

Review Article

Flunarizine: a review of its role in migraine prophylaxis

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ABSTRACT

Flunarizine, a potent calcium channel blocker has been used for more than three decades for the prophylactic management of migraine. Theories suggest that flunarizine may act through multiple mechanisms such as inhibition of cortical spreading depression, neurogenic inflammation and channelopathy. Flunarizine is efficacious in the management of various types of migraines such as common, classical, vestibular, abdominal, hemiplegic and pediatric migraine. It has a manageable safety profile with weight gain and drowsiness being commonly reported.

Keywords: Calcium channel, Channelopathy, Flunarizine, Hemiplegic, Migraine, Prophylaxis

INTRODUCTION

Migraine is a neurovascular disorder characterized by unilateral pulsating headache, photophobia and/or phonophobia, nausea/vomiting and often preceded by aura.¹ The prevalence of the disease in India is 14.12% to 25.2%.^{2,3} Studies conducted in South Indian population have shown that prevalence of migraine in women is more than 35%, which is strikingly high as compared to the Western population.⁴

Flunarizine, a calcium channel blocker is prescribed worldwide for migraine prophylaxis for more than 30 years and has demonstrated efficacy and safety in different migraine types and patient populations.^{5,6} It is approved in various countries and included in numerous national migraine prophylaxis treatment guidelines.^{5,7-9} This article aims to update the medical practitioners regarding the role of flunarizine in migraine prophylaxis

and the evidences that discuss the efficacy and safety of flunarizine.

REVIEW OF LITERATURE

Flunarizine: guideline recommendations

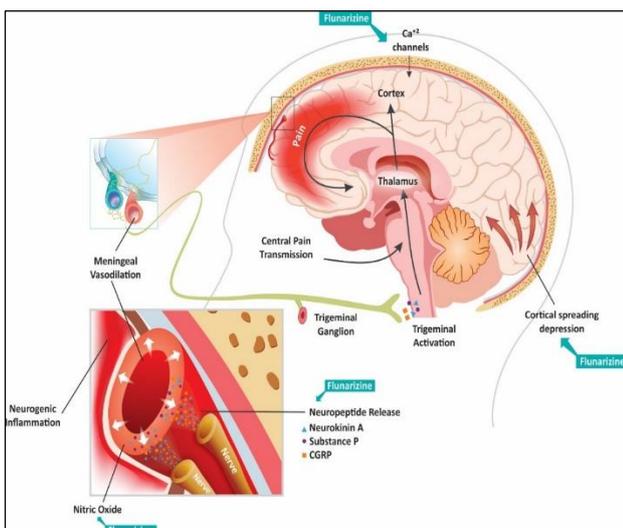
Various clinical practice guidelines recommend flunarizine as a first line drug for migraine prophylaxis in adults and pediatric population. Flunarizine-related clinical evidence has also been supported by systematic reviews and standard medical textbooks. (Table 1)

Flunarizine: role in migraine theories

Flunarizine has been proposed to act on the theories of channelopathy, cortical spreading depression and neurogenic inflammation by blocking the neuronal Ca²⁺ channels. (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

**Figure 1: Various mechanisms of migraine targeted by flunarizine.****Cortical spreading depression and channelopathy**

Cortical spreading depression and associated aura phase of the migraine is caused by enhanced activity of P/Q-type calcium channels.¹⁰ Flunarizine blocks these channels and raises the excitability threshold in spreading depression.¹¹

Neurogenic inflammation and channelopathy

It involves release of vasoactive neuropeptides (calcitonin gene-related peptide, (CGRP) substance P and neurokinin A) that cause inflammatory tissue responses such as arteriolar vasodilation, plasma protein extravasation, and degranulation of mast cells.^{12,13}

Flunarizine is effective in the prevention of neurogenic inflammation by blocking the calcium channel dependent release of these neuropeptides.¹⁴

Flunarizine: long term efficacy

In a 24-month follow-up of patients with migraine receiving flunarizine (10 mg once daily), 72% of participants were responders (decrease in the headache index by $\geq 60\%$) at 9th month without serious adverse events been reported.¹⁵

Flunarizine: efficacy after discontinuation

In a single blind randomized study, patients receiving prophylactic flunarizine (10 mg once daily, n=25) or nimodipine (40 mg thrice a day, n=25) for 6 month, after discontinuation of prophylactic dosing, the positive effect of treatment retained on average for 8 months in the flunarizine group and for 5 months in the nimodipine (p<0.05) group.

The longer retention of antimigraine effect in patients receiving flunarizine indicate that the site of action of the drug is neuronal rather than vascular, which involve slow rearrangement of central process in migraine.¹⁶

In another study, in patients with migraine (n=367) receiving flunarizine (10 mg once daily) for 6 months, at 3 and 6 months follow-ups after treatment discontinuation, Global Evaluation Scale values were maintained at 64.6% and 61.3%, respectively, which were below the baseline value (p<0.0001). The results suggested considerable retention of antimigraine activity 6 months after discontinuation of flunarizine treatment.¹⁷ Since this was an open-label study, the results should not be extrapolated to all the patients.

Flunarizine vs other anti-migraine drugs

Studies comparing efficacy and safety of flunarizine with other prophylactic drugs used for migraine such as propranolol, topiramate, amitriptyline and valproate suggest that efficacy of flunarizine is comparable to that of other antimigraine drugs (Table 2). Some of the former trials conducted with flunarizine have shortcomings in their design. They have included patients with older definition of migraine, not used intention-to-treat analysis and are non-randomized.

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

Flunarizine: use of low dose

In a randomized study, patients with migraine were treated with an initial single evening dose of flunarizine of 5 mg (group A) and 10 mg (group B) for a period of 2 months, which was then reversed. Each of the subsequent treatment periods lasted 2 months. Flunarizine proved to be efficacious in 80% of the patients initially treated (first 2 months) with the dose of 5 mg/day and in 90% of those treated with the dose of 10 mg/day.¹⁸

The analytic evaluation of the headache parameters of the group B already showed a significant decrease at the end of the first 2 month course of treatment; the results did not change when the patients passed on to the following course of treatment in which they received 5 mg daily dose. The group A patients who were initially treated with flunarizine 5 mg showed a significant decrease only for few headache parameters in the first 2 month course of treatment; however, the following course with flunarizine 10 mg caused a significant decrease in all the parameters considered.

Prodromes disappeared in 58% of the cases in group A and after following treatment with flunarizine 10 mg, both prodromes and accompanying symptoms disappeared in 100% of the cases.¹⁸

In group B, the side effects seen were weight gain (3.5 kg on average over 2 months) and tiredness. The appetite gain and tiredness decreased on shifting the patients to 5 mg. In group A, the side effects seen were weight gain (1 kg on average over 1 month) and slight tiredness, which spontaneously disappeared after the first 30 days of therapy. Shifting to doses of 10 mg/day caused increase in weight gain (4 kg on average over 2 months).¹⁸

The drug is more efficacious at the dose of 10 mg/day. Side effects, however, occurred more frequently during treatment with flunarizine at the dose of 10 mg/day.

The lower incidence of side effects with doses of 5 mg/day may be due to a dose-dependent receptor stimulation. The authors suggested the use of 5 mg/day of flunarizine when migraine is not too severe and when obesity prevents use at the "classical" dose of 10 mg.¹⁸

Flunarizine: role in different types of migraine**Vestibular migraine**

Vestibular migraine presents with attacks of spontaneous or positional vertigo, head motion-induced vertigo, and visual vertigo lasting 5 minutes to 3 days. It is observed in 9% of patients with migraine.¹⁹ The Canadian Headache Society (CHS) recommends the use of flunarizine for the management of vestibular migraine.⁹ The clinical evidence demonstrated efficacy of flunarizine in vestibular migraine and are in concordance with the recommendations of CHS. (Table 3)

Childhood migraine

Migraine is commonly observed in children with a prevalence of 5% in children of 7 to 10 years and 17% in adolescents.^{20,21} It is important to diagnose brief migraine attacks in children with less than one-hour duration and differentiate them from episodic tension type headaches.²² American Academy of Neurology guidelines for childhood migraine recommend the use of flunarizine.²³ Studies show that, flunarizine demonstrates good efficacy in the management of childhood migraine. (Table 3) Based on these evidences, flunarizine may be considered the drug of first choice for childhood migraine. Flunarizine 5 mg daily (at night) is the recommended dose for children aged 6 to 17 years of age.

Abdominal migraine

Abdominal migraine, an idiopathic recurrent disorder, is predominantly observed in children and has characteristic episodic midline umbilical pain and nausea/vomiting. Patients with abdominal migraine are often misdiagnosed for appendicitis, gastritis, worm infestation or food intolerance.²⁴ For the management of gastrointestinal disorders in migraine, prophylactic antimigraine therapy is recommended. Clinical studies demonstrated that prophylactic treatment with flunarizine is effective for the management of abdominal migraine (Table 3).

Hemiplegic migraine

Hemiplegic migraine is a migraine with aura including motor weakness.²⁵ For the management of hemiplegic migraine a prophylactic therapy is essential. Clinical studies indicate that flunarizine could be a beneficial option for prophylactic management of flunarizine (Table 3).

Flunarizine: safety concerns and their management

Flunarizine is a lipophilic, poorly water-soluble molecule that has a high blood brain barrier permeability and potential to interact with the neurotransmitters causing side effects.²⁶ The adverse effects associated with flunarizine are drowsiness, weight gain, extrapyramidal side effects and depression. However, these side effects are manageable by selection of appropriate dose, giving drug holidays, prescribing the drug at night and avoiding its use in older individuals (>60 years). (Table 4)

In a 24-month follow-up of migraine patients receiving flunarizine (10 mg once daily), drowsiness and weight gain (mean 4.7 kg) were commonly reported. Drowsiness was perceived more in the 1st month and diminished progressively with a significant reduction at the end of therapy. Depressive symptoms were reported in 9 cases (out of 120 patients). Six out of these required short-term pharmacological treatments and recovered within 4-6 weeks. Three out of these 6 cases had history of mood disorders.^{15,27}

A post-marketing study was designed to evaluate the safety of flunarizine in routine clinical practice (3186 patients). Overall, extrapyramidal symptoms were noted in only four patients and total 41 patients developed depression. Additional risk factors for depression were a history of depression and a high number of previous migraine treatments. Another prospective, open-label, multicenter

study conducted to evaluate the risk/benefit ratio of flunarizine in patients with migraine or vertigo demonstrated a significantly higher incidence of depression in the flunarizine group than in the propranolol group during the follow-up phase of the study. However, extrapyramidal symptoms were not observed.²⁸

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 effective in the prophylactic management of migraine, suggesting its multimodal mechanism of action. Clinical evidence suggests that efficacy of flunarizine is comparable to those of first-line drugs such as topiramate, propranolol and divalproex sodium.

Flunarizine has shown efficacy in a wide range of migraine types such as hemiplegic migraine, abdominal migraine, vestibular migraine and childhood migraine. Long-term prophylactic treatment of flunarizine is marked by a significant decline in the frequency and severity of the disease with manageable side-effects. After three decades since its first use, flunarizine remains a useful treatment option for migraine.

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