefore, excluded. Fifteen patients were treated with triptans (27%). One patient (7%) reported mild side-effects (fatigue and weakness of the legs). No severe side-effects occurred. Triptans were effective in 8/14 patients (57%) with available information on effectiveness and possibly effective in 3/14 patients (21%).

Out of the five patients for whom the effect was further specified, 2 out of 5 patients (40%) experienced a shorter attack duration, while 3 out of 5 patients (60%) were headache free after two hours.

### **Migraine treatment in RVCL-S**

Few RVCL-S patients used preventive migraine medication (3/12, 25%). Nonetheless, 9 different treatments were tried. Nonetheless, 9 different treatments were tried. Topiramate, acetazolamide, propranolol and valproic acid were considered effective (Table 2). Interestingly, one patient reported cessation of her migraine attacks after commencing an oral contraceptive. Another patient's migraine frequency increased after stopping oral contraceptive treatment, only to decrease again after restarting the oral contraceptive seven months later. In total, 5 out of 12 patients (42%) used triptans, which were effective in 3 out of 5 patients (60%) and showed some effect in the remaining two patients. No severe side-effects occurred.

## **Discussion**

Rare monogenic migraine syndromes offer valuable insights into migraine's underlying mechanisms, yet effective treatment remains challenging due to low patient numbers and lack of clinical trials. We evaluated migraine treatment response in patients with HM, CADASIL, and RVCL-S, focusing on treatment outcomes and adverse reactions to acute and preventive medications. Lamotrigine and valproic acid exhibited high effectiveness in treating HM attacks. For treating migraine in CADASIL, valproic acid was often effective. Most RVCL-S patients with migraine were not treated with preventive medication. As such, our data do not allow strong recommendations on migraine preventives in RVCL-S. We did observe effectiveness of acetazolamide and propranolol in RVCL-S patients. Side-effects were often reported with preventive migraine treatment. No long-lasting vascular and/or otherwise severe side-effects of triptans were reported in any of the patients with monogenic migraine syndromes.

To date, there have been no randomized controlled trials assessing migraine treatment in HM or CADASIL and no information is available on migraine treatment in RVCL-S. For HM and CADASIL, physicians rely on limited data from either small case studies, small retrospective studies, or expert opinion to guide treatment decisions for these patients (Table 3). For preventive treatment, options that have previously been tried include verapamil, acetazolamide, flunarizine, lamotrigine, betablockers, and one case series on a calcitonin gene-related peptide (CGRP) blocking drug. Reports of response are often conflicting. Several reports indicate that acetazolamide may be effective in

CADASIL<sup>6,9,17,18</sup> Unfortunately, none of the patients in our cohort were treated with this drug. The finding that betablockers ranked among the most frequently prescribed preventive treatments in this study aligns with general guidelines, which recommend these drugs as first-line options for common types of migraine but do not take the type of migraine into account. The only systematic review of migraine treatment in CADASIL indicated that treatment with betablockers was associated with an unfavorable response.<sup>10</sup> Our results support this, and also indicate that betablockers are less suitable for HM patients. Therefore, we recommend starting treatment with preventives such as valproic acid, acetazolamide, or lamotrigine.

There are concerns about prescribing topiramate and valproic acid for migraines to women of childbearing age due to their potential to cause birth defects and other pregnancy-related complications. Patients need to be informed about the risks and use adequate contraceptives. Nonetheless, in patient groups where there are limited effective treatment options, these treatments should still be considered, especially since these medications can be discontinued if pregnancy is desired.

The exact mechanisms through which most anti-migraine medications prevent migraine have not been completely established yet. The migraine preventatives discussed in this study are believed to suppress cortical spreading depolarization (CSD) and reduce neuronal sensitization. Valproic acid reduces glutamatergic neurotransmission by blockage of sodium and calcium channels and enhancement of GABAergic inhibition. Moreover, valproic acid reduces CGRP levels. Reduced glutamatergic neurotransmission, enhanced GABAergic inhibition, and reduced CGRP levels contribute to the inhibition of central pain transmission, neurogenic inflammation, and sensitization.<sup>19</sup> In rats, treatment with valproate decreased CSD propagation velocity.<sup>20</sup> Topiramate reduces hyperexcitability of neurons by enhancing the activity of inhibitory neurotransmitters like gamma-aminobutyric acid (GABA) and inhibiting the activity of excitatory neurotransmitters like glutamate. Topiramate also blocks certain types of voltage-gated calcium channels, which are involved in neurotransmitter release and neuronal excitability.<sup>21</sup> Topiramate has been shown in rats to make the cortex more resistant to CSD and to decrease CSD propagation speed.<sup>22</sup> Lamotrigine blocks voltage sensitive Na<sup>+</sup> channels, and by this mechanism of action it is able to block CSD.<sup>23</sup> In rats, lamotrigine decreased CSD frequency.<sup>20</sup> Interestingly, lamotrigine also increased resting motor threshold to transcranial magnetic stimulation in healthy men.<sup>24</sup> Acetazolamide inhibits carbonic anhydrase, leading to pH changes than can influence neuronal excitability.<sup>25</sup> Vice versa, CSD events may cause changes in pH, both extracellular and intracellular.<sup>26</sup> Acetazolamide's ability to alkalinize blood and tissues may help counteract these pH fluctuations.

**Table 3. Overview of preventive migraine treatment in hemiplegic migraine and CADASIL**

| Drug                       | Possible mechanism of action                                                                                                                                                                                                             | Dose                                          | Efficacy                                                                                                                               | Evidence                                              |
|----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| <b>Hemiplegic migraine</b> |                                                                                                                                                                                                                                          |                                               |                                                                                                                                        |                                                       |
| Acetazolamide              | Alterations in local pH surrounding the P/Q Ca <sup>2+</sup> channel could lead to enhanced channel function.                                                                                                                            | 250-500 mg twice a day                        | May be effective in lessening attack burden.                                                                                           | Low; case reports and small studies <sup>33-40</sup>  |
| Valproate                  | Inhibition gamma-aminobutyric acid (GABA) transaminase, activation glutamic acid decarboxylase and blocking Na <sup>+</sup> channels and low-voltage-activated T-type Ca <sup>2+</sup> channels, possibly enhancing neuronal inhibition. | 1000 mg per day                               | May be effective in lessening attack burden.                                                                                           | Low, case report and series <sup>7,41,42</sup>        |
| Lamotrigine                | blocking voltage-gated Na <sup>+</sup> -channels and N- and P/Q-type voltage-activated Ca <sup>2+</sup> -channels inhibits glutamate release.                                                                                            | 25 mg a day to max 300mg a day                | May be effective in lessening attack burden.                                                                                           | Low; case reports and small studies <sup>43-45*</sup> |
| Flunarizine                | Antagonism of non-selective calcium ion channels, dopamine receptors, 5-HT receptors and antihistamine receptors.                                                                                                                        | 10 mg a day                                   | May be effective in lessening attack burden.                                                                                           | Low; case reports <sup>41,46-49</sup>                 |
| Topiramate                 | Unknown.                                                                                                                                                                                                                                 | 25 mg a day                                   | Deterioration of symptoms observed in a single case of hemiplegic migraine. Another case showed absence of attacks for several months. | Low, single reports <sup>35,44</sup>                  |
| Verapamil                  | Antagonism of calcium on L-type calcium channels, blocking calcium influx and diminishing constriction. Effects on P/Q calcium channels are less pronounced.                                                                             | 120 mg twice or three times a day             | May be effective in lessening attack burden.                                                                                           | Low, case reports, case series <sup>50-54</sup>       |
| Propranolol                | Unknown.                                                                                                                                                                                                                                 | 30-50 mg a day                                | May be effective in lessening attack burden.                                                                                           | Low, case reports and case series <sup>5,39,55</sup>  |
| Galcanezumab               | Blockage of the CGRP pathway.                                                                                                                                                                                                            | 240mg loading dose, followed by monthly 120mg | May be effective in lessening attack burden.                                                                                           | Low, single case series <sup>56</sup>                 |

**CADASIL**

|               |                                                                                                                                                                                                                                          |                      |                                              |                                                                   |
|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|----------------------------------------------|-------------------------------------------------------------------|
| Acetazolamide | Alterations in local pH surrounding the P/Q Ca <sup>2+</sup> channel could lead to enhanced channel function.                                                                                                                            | 125 to 500 mg a day  | May be effective in lessening attack burden. | Low, case report and case series <sup>6,9,17,18</sup>             |
| Valproate     | Inhibition gamma-aminobutyric acid (GABA) transaminase, activation glutamic acid decarboxylase and blocking Na <sup>+</sup> channels and low-voltage-activated T-type Ca <sup>2+</sup> channels, possibly enhancing neuronal inhibition. | 1000-1250 mg per day | May be effective in lessening attack burden. | Low, case reports <sup>6,57,58**</sup>                            |
| Topiramate    | Unknown.                                                                                                                                                                                                                                 | -                    | May be effective in lessening attack burden. | Low, few cases <sup>58**</sup>                                    |
| Flunarizine   | Antagonism of non-selective calcium ion channels, dopamine receptors, 5-HT receptors and antihistamine receptors.                                                                                                                        | 10 mg a day          | May be effective in lessening attack burden. | Low, case report or one case in a larger study <sup>58,59**</sup> |
| Verapamil     | Antagonism of calcium on L-type calcium channels, blocking calcium influx and diminishing vasoconstriction. Effects on P/Q calcium channels are less pronounced.                                                                         | -                    | May be effective in lessening attack burden. | Low, two patients in a larger study <sup>58**</sup>               |
| Pizotifen     | Serotonin antagonist                                                                                                                                                                                                                     | -                    | May be effective in lessening attack burden. | Low, sixteen patients in a larger cohort study <sup>58**</sup>    |
| Propranolol   | Unknown.                                                                                                                                                                                                                                 | -                    | Neutral or unfavorable response              | Moderate, systematic review <sup>10</sup>                         |
| Metoprolol    | Unknown.                                                                                                                                                                                                                                 | 100 mg a day         | Neutral or unfavorable response              | Moderate, systematic review <sup>10</sup>                         |
| Erenumab      | Blockage of the CGRP pathway.                                                                                                                                                                                                            |                      | May be effective in lessening attack burden. | Low, single case report <sup>30***</sup>                          |

<sup>\*43</sup> Lampl et al. Authors describe that treatment effect of lamotrigine was not different for different types of aura. Eight patients with paresis were included. No specific statements about hemiplegic migraine were made. <sup>\*\*58</sup> Tan et al. Authors describe a cohort of 98 CADASIL patients in which treatment response is described of flunarizine n=1, verapamil n=2, topiramate n=3, valproate n=3, pizotifen n=16, propranolol n=16. <sup>\*\*\*</sup> Caution against treating patients with small vessel diseases, such as the monogenic disorder CADASIL, with anti-CGRP pathway medication should be taken until relevant safety data and long term follow up results are available.<sup>32</sup>

Regarding acute treatment, medications such as verapamil, nimodipine, ketamine, triptans, pulse steroids, and hypertonic saline have been utilized.<sup>27</sup> If simple analgesics provide inadequate headache relief, triptans should be considered for the treatment of migraine. Triptans are agonists for 5-HT<sub>1B/1D</sub> receptors and induce vasoconstriction and inhibit the secretion of neuropeptides. Patients with a history of stroke or transient ischemic attack (TIA), or those with a history of hemiplegic migraine or brainstem aura symptoms, are deemed to have a contraindication due to concerns that triptans may increase the risk of stroke. However, in our study only one patient, who had previously benefited from triptan use, experienced a severe HM attack and it remained unclear whether the worsening of this migraine attack was due to triptan intake. Our findings are in line with several previously reported small studies that indicate that triptans may be regarded safe to use in HM and CADASIL.<sup>13-15</sup> As our study and available literature indicates that most patients respond positively to triptans and vascular side-effects are absent, we believe these patients can be offered this treatment safely. With the emergence of 5HT-1F agonists like lasmiditan, there is a non-vasoconstrictive alternative for acute treatment. However, the significant central side-effects of this medication and limited availability in most countries should be taken into account.<sup>28</sup>

Compounds that either inactivate the CGRP molecule by binding to it or its receptor are effective in both acute and preventive treatment of migraine. CGRP might also serve as a protective vasodilator during ischemic events. Therefore, treatments inhibiting the CGRP system might possibly worsen ischemic events.<sup>29</sup> One CADASIL patient was treated with a CGRP receptor monoclonal antibody.<sup>30</sup> A favorable response was reported. Nonetheless, CGRP and its receptor are involved in cardiovascular homeostasis under (patho)physiological conditions. Also, real-world data have shown that blockage of CGRP may lead to an increase in blood pressure, whereas patients with monogenic vascular disorders should strive to control other vascular risk factors.<sup>31</sup> Therefore, we advise physicians to refrain from starting treatment with CGRP blocking agents until long-term vascular safety is proven,<sup>32</sup> at least for CADASIL and RVCL-S patients.

The strength of our study lies in the relatively large cohort of patients with rare monogenic migraine syndromes. Nonetheless, there are limitations to consider. The design could have introduced biases related to selection and recall bias. Assessment of treatment relied on medical records and not a standardized protocol. However, this study was conducted at a clinic specialized in migraine and these monogenic disorders and thus with relatively high-quality documentation in patients' medical records. This precise documentation likely led to a high reported incidence of adverse events in



our study, even if this did not always lead to discontinuation of medication. Most side-effects were mild in nature. Taking these limitations into account, it is important to realize that randomized controlled trials are not expected to be performed in these rare syndromes due to the limited number of patients.

In summary, our results suggest that lamotrigine, valproic acid, topiramate, and acetazolamide are effective preventive treatments for patients with HM. Our findings also indicate that valproic acid may be an effective treatment for migraine in CADASIL patients. As no significant (vascular) side-effects were observed with acute triptan treatment, triptans can be considered in patients with HM, CADASIL and RVCL-S.

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### **Clinical Implications**

- Lamotrigine, valproic acid, topiramate, and acetazolamide are effective in preventing hemiplegic migraine (HM) attacks, while valproic acid appears to be a promising treatment for migraine in CADASIL.
- Despite previous concerns, triptans are crucial for migraine management, showing safety and effectiveness even in high-risk patients.
- Betablockers have an unfavorable treatment response in both hemiplegic migraine and CADASIL.

## References

- de Boer I, Terwindt GM, van den Maagdenberg A. Genetics of migraine aura: an update. *J Headache Pain*. 2020;21:64.
- de Boer I, Hansen JM, Terwindt GM. Hemiplegic migraine. *Handb Clin Neurol*. 2024;199:353-365.
- Guey S, Mawet J, Herve D, et al. Prevalence and characteristics of migraine in CADASIL. *Cephalalgia*. 2016;36:1038-1047.
- Wilms AE, de Boer I, Terwindt GM. Retinal Vasculopathy with Cerebral Leukoencephalopathy and Systemic manifestations (RVCL-S): An update on basic science and clinical perspectives. *Cerebral Circulation - Cognition and Behavior*. 2022;3:100046.
- Lai CW, Ziegler DK, Lansky LL, Torres F. Hemiplegic migraine in childhood: diagnostic and therapeutic aspects. *J Pediatr*. 1982;101:696-699.
- Forteza AM, Brozman B, Rabinstein AA, Romano JG, Bradley WG. Acetazolamide for the treatment of migraine with aura in CADASIL. *Neurology*. 2001;57:2144-2145.
- Pelzer N, Stam AH, Carpay JA, et al. Familial hemiplegic migraine treated by sodium valproate and lamotrigine. *Cephalalgia*. 2014;34:708-711.
- Martikainen MH, Roine S. Rapid improvement of a complex migrainous episode with sodium valproate in a patient with CADASIL. *J Headache Pain*. 2012;13:95-97.
- Donnini I, Nannucci S, Valenti R, et al. Acetazolamide for the prophylaxis of migraine in CADASIL: a preliminary experience. *J Headache Pain*. 2012;13:299-302.
- Glover PA, Goldstein ED, Badi MK, et al. Treatment of migraine in patients with CADASIL: A systematic review and meta-analysis. *Neurol Clin Pract*. 2020;10:488-496.
- Lauritzen M, Skyhøj Olsen T, Lassen NA, Paulson OB. Changes in regional cerebral blood flow during the course of classic migraine attacks. *Ann Neurol*. 1983;13:633-641.
- Benemei S, Cortese F, Labastida-Ramírez A, et al. Triptans and CGRP blockade - impact on the cranial vasculature. *J Headache Pain*. 2017;18:103.
- Artto V, Nissilä M, Wessman M, Palotie A, Färkkilä M, Kallela M. Treatment of hemiplegic migraine with triptans. *Eur J Neurol*. 2007;14:1053-1056.
- Klapper J, Mathew N, Nett R. Triptans in the treatment of basilar migraine and migraine with prolonged aura. *Headache*. 2001;41:981-984.
- Mathew PG, Krel R, Buddhdev B, et al. A retrospective analysis of triptan and dhe use for basilar and hemiplegic migraine. *Headache*. 2016;56:841-848.
- ICHD-3. The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38:1-211.
- Weller M, Dichgans J, Klockgether T. Acetazolamide-responsive migraine in CADASIL. *Neurology*. 1998;50:1505.
- Toni-Uebari TK. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL): a rare cause of dementia. *BMJ Case Rep*. 2013;2013.
- Sprenger T, Viana M, Tassorelli C. Current Prophylactic Medications for Migraine and Their Potential Mechanisms of Action. *Neurotherapeutics*. 2018;15:313-323.
- Bogdanov VB, Multon S, Chauvel V, et al. Migraine preventive drugs differentially affect cortical spreading depression in rat. *Neurobiol Dis*. 2011;41:430-435.
- Latini G, Verrotti A, Manco R, Scardapane A, Del Vecchio A, Chiarelli F. Topiramate: its pharmacological properties and therapeutic efficacy in epilepsy. *Mini Rev Med Chem*. 2008;8:10-23.
- Ayata C, Jin H, Kudo C, Dalkara T, Moskowitz MA. Suppression of cortical spreading depression in migraine prophylaxis. *Ann Neurol*. 2006;59:652-661.
- Akerman S, Holland PR, Goadsby PJ. Mechanically-induced cortical spreading depression associated regional cerebral blood flow changes are blocked by Na<sup>+</sup> ion channel blockade. *Brain Res*. 2008;1229:27-36.
- Li X, Ricci R, Large CH, Anderson B, Nahas Z, George MS. Lamotrigine and valproic acid have different effects on motorcortical neuronal excitability. *J Neural Transm*. 2009;116:423-429.

25. Van Berkel MA, Elefritz JL. Evaluating off-label uses of acetazolamide. *Am J Health Syst Pharm.* 2018;75:524-531.
26. Csiba L, Paschen W, Mies G. Regional changes in tissue pH and glucose content during cortical spreading depression in rat brain. *Brain Res.* 1985;336:167-170.
27. Di Stefano V, Rispoli MG, Pellegrino N, et al. Diagnostic and therapeutic aspects of hemiplegic migraine. *J Neurol Neurosurg Psychiatry.* 2020;91:764-771.
28. Puledra F, Younis S, Huessler E-M, et al. Efficacy, safety and indirect comparisons of lasmiditan, rimegepant, and ubrogepant for the acute treatment of migraine: A systematic review and network meta-analysis of the literature. *Cephalalgia.* 2023;43:03331024231151419.
29. Mulder IA, Li M, de Vries T, et al. Anti-migraine Calcitonin Gene-Related Peptide Receptor Antagonists Worsen Cerebral Ischemic Outcome in Mice. *Ann Neurol.* 2020;88:771-784.
30. Goldstein ED, Badi MK, Meschia JF. Treating chronic migraine in CADASIL with calcitonin gene-related peptide receptor antagonism. *Neurol Clin Pract.* 2019;9:277-278.
31. de Vries Lentsch S, van der Arend BWH, Maassen VanDenBrink A, Terwindt GM. Blood Pressure in Patients With Migraine Treated With Monoclonal Anti-CGRP (Receptor) Antibodies: A Prospective Follow-up Study. *Neurology.* 2022;99:e1897-e1904.
32. de Boer I, MaassenVanDenBrink A, Terwindt GM. The potential danger of blocking CGRP for treating migraine in CADASIL patients. *Cephalalgia.* 2020;40:1676-1678.
33. Athwal BS, Lennox GG. Acetazolamide responsiveness in familial hemiplegic migraine. *Ann Neurol* 1996; 40: 820-821.
34. Battistini S, Stenirri S, Piatti M, et al. A new CACNA1A gene mutation in acetazolamide-responsive familial hemiplegic migraine and ataxia. *Neurology* 1999; 53: 38-43.
35. Striano P, Zara F, Santorelli FM, et al. Topiramate-associated worsening symptoms in a patient with familial hemiplegic migraine. *J Neurol Sci* 2008; 272: 194-195.
36. Suzuki M, Fujiwara K, Tsubuku T, et al. Time course of downbeat positioning nystagmus in familial hemiplegic migraine type 1 treated with acetazolamide. *J Neurol Sci.* 2016; 368: 206-208.
37. Vanmolkot KR, Stroink H, Koenderink JB, et al. Severe episodic neurological deficits and permanent mental retardation in a child with a novel FHM2 ATP1A2 mutation. *Ann Neurol.* 2006; 59: 310-314.
38. Spadaro M, Ursu S, Lehmann-Horn F, et al. A G301R Na<sup>+</sup>/K<sup>+</sup> -ATPase mutation causes familial hemiplegic migraine type 2 with cerebellar signs. *Neurogenetics* 2004; 5: 177-185.
39. Kors EE, Haan J, Giffin NJ, et al. Expanding the phenotypic spectrum of the CACNA1A gene T666M mutation: a description of 5 families with familial hemiplegic migraine. *Arch Neurol* 2003; 60: 684-688.
40. Koch HJ, Sykora A, Hausn P. [Off-label use of acetazolamide in a patient with familial hemiplegic migraine and concomitant psychotic episodes]. *Psychiatr Praxis* 2010; 37: 148-151.
41. Pelzer N, Hoogeveen ES, Ferrari MD, et al. Brain atrophy following hemiplegic migraine attacks. *Cephalalgia* 2018; 38: 1199-1202.
42. Lebas A, Guyant-Maréchal L, Hannequin D, et al. Severe attacks of familial hemiplegic migraine, childhood epilepsy and ATP1A2 mutation. *Cephalalgia* 2008; 28: 774-777.
43. Lampl C, Katsarava Z, Diener HC, et al. Lamotrigine reduces migraine aura and migraine attacks in patients with migraine with aura. *J Neurol Neurosurg Psychiatry* 2005; 76: 1730-1732.
44. Camia F, Pisciotto L, Morana G, et al. Combined early treatment in hemiplegic attacks related to CACNA1A encephalopathy with brain oedema: Blocking the cascade? *Cephalalgia* 2017; 37: 1202-1206.
45. Pascual J, Caminero AB, Mateos V, et al. Preventing disturbing migraine aura with lamotrigine: an open study. *Headache* 2004; 44: 1024-1028.
46. Tobita M, Hino M, Ichikawa N, et al. A case of hemiplegic migraine treated with flunarizine. *Headache* 1987; 27: 487-488.
47. Bhatia R, Desai S, Tripathi M, et al. Sporadic hemiplegic migraine: report of a case with clinical and radiological features. *J Headache Pain* 2008; 9: 385-388.
48. De Cunto A, Bensa M, Tonelli A. A case of familial hemiplegic migraine associated with a novel ATP1A2 gene mutation. *Pediatr Neurol* 2012; 47: 133-136.

49. Peer Mohamed B, Goadsby PJ, Prabhakar P. Safety and efficacy of flunarizine in childhood migraine: 11 years' experience, with emphasis on its effect in hemiplegic migraine. *Dev Med Child Neurol* 2012; 54: 274-277.
50. Razavi M, Razavi B, Fattal D, et al. Hemiplegic migraine induced by exertion. *Arch Neurol* 2000; 57: 1363-1365.
51. Yu W, Horowitz SH. Treatment of sporadic hemiplegic migraine with calcium-channel blocker verapamil. *Neurology* 2003; 60: 120-121.
52. Hsu DA, Stafstrom CE, Rowley HA, et al. Hemiplegic migraine: hyperperfusion and abortive therapy with intravenous verapamil. *Brain Dev* 2008; 30: 86-90.
53. Rispoli MG, Di Stefano V, Mantuano E, et al. Novel missense mutation in the ATP1A2 gene associated with atypical sporadic hemiplegic migraine. *BMJ Case Rep* 2019; 12.
54. Yu W, Horowitz SH. Familial hemiplegic migraine and its abortive therapy with intravenous verapamil. *Neurology* 2001; 57: 1732-1733.
55. Mjåset C, Russell MB. Intravenous nimodipine worsening prolonged attack of familial hemiplegic migraine. *J Headache Pain*. 2008; 9: 381-384.
56. Danno D, Ishizaki K, Kikui S, et al. Treatment of hemiplegic migraine with anti-calcitonin gene-related peptide monoclonal antibodies: A case series in a tertiary-care headache center. *Headache* 2023; 63: 984-989.
57. Wang J, Li J, Kong F, et al. Bipolar II disorder as the initial presentation of CADASIL: an underdiagnosed manifestation. *Neuropsychiatr Dis Treat* 2017; 13: 2175-2179.
58. Tan RY, Markus HS. CADASIL: Migraine, Encephalopathy, Stroke and Their Inter-Relationships. *PLoS One* 2016; 11: e0157613.
59. Monteiro C, Barros J, Taipa R, et al. Sporadic hemiplegic migraine with normal imaging as the initial manifestation of CADASIL. *Cephalalgia* 2012; 32: 255-257.

**Supplementary table 1. Effectiveness of preventive migraine medication in patients with hemiplegic migraine and a pathogenic mutation**

| Medication                              | Treated, n | Adverse events, n | Effective, n | Discontinued before last follow-up | Reason for discontinuation                                                                          |
|-----------------------------------------|------------|-------------------|--------------|------------------------------------|-----------------------------------------------------------------------------------------------------|
| Valproic acid <sup>a</sup><br>3 x 300mg | 10         | 9/9               | 6/6          | 8/10                               | Ineffective (1/7), side-effects (6/7)                                                               |
| Acetazolamide <sup>b</sup><br>3 x 250mg | 6          | 4/6               | 4/5          | 5/6                                | Ineffective (2/4), ineffective + side-effects (1/4), low attack frequency (1/4)                     |
| Topiramate <sup>c</sup><br>2 x 50mg     | 5          | 3/3               | 3/4          | 4/5                                | Ineffective (1/4), side-effects (1/4), ineffective + side-effects (1/4), low attack frequency (1/4) |
| Flunarizine <sup>d</sup><br>1 x 10mg    | 7          | 3/3               | 3/4          | 6/7                                | Ineffective (2/5), side-effects (3/5)                                                               |
| Lamotrigine <sup>e</sup><br>2 x 50mg    | 8          | 5/6               | 4/6          | 4/8                                | Ineffective (2/4), side-effects (2/4)                                                               |
| Candesartan<br>1 x 16mg                 | 2          | -                 | 1/2          | 0/2                                | -                                                                                                   |
| Metoprolol<br>1x 100mg                  | 2          | -                 | 1/2          | 1/2                                | Ineffective (1/1)                                                                                   |
| Verapamil <sup>f</sup><br>3 x 120mg     | 1          | 1/1               | 0/1          | 1/1                                | Ineffective + side-effects (1/1)                                                                    |
| Propranolol <sup>g</sup><br>1 x 80mg    | 5          | 2/2               | 0/1          | 5/5                                | Ineffective (1/3), side-effects (2/3)                                                               |
| Pizotifen<br>1 x 1.5mg                  | 3          | -                 | 0/1          | 3/3                                | Ineffective (1/1)                                                                                   |

<sup>a</sup> Four patients used less than 900 mg per day, of whom one experienced effectiveness. For the other three patients information on effectiveness was not available. <sup>b</sup> One patient used less than 750 mg per day (2 x 250mg) and experienced treatment effect. <sup>c</sup> One patient used less than 100 mg per day. Information on effectiveness was not available. <sup>d</sup> Two patients used 5 mg per day, in one of these patients treatment was effective. <sup>e</sup> One patient did not reach adequate dosage due to side-effects. <sup>f</sup> One patient was treated with a daily dosage of 240mg. Treatment was discontinued as it proved ineffective and side-effects occurred. <sup>g</sup> One patient used less than 40 mg per day and discontinued treatment due to side-effects.