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A REVIEW ON A FIRST-LINE MEDICATION FOR MIGRAINE FLURAZINE

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ABSTRACT

It's been used for more than 30 years to prevent migraines a powerful calcium channel blocker. Multiple mechanisms, such as suppression of cortical spreading depression, neurogenic irritation and channelopathy, are hypothesized to be involved in flunarizine's action. As an antidote to various types and severity of migraines, Flunarizine is a safe and effective treatment option. Weight gain and tiredness are frequent side effects, although they are tolerable.

KEYWORDS: Calcium channel, Channelopathy, Flunarizine, Hemiplegic, Migraine, Prophylaxis.

INTRODUCTION

It is a neurovascular illness marked by pulsing headache, photophobia or phonophobia, nausea/vomiting, and often accompanied by a suspicion of an attack.[1] In India, anything from 14.12 per cent to 25.2 per cent of people are infected. Two studies demonstrate that more than a third of women in the South Indian population suffer from migraines.[4] Efficacy and safety have been established in various migraine types and patient demographics by the calcium channel blocker Flunarizine, which has been prescribed globally for more than 30 years. Numerous national recommendations for prophylactic migraine medication mention it, and it has been authorized in several countries.[5,6,5,7-9] It is the goal of this page to provide up-to-date information to medical professionals on flunarizine's efficacy and safety as a migraine prevention drug.

REVIEW OF LITERATURE Flunarizine

According to several clinical practice recommendations, Flunarizine is a first-line medication for migraine prevention in both adults and children. Medical textbooks and systematic studies have also validated flunarizine-related clinical data. (Table 1)

Theories on flunarizine's effect in migraines

Channelopathy, cortical spreading depression, and neurogenic inflammation may be influenced by flunarizine's ability to inhibit Ca+2 channels in the neurons of the central nervous system. As seen in (Figure 1),

Table 1: Recommendations for use of flunarizine in migraine.

Guideline/Review/Books	Recommendation
Guidelines	
American Academy of Neurology (AAN) Guidelines 2004: Quality Standards Sub-Committee and Practice Committee of the Child Neurology Society[23]	Flunarizine has been evaluated for several trials in childhood migraine and can be considered for this purpose but it is not available in the United States. (Class I, Level B) There is insufficient evidence to make any recommendations concerning the use of amitriptyline, divalproex sodium, topiramate and propranolol
Recommendations of the German Society for Neurology and the German Migraine and Headache Society[29]	Flunarizine is recommended as one of the drugs of first choice in prophylaxis of migraine
European Federation of Neurological Societies Guidelines 2009[8]	Class A evidence suggest that flunarizine is a first-choice drug in migraine prophylaxis
Italian guideline for primary headaches[30]	Flunarizine is recommended as a class I medication for migraine
Danish Headache Society-diagnosis and treatment of headache disorders[31]	For migraine prophylaxis flunarizine could be in the first line of treatment
National Institute of Care and Excellence guidelines 2014- Migraine prophylaxis: flunarizine[32]	Flunarizine has comparable efficacy as propranolol or topiramate in reducing the frequency of migraines in adults
Clinical Practice Guidelines. Diagnosis and Management of Headache by Ministry of Health, Singapore. 2007[33]	Grade A evidence suggest that flunarizine could be used for migraine prophylaxis
Guidelines on the diagnosis and the current management of headache and related disorders Indian expert panel[34]	Flunarizine could be used as a first line migraine prophylactic drug
Review	
Cochrane Database System Reviews 2003: Drugs for preventing migraine headaches in children[35]	Flunarizine is the only agent that has been studied in rigorous controlled trials and found to be effective in childhood migraine
Book	
Harrison's Textbook of Internal Medicine 20th Edition[36]	Flunarizine is effective in migraine prevention. It is not available in the US. Local guidelines to be considered for use

Cortical depression and channelopathy extend throughout the brain

The increased activity of P/Qtype calcium channels is responsible for the aura phase of the migraine's cortical spreading depression. 10 For example, flunarizine acts as an inhibitor of these channels, raising the threshold for agitation.[11]

Inflammation of the nervous system and channelopathy

Inflammatory tissue responses, such as arteriolar vasodilation, plasma protein extravasation, and degranulation of mast cells, are caused by the release of vasoactive neuropeptides (CGRP, substance P, and neurokinin A).[12,13] In order to avoid neurogenic inflammation, flunarizine blocks the production of these neuropeptides by calcium channel inhibition.[14]

Effectiveness of Flunarizine over time

One in every three migraine sufferers who took the medication for 24 months had an improvement in their symptoms at the 9th month, with no major side effects noted, according to a new study.[15]

Effects after cessation of Flunarizine

After discontinuing prophylactic flunarizine or nimodipine (40 mg three times daily, n=25) dosing for six months, patients in a single-blind randomized study found that the beneficial effects of treatment lasted an average of eight months for the flunarizine group and five months for the nimodipine group.

Flunarizine may have a neuronal rather than a vascular impact on migraine because of the prolonged duration of antimigraine effect in people taking medicine.[16]

Analgesics for migraines

Flunarizine vs other options Flunarizine's efficacy and safety have been compared to other antimigraine medications such as propranolol, topiramate, amitriptyline, and valproate in studies assessing their effectiveness and safety (Table 2). Flunarizine experiments were undertaken before this one had flaws in their design. This study is not randomized, does not cover individuals with an earlier definition of migraine, and does not utilize intention-to-treat analyses. At 3 and 6 months after termination of flunarizine (10 mg once daily), Global Evaluation Scale values were 64.6 per cent and 61.3 per cent, respectively, which were lower than baseline values (p 0.0001) in patients with migraine (n=367). Six months after stopping flunarizine medication, the researchers found that the drug's antimigraine effects remained quite potent.[17] Results from this open-label trial cannot be generalized to all patients.

Compared with other antimigraine medications, flunarizine Flunarizine's efficacy and safety have been compared to other antimigraine drugs such as propranolol and topiramate amitriptyline, and valproate in studies assessing their effectiveness and safety (Table 2). As some of the results show, Flunarizine experiments done in the past had flaws in their planning. Patients who meet an earlier definition of migraine were included,

although the study did not employ intention-to-treat analysis or randomization.

Table 2: Comparative efficacy and safety studies of flunarizine.

Study	Duration	Efficacy	Conclusion
Lücking et al.[37]	4 months	↓ in the average number and duration of attacks in both FLU and PROP group was similar.	FLU and PROP had similar efficacy profile in migraine prophylaxis.
Ludin et al.[38]	4 months	1. ↓ in the number of attacks: FLU=48.1%, PROP=50.0% 2. ↓ in the duration of attacks: FLU=22.2%, PROP=31.2% 3. ↓ in the intensity of migraine attacks: FLU=22.2%, PROP=28.1% 4. Consumption of analgesics during the migraine attacks: FLU=66.6%. PROP=62.4%	Efficacy and safety profile of both the PROP and FLU were comparable.
Shimell et al.[39]	4 months	Both the groups had 4-fold decrease in the migraine attack frequency.	Both FLU and PROP were effective. FLU had lesser safety concerns.
Gawel et al.[40]	4 months	Positive responders: FLU= 67% and PROP= 51%	Efficacy of both FLU and PROP were comparable. FLU may have a better safety profile.
Bordini et al.[41]	4 months	1. Migraine index: PROP=23.4*, FLU=18.7* and both drugs=14.4*. 2. Mean frequency of attacks: PROP=1.26**, FLU=1.2** and both drugs=1.13** (*p < 0.05, **p < 0.01)	Efficacy across treatment groups was similar. The therapeutic effect was maintained for up to 45 days of flunarizine after drug withdrawal.
Diener et al.[42]	4 months	% responders: FLU 5 mg=46%, FLU 10 mg=53%, PROP=48%	FLU efficacy was noninferior compared with PROP.
Luo et al.[43]	12 months	1. ↓ in the monthly headache frequency by >50%: FLU= 66.7%; TOP= 72.7%;	Both FLU and TOP were effective.
Gracia-Naya et al.[44]	4 months	1. ↓ in the frequency of migraine attacks: TOP=59%; FLU=58.5% 2. Responders: TOP=57%; FLU=64% 3. Treatment satisfaction: TOP=78.9%; FLU=75%	Both FLU and TOP had similar efficacy profile.

FLU: Flunarizine, PROP: Propranolol, TOP: Topiramate

Use of low doses of Flunarizine Patients with migraine was randomly assigned to one of two groups and given a single evening dosage of flunarizine (5 mg in group A and 10 mg in group B) for two months before the treatment was switched to the other. Following then, each therapy cycle lasted for two months. More than 80% of patients treated with 5 mg/day for the first two months of their illness showed improvement, whereas 90% of those treated with 10 mg/day saw improvement. 18 During the first two months of therapy, the analytic evaluation of group B's headache parameters indicated a substantial decrease; the results did not alter when the patients were given a daily dose of 5 mg. There was a substantial drop in a few headache measures in group A patients who have first treated with flunarizine 5 mg for the first two months of treatment; however, the next course with flunarizine 10 mg reduced all of the metrics. In group A, prodromes disappeared in 58% of instances, and in those who received flunarizine 10 mg as follow-up treatment, both prodromes and concomitant symptoms vanished in 100% of the cases. 18 Group B had a weight increase (an average of 3.5 kg over two months) and fatigue. There was a reduction in hunger and weariness when individuals were switched to 5 mg. After the first 30 days of treatment, the adverse effects in group A were weight gain (1 kg on average over a month) and mild weariness. After switching to 10 mg/day dosages (4 kg on average over two months). 18 At a daily dose of 10 mg, the medication is more effective. However, flunarizine side effects were more prevalent with a daily dosage of 10 mg. Dose-dependent receptor activation may explain the reduced prevalence of adverse effects with daily dosages of 5 mg. At a dose of 5 mg per day, Flunarizine was recommended by the authors when migraines were not severe enough to warrant the "traditional" dose of 10 mg.[18]

Efficacy of Flunarizine in Different Migraine Types

Migraine of the ear Vestibular migraines is characterised by occurrences of vertigo that last anywhere from five minutes to three days, whether spontaneous or positional, caused by head motion or by a visual source. Nine per cent of migraine sufferers have it.[19] Flunarizine is recommended for the treatment of vestibular migraine by the Canadian Headache Society (CHS).[9] Flunarizine's clinical effectiveness in the treatment of vestibular migraine is supported by the recommendations of the CHS. A (Table 3)

As a child, I suffered from migraines.

Children as young as seven and as old as ten are more likely than younger children (ages 11 to 14) to suffer migraines.[20,21] It is critical to distinguish between episodic tension-type headaches and transient migraine attacks in youngsters within less than one hour. the American Academy of Neurology recommends[22] Flunarizine to treat paediatric migraines.[23] Several studies have found that flunarizine is effective in treating paediatric migraines. Based on these findings, a (Table 3) Flunarizine may be the first-choice medication for children with migraines. It is advised that youngsters

between the ages of 6 and 17 take 5 mg of flunarizine every day (at night).

Migraine that affects the abdomen

Children are more likely to suffer from abdominal migraine, and idiopathic recurring condition that causes pain in the midline umbilical area and nausea/vomiting. Appendicitis, gastritis, worm infestation, and food intolerance are common misdiagnoses in abdominal migraine patients.[24] Prophylactic antimigraine medication is suggested to treat gastrointestinal issues in migraineurs. Efficacy studies have shown that flunarizine can be a preventative therapy for abdominal migraine (Table 3).

Migraine with hemiplegia

Those who suffer from hemiplegic migraines experience various symptoms, including loss of motor function.[25] A preventative therapy is crucial for the treatment of hemiplegic migraine. Flunarizine has shown promise in clinical trials as a flunarizine prophylactic treatment (Table 3).

Safety and management issues with Flunarizine

When used in large doses, flunarizine can potentially interact with the brain's neurotransmitters, which might result in unpleasant side effects.[26] There include tiredness, weight gain, extrapyramidal side effects and depression related to flunarizine. But these adverse effects may be managed by selecting the right dosage, offering medication holidays, prescribing at night, and avoiding its usage in elderly adults (>60 years). Table 4 shows the data. Patients who took flunarizine (10 mg once a day) for 24 months experienced tiredness and weight increase (mean 4.7 kg). The drowsiness was more noticeable in the first month and decreased significantly after treatment. Nine people had indications of depression (out of 120 patients). They all recovered after six weeks of being given short-term pharmaceutical therapy. These six cases included three people who had a history of mental illness.[15,27] Flunarizine's safety in ordinary clinical practice was tested in post-marketing research (3186 patients). Only four patients had extrapyramidal symptoms, whereas 41 patients experienced depression. A history of depression and many migraine treatments were additional risk factors for depression. Open-label, multi-institutional, as well.

Table 3: Efficacy of flunarizine in different migraine types.

Study	Study details	Results	Conclusion
Vestibular migraine			
Lepcha et al.[45]	Group 1: Flunarizine (10 mg daily) + betahistine (16 mg thrice a day) + paracetamol (1 gm daily) Group 2: Betahistine (16 mg thrice a day) + paracetamol (1 gm daily) Duration: 12 weeks	Improvement in episodes (p=0.010) and frequency (p=0.046) of vestibular migraine in flunarizine group.	Flunarizine is effective in vestibular migraine.
Liu et al.[46]	Treatment: Venlafaxine or valproic acid or flunarizine Duration: 3 months	Improvement in dizziness handicap inventory score (p=0.019) and vertigo severity score (p=0.03) in patients receiving flunarizine	Flunarizine has better efficacy compared with venlafaxine and valproic acid.
Childhood migraine			
Visudtibhan et al.[47]	Age: 7 to 15 years Flunarizine: 5 mg or 10 mg	No recurrent migraine: 23% >50% reduction in the migraine frequency: 42%	Flunarizine was effective in the treatment of childhood migraine.
Guidetti et al.[48]	Age: 10 to 13 years Flunarizine: 5 mg Duration: 2 months	Flunarizine decreased migraine frequency, without affecting human growth hormone, thyrotropin releasing hormone, and HbA1c levels	Flunarizine decreased the childhood migraine frequency, without major safety concerns.
Kim et al.[49]	Age: 9 to 15 years Flunarizine: 5 mg Duration: ~6 months	1. Responder rate: FLU= 80%, TOP= 81% 2. Retention rate: FLU= 67%, TOP= 63%	Flunarizine was efficacious in the management of childhood migraine and did not have major side effects.
Mohamed et al.[50]	Age: 1.5 years to 17 years Flunarizine: 2.5 mg to 10 mg Duration: 12 months	Number of patients with >50% reduction in the frequency of migraine: 57%	Children receiving flunarizine demonstrated notable reduction in the migraine frequency and acceptable tolerability.
Abdominal migraine			
Boccia et al.[51]	Treatment: Flunarizine (5 mg, o.d.)	Reduction in: Headache- frequency (p<0.05) duration (p<0.01); Total gastric emptying time (p=0.002), Abdominal pain (p<0.001), Vomiting per month (p<0.01)	Flunarizine alleviated the gastrointestinal symptoms of migraine in children.
Kothare et al.[52]	Cyclic vomiting syndrome: 5 mg; Abdominal migraine: 7.5 mg	Reduction in, Cyclic vomiting syndrome: frequency (57%) and duration (44%); Abdominal migraine: frequency (61%) and duration (51%)	Flunarizine was efficacious in the management of abdominal symptoms of migraine.
Hemiplegic migraine			
Mohamed et al.[50]	Treatment: Flunarizine Duration: 12 months	≥50% reduction in attack frequency in patients with, Hemiplegic migraine: 80% Non-hemiplegic migraine: 57%	Flunarizine had a better efficacy in the patients with hemiplegic migraine than with non-hemiplegic migraine

FLU: flunarizine; TOP: topiramate

Table 4: Flunarizine side effects and their management.

Side effect	Proposed mechanism	Management
Weight gain associated with increased appetite [53]	5-HT antagonism and NA reuptake inhibition and resistance to leptin hormone	Start with 5 mg in first month before using 10 mg Advise patient to follow his or her usual diet without any increase in portion size from day one of therapy Record weight at start and on each follow up
Extrapyramidal side effects[54]	Pre-synaptic (loss of tyrosine hydroxylase in monoaminergic and serotonergic neurons leading to dopamine depletion) and post-synaptic one's factors (blocking striatal dopaminergic receptors)	Not to be prescribed in patients with history of pre-existing symptoms of Parkinson's disease or other extrapyramidal disorders Avoid use in elderly patients (>60 years) If the patient responds satisfactorily after 3 months of therapy and if a maintenance treatment is needed, the dosage schedule should be changed. Each week the patient should receive 5 days of treatment at the same daily dose and 2 successive drug-free days (Drug Holidays).
Depression, mood swings[55,56]	Imbalance in 5-HT and NA	Not to be prescribed in patients with history of depressive illness Sequential treatment with drug holidays
Drowsiness or Somnolence[55,57]	Antihistaminic action	Always give the drug at night-time Start with 5 mg in first month before using 10 mg. At the start of the treatment, patient should be cautioned during activities such as driving or operating dangerous machinery

5-HT: 5-hydroxy tryptamine; NA: noradrenalin

DISCUSSION

Flunarizine is beneficial in the preventative treatment of migraine, demonstrating its multimodal mode of action. Clinical data shows that the efficacy of flunarizine is equivalent to that of first-line medications such as topiramate, propranolol and divalproex sodium. Flunarizine has proven effective in a wide range of migraine types, such as hemiplegic headache, abdominal migraine, sensory migraine and infantile migraine. Long-term preventive therapy with flunarizine is defined by a considerable drop in the frequency and severity of the disease with tolerable side effects. After three decades since its first usage, flunarizine remains a practical therapy choice for migraine.

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