Migraine is a common neurological problem in children that can cause considerable disability.¹ The prevalence rate varies with age and ranges from 3 to 17%.²³ The symptomatology can vary considerably from that of adults, which is reflected in the International Headache Society’s revised diagnostic criteria (2004).⁴

Management of migraine is multimodal, including pharmacological and non-pharmacological strategies. Factors which influence the need for preventative therapy include attack severity, frequency, and impairment of social or educational activities.⁵ A wide range of pharmacological agents such as antihypertensives, antiserotoninerics, antidepressants, anti-convulsants, and calcium channel blockers have been used for this purpose with variable rates of success. Hemiplegic migraine, in which the aura symptoms include motor weakness, poses a particular challenge as the diagnosis is often delayed and no specific preventative agent has been found to be effective.⁶

Flunarizine, a long-acting calcium channel blocker, was originally introduced in the 1970s for the treatment of occlusive vascular diseases. The mechanism of action of flunarizine in migraine is unclear, although its calcium and dopaminergic antagonism may offer some insights into possible subcortical brain targets.⁷ Several studies have demonstrated its efficacy in migraine prophylaxis in adults.⁸⁻¹²

The Children’s Headache Clinic at Great Ormond Street Hospital, London, is a national referral centre and flunarizine has been used in this clinic since 1998. An audit into the use of flunarizine was conducted as part of clinical governance relating to individual safety.

METHOD

This study was registered as an audit with our local research and development department.

We searched our hospital electronic database for all children treated with flunarizine from 1998 to 2009. These data were cross-referenced with the hospital pharmacy records. Individuals with a diagnosis of migraine and who had had at least one follow-up assessment and a minimum of 3 months’ treatment with flunarizine were included in the study. Headache diagnosis was based on the International Classification of
Headache Disorders. The second edition of the International Classification of Headache Disorders \(^4\) was used from 2004 onwards.

A total of 102 children were initially identified. Of these, 72 children (40 male; 32 female; mean age 13y; age range 1y 6mo–17y; diagnoses are listed in Table I) were included in the final analysis (Fig. 1). Thirty children were excluded for the following reasons: 13 had not had a follow-up assessment at the time of the study, nine were non-migraineurs, four had incomplete medical records, and four had an inadequate treatment duration (<3mo).

For each individual, the following data were collected: basic demographic details, disease characteristics before and after treatment with flunarizine, prophylactic medications tried before flunarizine, dosage and duration of treatment with flunarizine, side effects, and reason for discontinuation of flunarizine.

For each individual, the following data were collected: basic demographic details, disease characteristics before and after treatment with flunarizine, prophylactic medications tried before flunarizine, dosage and duration of treatment with flunarizine, side effects, and reason for discontinuation of flunarizine.

Therapeutic outcome was measured by analysing the frequency of attacks before and after starting treatment. Successful prophylaxis was defined as a 50% reduction in frequency of attacks over a 3-month period. In most cases, frequency of attacks was based on the recollection of the individual/caregiver. Daily diary monitoring was also used, where available.

**Statistical analysis**
Summary data are presented as median and ranges.

**RESULTS**
The median duration of the disease until referral was 4 years (range 3mo–13y 10mo). The duration was shorter in individuals with hemiplegic migraine (3y 1mo) than in individuals with non-hemiplegic migraine (4y). Apart from six, all individuals had tried at least one preventative medication before trying flunarizine therapy. An average of three preventives (range 1–10) had been tried per individual before commencement of flunarizine. Table II lists these medications and the number of children that used each of these medications.

**Migraine characteristics**
The median duration of migraine at the time of commencing flunarizine therapy was 4 years and 10 months (range 6mo–14y). The median frequency of attacks for the entire cohort was eight per month (range 0.3–30). The frequency of attacks was four per month (range 0.3–12) in the group with hemiplegia and 12 per month in the remainder.

**Flunarizine dosing**
The initial dose of flunarizine for individuals was determined by the clinician (PJG, PP). The standard dose was 5mg. Dose escalation was made when there was no response to the starting dose or in order to optimize response to treatment. This was done at the discretion of the clinician, usually at the first follow-up.

Flunarizine treatment was commenced after a median interval of 6 months (range 2mo–4y) after referral to the clinic.

**What this paper adds**
- Flunarizine appears to be more effective in treating hemiplegic migraine than other subtypes.
- Side effects lead to withdrawal of flunarizine in around one in five patients.

---

**Table I:** Diagnosis: subcategories

<table>
<thead>
<tr>
<th>ICHD2 code</th>
<th>Category</th>
<th>Number of individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Migraine without aura</td>
<td>44</td>
</tr>
<tr>
<td>1.2.1</td>
<td>Typical aura with migraine headache</td>
<td>13</td>
</tr>
<tr>
<td>1.2.5</td>
<td>Sporadic hemiplegic migraine</td>
<td>8</td>
</tr>
<tr>
<td>1.2.4</td>
<td>Familial hemiplegic migraine</td>
<td>5</td>
</tr>
<tr>
<td>1.3.2</td>
<td>Abdominal migraine</td>
<td>1</td>
</tr>
<tr>
<td>1.3.3</td>
<td>Benign paroxysmal vertigo of childhood</td>
<td>1</td>
</tr>
</tbody>
</table>


**Table II:** Preventative medication used

<table>
<thead>
<tr>
<th>Preventative medication</th>
<th>Number of individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pizotifen</td>
<td>48</td>
</tr>
<tr>
<td>Propranolol</td>
<td>35</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>23</td>
</tr>
<tr>
<td>Topiramate</td>
<td>15</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>9</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>8</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>4</td>
</tr>
<tr>
<td>Clonidine</td>
<td>2</td>
</tr>
</tbody>
</table>

---

**Figure 1:** Flow chart depicting the selection of patients for the final cohort.
This interval was similar in the groups with and without hemiplegic migraine (6mo). The starting dose of flunarizine was 5mg in 62 individuals, 10mg in six, 2.5mg in three, and 7.5mg in one. The dose was escalated in 43 individuals after a median duration of 5 months (range 1–24mo).

Duration of use and tolerability
Individuals were followed up for a median of 24 months (range 3mo–8y 6mo), at 6-monthly intervals, with follow-up over telephone in the interim, if needed. The duration of flunarizine use in this cohort was 12 months (range 3mo–8y).

Side effects
Of the 89 individuals who started treatment with flunarizine, side effect data were available in 76, including all 72 individuals in the final cohort. Of the 72 individuals, 15 (21%) experienced side effects: depression or mood swings in six, weight gain and/or increased appetite in five, tiredness or sedation in two, worsening of headache in one, and both tiredness and worsening of headache in one. Thirteen individuals discontinued treatment, whereas the remaining two continued despite feeling tired as their migraine frequency had improved. Of the four individuals who were not included in the cohort owing to inadequate treatment duration, two developed tiredness leading to withdrawal within 6 weeks. The incidence of side effects in this cohort of 76 individuals was 22%. All the side effects resolved promptly on cessation of therapy.

Discontinuation
Flunarizine was discontinued in 34 individuals: 16 individuals (22%) discontinued after a median interval of 7.5 months (range 3–24mo) because of lack of response, and 13 (18%) because of side effects, and in five children the drug was withdrawn after a median duration of 16 months following complete remission of migraine.

Therapeutic outcome
Forty-one individuals (57%) experienced at least a 50% reduction in frequency (Table III) of attacks. A reduction in frequency of less than 50% was seen in five individuals (7%), while no change was seen in 25 individuals (35%). An increase in the frequency of attacks was observed in one individual.

Hemiplegic migraine group
In the familial hemiplegic group (n=5), of the three individuals tested, two were \(\text{CACNA1A}\) mutation positive. In this group, 11 individuals (85%) showed improvement in the frequency of the attacks by at least 50%.

**DISCUSSION**
This is a retrospective, observational audit in a highly selective individual group, thus limiting the conclusions that can be drawn from the data. The headache clinic in which the audit was conducted is a national referral centre, which partly explains the significantly long duration of migraine (5y 1mo) and therapy with a number of preventative drugs prior to referral to this clinic. The reasons for the therapeutic failure with preventative medications used before referral to this clinic were not studied in detail but could potentially include inadequate treatment duration, parental and individual reluctance to persevere, and side effects. Therefore, this cohort does not necessarily represent refractory migraine.

A systematic Cochrane review of migraine prophylactics in children found beneficial effects for only two drugs, namely propranolol and flunarizine, from a small pool of data, that is, one study for each drug. There is now emerging evidence that topiramate is also effective. Few studies have been carried out to date regarding the effectiveness and side effects of flunarizine in children with migraine. A double-blind, placebo-controlled crossover trial of 70 children conducted by Sorge et al. in the late 1980s showed a significant reduction in frequency and duration of attacks. The reported side effects in this study were weight gain in 22% and drowsiness in 9%. A similar side effect profile has been noted in other adult studies. A large study in adults comparing treatment with flunarizine and propranolol found that the incidence and severity of the side effects were similar in the two groups.

In this audit, side effects were reported in 21% of the children, leading to discontinuation of the medication in the majority of affected children. Depression and/or mood swings were the commonly seen side effects. In one child, there was a past history of depression which appeared to have been reactivated by flunarizine. Actual weight gain was seen in only one child, with the remainder of cases reporting perceived weight gain or increased appetite. All the side effects resolved on discontinuation of treatment. The side effect profile in this cohort was more or less similar to that seen in previous adult and paediatric studies.

In terms of efficacy, 57% of children in the cohort benefited by way of reduction in attack frequency. This is comparable to the outcome data already available from adult and paediatric studies.

<table>
<thead>
<tr>
<th>Type</th>
<th>Improved</th>
<th>Slight improvement</th>
<th>No improvement</th>
<th>Worsening</th>
</tr>
</thead>
<tbody>
<tr>
<td>All forms of migraine</td>
<td>41/72 (57)</td>
<td>5 (7)</td>
<td>25 (35)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hemiplegic migraine</td>
<td>11/13 (85)</td>
<td>1 (7)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Other subtypes</td>
<td>30/59 (51)</td>
<td>4 (7)</td>
<td>24 (41)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>
However, of note is the relatively higher rate of therapeutic efficacy in hemiplegic migraine (85% vs 51%) in this cohort. Moreover, as far as we are aware, this is the largest reported cohort of pediatric hemiplegic migraine treated with flunarizine. Hemiplegic migraine is very rare, so randomized controlled trials are simply not feasible, and this underlines the necessity of carefully collecting clinical data in referral centres.

In terms of treatment duration, 3 months is usually considered adequate to assess efficacy in adults, although one of the authors (PJG) would typically treat for 6 months, especially in hemiplegic migraine. In children, a longer duration has usually been necessary to reach therapeutic efficacy, as seen in our cohort. The treatment effect may be delayed and when it occurs is often robust and long-lasting. Our experience has led us to regard flunarizine as the treatment of choice for hemiplegic migraine.

**CONCLUSION**

Within the limitations associated with the highly selective nature of the individuals and the study methodology, flunarizine appears to be effective in reducing attack frequency in childhood migraine in 57% of children in this cohort, which is consistent with published data. The efficacy, however, appears to be much higher (85%) in children with hemiplegic migraine than in those with the other subtypes. The present authors use flunarizine as first-line medication in children with hemiplegic migraine. Reversible side effects were seen in about one in five of the children studied, with depression and weight gain or increased appetite being the commonest. A multicentre prospective, blinded randomized controlled trial would be needed to substantiate the therapeutic difference observed between children with and without hemiplegic and non-hemiplegic migraines, although given the rarity of hemiplegic migraine this may not be practical.

**REFERENCES**