

Preventive treatment of migraine

Tratamiento preventivo de la migraña

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RESUMEN

Many of the patients with migraine require a preventive therapy to reduce frequency, severity and duration of the crisis, to improve the quality of life, and to improve the response to abortive therapy of attacks. The treatment can be pharmacological, non pharmacological, or the combination of both.

This article reviews the indications for the prophylaxis of migraine, the different drugs that are, their mechanisms of actions, their adverse effects therapeutic limitations, and cautions when combining the abortive and prophylactic therapy of migraine.

PALABRAS CLAVES: migraine, preventive therapy, pharmacotherapy, botox.

(Ninan Mathew. Preventive treatment of migraine. *Acta Neurol Colomb* 2008;24:S53-S71).

SUMMARY

Muchos de los pacientes con migraña requieren un tratamiento preventivo, para disminuir la frecuencia, la intensidad y la duración de las crisis, mejorar la calidad de vida, y mejorar la respuesta a los tratamientos abortivos para los ataques. El tratamiento puede ser farmacológico, no farmacológico, o la combinación de ambos.

En este artículo se revisan las indicaciones para la prevención de la migraña, los diferentes medicamentos que se utilizan, sus mecanismos de acción, efectos adversos y limitaciones terapéuticas, y las precauciones que se deben tener al combinar la terapia abortiva y preventivo de la migraña.

KEY WORDS: migraña, tratamiento preventivo, farmacoterapia, botox.

(Ninan Mathew. Tratamiento preventivo de la migraña. *Acta Neurol Colomb* 2008;24:S53-S71).

Treatment of individual attacks of migraine generally does not prevent the next attack coming on. On the other hand, frequent use of acute medications, whether they are over-the-counter nonprescription agents or prescription drugs may result in increased number of headache leading to medication over-use headache. Therefore, a significant number of patients with migraines require preventive treatment, which can be divided into pharmacological and nonpharmacological approaches. Many chronic migraine patients may

require a combination of pharmacological and nonpharmacological treatment.

GOALS OF PREVENTIVE TREATMENT

Goals of preventive treatment of migraine are: 1) reduction in the frequency, severity and duration of migraine attacks, 2) reduction of disability and improvement of the quality of life, 3) improvement of the responsiveness of acute attacks to abortive therapy.

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INDICATIONS FOR PHARMACOLOGICAL PREVENTIVE TREATMENT

The following is a modified list from the U.S. Headache Consortium Guidelines.

Migraine that substantially interferes with patient's daily routine despite acute treatment. Missing work, being ineffective at work or interference with routine household tasks and activities or inability to plan and enjoy social and leisure activities are considerations for prophylactic treatment.

1. High frequency of migraine attacks (usually more than two per week). High frequency results in increased disability and higher chances of increased acute medication over-use.
2. Chronic migraine.
3. Failure of acute medications.
4. Contraindications to acute medications, especially those with ischemic heart disease.
5. Troublesome adverse events from acute medications.
6. Acute medications over-use (more than two times a week).
7. Special circumstances such as hemiplegic or basilar migraine with risk of neurological injury.

Table 1 lists the currently used medications for migraine prevention.

HOW DO PREVENTIVE MEDICATIONS WORK?

Potential mechanisms of migraine preventive medications are given in table 2.

There is ample evidence to suggest that there is a central neuronal hyperexcitability in patients with migraine. Agents that reduce frequency and severity of migraine may be acting by decreasing central hyperexcitability, thereby raising the threshold for cortical spreading depression (CSD). Commonly used agents such as topiramate, valproate, propranolol, amitriptyline and methysergide inhibit CSD in a dose dependent fashion by about 40-80 percent (Figure 1). Longer chronic treatment duration produced stronger

TABLE 1. CURRENTLY USED MEDICATIONS FOR MIGRAINE PREVENTION.

Beta-adrenergic blockers Propranolol* Timolol* Nadolol Metoprolol
Tricyclic antidepressants Amitriptyline Nortriptyline Protriptyline Doxepin
Other antidepressants SSRIs** SNRIs (venlafaxine, duloxetine)
Antiepileptic agents Divalproex sodium* Topiramate* Gabapentin Lamotrigine Levetiracetam Zonisamide
Calcium channel blockers Verapamil Flunarizine Diltiazem
5-HT2 antagonists Methysergide Methylergonovine Cyproheptadine Pizotifen
Neurotoxins Botulinum toxin type A - Botox
Nonsteroidal antiinflammatory agents Naproxen, fenamate
Angiotensin inhibitors - Angiotensin converting enzyme (ACE) inhibitor - lisinopril - Angiotensin II type 1 (AT1) receptor blocker - candesartan, olmesartan
Atypical antipsychotics - Quetiapine fumarate
Miscellaneous agents Riboflavin Coenzyme Q10 Feverfew, Magnesium Petadolex (butterbur)
*Approved by FDA in the U.S. **Migraine preventive efficacy of SSRIs has not been shown.

TABLE 2. POTENTIAL MECHANISMS OF MIGRAINE PREVENTIVE MEDICATIONS.

- Raising the threshold for CNS activation
- Enhancing antinociception
- Inhibiting CSD
- Inhibiting peripheral and central sensitization
- Blocking neurogenic inflammation
- Modulating sympathetic, presympathetic or serotonergic tone

CSD suppression. They may reduce activation of “migraine generators” and enhance central antinociception.

A number of biochemical and neurophysiologic observations suggests that mobilization of serotonin (5-HT) may precipitate a migraine attack. The preventive medications have diverse mode of action centrally in the brain. It may involve one or many of the following mechanisms: 5-HT₂ antagonism, regulation of voltage gated ion channels, modulation of central neurotransmitters (norepinephrine, serotonin and dopamine), enhancement of GABAergic inhibition and alteration in neuronal oxidative metabolism. None of the migraine preventive agents are specific for migraine and none of them are effective in more than 60-65 percent of patients. They all have other primary indications.

DRUG SELECTION FOR PREVENTION

Factors determining the selection of agents depend on: 1) patient profile, age, frequency and severity of migraine attacks and the degree of disability, 2) relative efficacy of the drug, 3) comorbidity, 4) side effect profile of the drug, and 5) risk-to-benefit ratio.

FACTORS THAT INTERFERE WITH THE EFFECT OF PREVENTIVE MEDICATIONS

- 1) Concomitant frequent use of analgesics, particularly combination analgesics containing caffeine, butalbital and opioids.
- 2) Over-use of 5-HT₁ agonist, including ergotamine and triptans.

- 3) Vasodilatory drugs such as nitroglycerin and nifedipine.
- 4) Oral contraceptives (in some patients).

REASONS FOR FAILURE OF PREVENTIVE THERAPY

The reasons of failure of preventive therapy include incorrect diagnosis, failure to recognize comorbidities, concomitant use analgesic rebound producing agents, inadequate doses, inadequate treatment period, and not adopting strategic copharmacy (described later) and unrealistic expectations. Since none of the preventive medications are more than 60-65 percent effective and chronic frequent migraines are difficult to be fully controlled. These facts should be explained to the patient before treatment is begun, so that patient will have realistic expectations about the outcome of their treatment.

Not addressing behavioral and lifestyle issues (nonpharmacological treatments) while on medication is another major reason for treatment failure.

PRACTICAL CONSIDERATIONS IN PREVENTIVE PHARMACOTHERAPY

The following are some of the practical considerations while using preventive therapy.

- 1) Start small, go slow. It is extremely important to start with small doses of prophylactic medication initially and to build up the dosage gradually because patients tolerate the medication better with this strategy. For initial therapy, choose the most effective agent with fewer side effects. Large doses of any agents on the first day may cause significant side effects and the patient may hesitate to continue the medication. This is particularly true since medications such as amitriptyline and topiramate. Migraine patients frequently require lower dose of a preventive medication than needed for other conditions. For example, migraine patients require amitriptyline generally in the dose of 25-50 milligrams, whereas, larger doses are used for patients with depression. Similarly, topiramate dose for migraine is around 100 mg per day, whereas,

patients with epilepsy may require 400 mg or more per day. Gradual building up of the dose to therapeutic level cannot be over emphasized.

- 2) Give adequate trial with optimum dose, for at least three months before medication is pronounced ineffective.
- 3) Withdraw medication gradually. This is particularly important in beta-blockers, calcium channel blockers and selective serotonin uptake inhibitors (SSRIs). If headaches are well-controlled, a drug holiday can be undertaken following slow taper program. Many patients experience continual relief after discontinuing medications or may not need the same dose. Dose reduction may provide better risk-to-benefit ratio. However, significant number of patients with frequent or chronic migraine may need to continue their medications for a long time.

THE STEPS BEFORE PREVENTIVE THERAPY IS INITIATED

Steps before preventive therapy is initiated include recognition of medical comorbidities such as hypertension and asthma and psychiatric comorbidities such as depression and panic attacks, anxiety and bipolar illness. Analgesic/ergotamine and triptan rebound must be recognized. Such patients must be detoxified from the offending medications before preventive treatment is prescribed. Always combine pharmacotherapy with nonpharmacological approaches including dietary adjustments, physical exercise, relaxation using any suitable technique particularly biofeedback and behavioral counseling. Lifestyle changes such as regular sleep habits and avoiding unnecessary stressful routines are essential. Adequate contraception for women with the potential to become pregnant is extremely important. Whenever possible, use one agent at a time. There is a place for rational strategic copharmacy, which will be discussed later.

LENGTH OF TREATMENT

There is no set rule for the length of treatment using preventive medications. Generally, preventive treatment is given for at least six months. It is very important that patients understand that

preventive medications take a number of weeks to show the desired effect. Premature discontinuation and frequent switching of medications should be discouraged. Many patients with chronic migraine need continuous prophylactic therapy.

TACHYPHYLAXIS TO PREVENTIVE THERAPY

Clinical experience has indicated that tachyphylaxis becomes a problem in long-term management with preventive agents. Even very effective medications such as methysergide may produce tachyphylaxis after a while; therefore, it is important to monitor the patient over a period of time and adjust the dosage or change medication if necessary.

Overall, assessment of success of prophylactic therapy may become difficult because of spontaneous improvement in migraine, unpredictable cycles of worsening in some patients and high placebo response.

BETA ADRENERGIC BLOCKING AGENTS

Table 3 lists the usual dosages of the commonly used beta adrenergic blocking agents, which are effective in migraine prevention.

Biologic basis of the effect of beta-blockers in migraine may include 5-HT_{2B} antagonism, reduction of the amplitude of contingent negative variation (CNV), and blockage of the nitric oxide activity. Clinical efficacy of beta-blockers has been shown to have no correlation of its ability to enter the central nervous system, membrane stabilizing properties, 5-HT₂ blocking properties or beta receptor selectivity.

Beta-blockers are particularly effective for patients with migraine associated with stress, hypertension and angina. The anti-anxiolytic property of beta-blockers help particularly for people under stress who cannot relax and have frequent migraine.

Beta-blockers are generally fairly tolerated by healthy young adults. However, they can produce fatigue, lethargy, depression and mild cognitive impairment. Nocturnal hallucinations are not uncommon with agents like propranolol whereas it

TABLE 3. BETA ADRENERGIC BLOCKING AGENTS.

Medication	Dosages
Propranolol (Inderal)*	40-240 mg per day in divided doses
Propranolol long-acting (Inderal LA)*	60-60 mg once daily
Nadolol (Corgard)	40-160 mg once daily
Timolol (Blocadren)*	Up to 20 mg twice daily
Metoprolol (Lopressor)	50-100 mg per day
Atenolol (Tenormin)	50-100 mg per day
*FDA approved for migraine in the U.S.	

is rare with nadolol. Fatigue is also more commonly seen with propranolol than with nadolol. Beta-blockers generally should be avoided in patients with severe depression. Decreased exercise tolerance may be a problem and may restrict their use by athletes. Decreased exercise tolerance has to be explained to the patient before it is prescribed. Less common adverse events include male impotence, orthostatic hypotension and bradycardia. Beta-adrenergic agents are contraindicated in patients with congestive cardiac failure, asthma, Raynaud's Disease and in insulin dependent diabetics. Beta-blockers should be avoided in asthenic patients with low energy levels.

For comparison purposes, Pfelt-Hansen and Welch developed a scheme of rating clinical efficacy, scientific proof of efficacy and potential for side effects rated from a scale from 1+ to 4++++. Table 4 gives a rating modified from Pfelt-Hansen and Welch. Beta-blockers in general are rated high in their clinical efficacy.

ANTIEPILEPTIC DRUGS

Normally, a balance exists between GABAergic inhibition and aminoacid mediated excitation in the central nervous system. It is possible that there is a disinhibition due to decreased GABAergic inhibition that results in central neuronal hyperexcitability in migraine patients. This situation is similar to what one might see in epilepsy. GABA is highly concentrated in the visual cortex and periaqueductal area of the brain stem. GABA receptor subunits are expressed in cerebral blood vessels as well.

VALPROATE

There is a dual action of valproate that results in reduction of migraine frequency and severity. The central action in the brain includes an elevation of brain GABA levels, reduction of the firing rates of serotonergic cells in the dorsal raphe and reduction of C-Fos activation in the trigeminal nucleus caudalis. The peripheral effects include reduction of experimental neurogenic inflammation in the trigeminal vascular system, an effect mediated through GABAA receptor agonism. A number of randomized double-blind placebo controlled clinical trials have been done on valproate in migraine that proved efficacious. Divalproex sodium (Depakote) 500 to 1000 mg and sodium valproate are effective as is the extended relief formulation (Depakote ER). The comparative study with propranolol has shown that the efficacy of valproate is more or less equal to that of propranolol, as for the frequency of reduction and reduction of headache days per month.

The most common initial side effect of valproate is nausea and/or vomiting, but as treatment continues, this side effect gradually lessens. It appears that the extended release divalproex sodium (Depakote ER) has less side effects compared to the original preparation. Gradually increasing small doses over a period of 2-3 weeks is recommended. Most patients benefit at doses of 500-1500 mg per day. Other adverse effects include tremor, weight gain, asthenia, and loss of hair, which makes valproate less acceptable to many. Fear of hepatotoxicity is unfounded in healthy individuals. Hepatitis and other hepatic dysfunctions are contraindications. There is no correlation between the blood levels of valproate and its clinical effects; therefore, estimation of blood levels is not absolutely necessary. However, it is recommended that blood count and liver enzymes be tested periodically, possibly once every three months to monitor any change in the profile. The divalproex is definitely contraindicated during pregnancy because of the teratogenic effects, particularly neural tube abnormalities. Interaction with barbiturates should be kept in mind, and it is better to avoid barbiturate (butalbital) containing immediate relief medications in patients receiving valproate. Valproate is now approved for three different indications - epilepsy,

TABLE 4. CLINICAL EFFICACY *, SCIENTIFIC PROOF OF EFFICACY, AND POTENTIAL FOR SIDE EFFECTS*, RATED ON A SCALE FROM + TO ++++ FOR SOME DRUGS USED IN MIGRAINE PROPHYLAXIS.

Drug	Clinical efficacy efficacy	Scientific proof of	Side effect potential	Examples of side effects (examples of contraindications)
Beta-blockers Propranolol	++++	++++	++	fatigue, cold extremities, vivid dreaming, Nadolol depression (asthma, brittle diabetes, atrial ventricular conduction defects)
Timolol Metoprolol				
Antiepileptic drugs Valproate	++++	++++	++	nausea, asthenia, tremor, weight gain, and hair loss (liver disease) paresthesias, cognitive impairment (glaucoma, kidney stones) drowsiness
Topiramate	++++	++++	++	
Gabapentin	+++	+++	+	
Antiserotonin drugs Methysergide	++++	++	++++	chronic use, fibrotic disorders (cardiovascular disease) weight gain, sedation (obesity)
Pizotifen	+++	++	+++	
Tricyclic antidepressants Amitriptyline	+++	++	++	sedation, dry mouth, weight gain (glaucoma) sexual dysfunction
SSRIs	++	+	++	
Calcium channel blockers Flunarizine	+++	++++	+++	sedation, weight gain, depression, parkinsonism (depression, parkinsonism) constipation, water retention (bradycardia, AV conduction defects)
Verapamil	++	+	++	
NSAIDs Naproxen	++	+++	++	dyspepsia, peptic ulcer (active peptic ulcer, renal disease) dyspepsia, peptic ulcer (active peptic ulcer, renal active peptic ulcers, renal disease)
Tolfenamic acid	++	+++	++	
Neurotoxins Botulinum toxin type A	++++	++	+	(myasthenia gravis, (in chronic migraine) patients on aminoglycosides)

Modified from Pfelt-Hansen P, Welch KMA, Migraine; prioritizing prophylactic treatment. In: Olesen J, Pfelt-Hansen, Welch KMA eds. The Headaches 2nd Ed. Philadelphia; Lippincott, Williams & Wilkins 2000:500

*Rating is based on a combination of published literature and personal experience of the above authors and the present author.

migraine and mania. Therefore, if comorbidities such as epilepsy and bipolar illness exist with migraine, valproate may be an appropriate choice.

A rare complication such as pancreatitis has to be kept in mind. If a person receiving valproate complains of persistent upper abdominal pain, the possibility of pancreatitis has to be thought of even though it is a rare adverse event. It is controversial whether long-term valproate therapy produces ovarian dysfunction as a result of multiple ovarian cyst formation, which may lead to menstrual irregularities. Overall, the author tries to avoid valproate in young females because of that reason as well as of the inherent tendency of weight gain with valproate.

TOPIRAMATE

In patients with episodic migraine with aura and migraine without.

Topiramate, a D-fructose derivative has been found to be effective in two large double-blind placebo controlled multicenter trials. Topiramate, both 100 mg and 200 mg are effective in reducing migraine attack frequency by 50 percent in half the patients. The reduction in migraine frequency was statistically significant by the end of the first month and the effect persisted throughout the study showing further decrease in frequency (figure 2). It is recommended to titrate the dose gradually. The recommendation is to start at 25 mg of topiramate daily for a week, increase to 50 mg on the second week, 75 mg third week and 100 mg the fourth week. The efficacy difference between 100 mg and 200 mg is not significant. However, the side effects are more with 200 mg. If a patient cannot tolerate 100 mg, it may be reduced to 75 or 50 (to a tolerable dose). There are many patients who may respond to as little as 25 or 50 mg of topiramate a day.

The immediate side effects are paresthesias involving the extremities and lips and face in some patients. The gradual titration of the dose usually will avoid this problem and a prior explanation of the possible side effect will also help patients. They should be reassured that the paresthesias will disappear as they continue to use the medication. The other important adverse event is cognitive

impairment, which results in difficulty finding the right word, difficulty concentrating and focusing. This may also be explained to the patient beforehand, so that they can adjust the dose according to the tolerable levels. There are patients who may have significant cognitive side effects and the medication may have to be discontinued.

WEIGHT LOSS WITH TOPIRAMATE

One of the desirable side effects of topiramate is weight loss as unlike valproate where weight gain is a major problem. Weight loss is welcomed by patients and, therefore, it becomes an ideal drug for young females with frequent migraine. The topiramate may alter the taste for certain items, particularly for soft drinks, which is a very welcomed adverse event. In the clinical trials, an average weight loss was 4-5 percent of body weight. In clinical practice, we see some patients losing up to 30 percent of their body weight.

Rare adverse events include renal stone formation, which occurs in less than 2 percent of patients and occasional development of glaucoma. If a patient on topiramate complains of eye pain or blurred vision, it is imperative that an ophthalmological examination to rule out glaucoma be done.

Oral contraceptive and topiramate. It has been determined that up to 200 mg of topiramate per day does not interfere with the effectiveness of oral contraceptives. The majority of patients with migraine do not need more than 200 mg of topiramate.

The exact mode of action of topiramate in migraine is not known. It has multiple effects, which include increase in GABA levels in the brain, effects on voltage gated ion channels including calcium channels, and carbonic dehydrase inhibition. Because of the latter, topiramate may be an effective agent for the treatment of idiopathic intracranial hypertension with headache as it helps to reduce the increased intracranial pressure as well as reduce the weight in patients with that condition. Topiramate may also be a good choice for diabetic patients with migraine as it was initially developed as an antidiabetic agent.

TOPIRAMATE IN CHRONIC MIGRAINE

The first major multicenter randomized procedure controlled double-blind preventive treatment study was conducted using topiramate in patients with chronic migraine recently. Chronic migraine patients included in the study were required to have experienced 15 or more headache days, at least half with migraine or migrainous headache. They should have had a MIDAS scale of 11 or more during 28-day baseline phase, prior to randomization to topiramate 100 mg per day or placebo. Migraine was defined according to ICHD-2 criteria. Migrainous headache was moderate to severe in intensity, with one additional migrainous feature (unilateral, pulsatile, photophobia or sonophobia, nausea or vomiting, worsened by physical activity). Figure 3 and 4 shows the results. Topiramate 100 mg produced statistically significant reduction in the mean number of monthly migraines/migrainous headache days and mean monthly migraine days. Adverse events were more or less the same as that was reported in the episodic migraine studies.

GABAPENTIN

Gabapentin has been shown to be effective in a randomized double-blind placebo controlled trial for prophylaxis of migraine. Gabapentin increases the GABA levels in the brain, but its precise mechanism of action is unknown. Gabapentin is a fairly well tolerated medication, and a dose up to 2400 mg per day is tried. An initial open label study showed efficacy of Gabapentin in migraine and transformed migraine. Gabapentin has been shown to have a beneficial effect on neuropathic pain states such as diabetic neuropathy. Post herpetic neuralgia, trigeminal neuralgia and complex regional pain syndrome. It has also been shown to be as effective as propranolol in the treatment of essential tremor. Low side effect profile of Gabapentin is a distinct advantage over valproate and topiramate even though the clinical efficacy is not as good.

Gabapentin has been shown to have beneficial effects in patients with chronic daily headache. The efficacy and safety of gabapentin 2,400 mg/d was evaluated in a 21-week, multicenter, crossover trial. Patients (N=133) with headaches of greater than 4 hours' duration on at least 15 days per month over

the 6 months preceding the trial were the focus of the analysis. Approximately two thirds of the patients had a combination of migraine and tension type headaches and almost equal proportions of the remainder of patients had one of these two types of headaches. After a 4-week baseline period, patients were randomized to either gabapentin (n=68) or placebo (n=65) and entered a 2-week, dose-titration period followed by six weeks of maintenance. A 1-week washout preceded treatment crossover, followed by an identical 2-week titration and 6-week maintenance period. Efficacy was reported only in those patients who completed the trial; the analysis of the intent-to-treat population was not reported.

After the treatment periods, the percentage of headache-free days per month showed a 9.1 percent difference favoring gabapentin (P=0.0001). The mean reduction in the headache days per month was significantly greater after gabapentin treatment (P=0.0004).

Adverse events were experienced by 47 (39 percent) patients in the gabapentin group and 17 (14 percent) patients in the placebo group. Somnolence, dizziness and edema were some of the common AEs.

Other antiepileptic drugs such as levetiracetam, zonisamide, and lamotrigine have not been proven to be useful in double-blind placebo controlled trials. However, certain physicians use them and there may be some usefulness for these agents in some patients.

CLINICAL USE OF ANTIEPILEPTIC DRUGS

Although beta-blockers are widely use as an initial drug in migraine prevention, antiepileptics may be considered as first line drug under many circumstances. When beta-blockers are contraindicated in such conditions as asthma, congestive cardiac failure, low blood pressure, orthostatic hypotension, cardiac conduction defects, anticonvulsants become first line drugs. Beta-blockers are known to produce depression in some patients; therefore, they can be replaced by an anticonvulsant. Patients with migraine who are on immunotherapy for allergy treatments, should not take beta-blockers concomitantly and, therefore,

they may be switched to an antiepileptic drug. Beta-blockers are known to reduce exercise tolerance in those who exercise regularly. Antiepileptic drugs have no effect on exercise tolerance. When there is comorbid epilepsy and migraine or epilepsy and bipolar illness, antiepileptics may be considered as first line drugs.

Among the antiepileptic drugs currently used, topiramate should be the first choice because of its proven efficacy and ability of the compound to cause weight loss. Gradual titration of the dose and adjustment according to the tolerability is important. There is no interaction between antiepileptic drugs and 5-HT₁ agonists such as ergotamine and triptans.

ANTIDEPRESSANTS

Tricyclic compounds

Antidepressants, particularly tricyclic compounds, are widely used in the prophylaxis of migraine and tension-type headache. Amitriptyline (Elavil) in doses ranging from 10 to 200 mg per day is probably the most commonly used antidepressant in migraine prevention. Biologic basis of its action include modulation of 5-HT and norepinephrine. Amitriptyline has been shown to inhibit trigeminal neuronal activation experimentally. Antidepressant effect adds to the clinical benefit even though the antimigraine effect of amitriptyline has been shown to be independent of the antidepressant effect.

Tricyclic antidepressants are particularly effective in patients with frequent migraine attacks, migraine with medication over-use, migraine with insomnia, migraine with interictal tension-type headache, chronic daily headache and migraine with depression. Combination therapy of tricyclic antidepressants, particularly amitriptyline, with beta-blockers is a very practical way of treating patients with frequent migraine, particularly those associated with depression, stress, anxiety and sleep problems.

Amitriptyline causes more anticholinergic side effects such as dry mouth and dysuria than nortriptyline. The later is a good choice for those with the above side effects with amitriptyline.

SSRIs

In one trial, fluoxetine, an SSRI antidepressant, was not found to be more effective than placebo for migraine prophylaxis. The same study reported that fluoxetine is useful in treating chronic daily headaches. However, SSRIs are used extensively in patients with chronic migraine, particularly because of the comorbid depression and anxiety. F-fluoxetine was found to produce statistically significant improvement of attack frequency, headache days per month, and patients' global satisfaction of its usefulness.

The major disadvantage of SSRIs is the sexual dysfunction side effects and the withdrawal effects on the patient when medication is discontinued. Withdrawal is worse for paroxetine. In general, tricyclic antidepressants are preferred over SSRIs in the preventive treatment of migraine.

SNRIs

Venlafaxine (Effexor), the first specific serotonin and norepinephrine uptake inhibitor (SNRI), may be effective in migraine prophylaxis and is used by many physicians even though there are no double-blind placebo controlled trials. The author uses venlafaxine more often than SSRIs. Anxiety reducing property of this compound is an added advantage. Duloxetine, another SNRI, may be a useful agent, even though there are no controlled trials in preventive treatment of migraine. It has been reported to be useful in patients with neuropathic pain.

CALCIUM CHANNEL BLOCKERS

The agency for healthcare policy and research analyzed 45 controlled trials. Flunarizine was found to be most effective, nimodipine had mixed results and nifedipine was difficult to interpret. Verapamil was more effective than placebo in two of three trials, but those two trials had high dropout rates rendering the findings uncertain.

However, the most commonly used calcium channel blocker for prophylaxis of migraine is verapamil, even though it has lesser clinical

efficacy compared to flunarizine. It is a well-tolerated medication; therefore, many physicians are comfortable using it on a long-term. Verapamil is the drug of choice in the prophylaxis of cluster headache where larger doses like 480 mg or more may be used. For migraine prophylaxis, the average dose is 180 mg-240 mg per day. Sustained release formulations are available making it convenient for use one dose a day. Patients with complicated migraine, with neurological symptoms (prolonged aura) may benefit from verapamil preventive therapy. However, there are no studies to support that clinical impression. Many physicians use verapamil to treat late life transient migraine accompaniments, described by Miller Fisher. Verapamil is especially useful in patients with comorbid hypertension or in those with contraindications for beta-blockers such as asthma or Raynaud's disease. The most common adverse events of verapamil are constipation and water retention.

Flunarizine is the most effective calcium channel blocker; however, it is not available in the United States. It is widely used in many parts of the world. Adverse events include parkinsonism, depression and weight gain.

It is interesting to note that many of the prophylactic agents for migraine effect voltage gated ion channels particularly, calcium channels. These include calcium channel blockers, valproate, topiramate and propranolol through its membrane stabilizing effect. Developing the specific antagonist that act on P/Q type calcium channel (based on the finding of specific P/Q calcium channel chromosome 19 abnormality (CACNA 1A) in familial hemiplegic migraine) may improve preventive therapy of migraine.

5-HT₂ ANTAGONISTS

Methysergide has remained one of the most effective antimigraine prophylactic agents. However, as shown in table 3, the potential side effects might be viewed as less than attractive.

Methysergide may cause weight gain and peripheral edema. With more than six months of use, retroperitoneal, pericardial and subendocardial fibrosis may occur, a rare complication (1 in 2500). It appears to be an idiosyncratic reaction, as the

great majority of patients do not develop these complications. Major vessel constriction, mesenteric vascular fibrosis and small bowel infarctions have been reported rarely. Concurrent use with other ergots alkaloids, beta-adrenergic blockers, dopamine, erythromycin or troleandomycin may increase the risk for arterial spasms and occlusion. Methysergide should not be combined with triptans. Methysergide should be reserved for very refractory severe migraine patients. Many clinicians recommend an interval without the drug for four weeks every six months, but whether this practice decreases the toxicity is unclear. If one were to use Methysergide over a long-term, periodic check ups for fibrotic reactions - including chest x-ray, echocardiogram and CT of the abdomen - are recommended. Methysergide is not easily available at the present time. Compounding pharmacies in various cities might be able to dispense it.

CYPROHEPTADINE

Cyproheptadine appears to be an effective agent in the preventive treatment of migraine in children and may be the drug of choice in the pediatric age group, even though they are no controlled trials to support this practice. It has no major side effects except increased appetite, weight gain and slight drowsiness. Best indication is in smaller children in the age range of 7 to 10, who have very frequent migraine episodes.

PIZOTIFEN

Pizotifen, a benzocycloheptathiophene derivative, is also effective. Adverse events include drowsiness, increased appetite and weight gain. It is not available in the U.S., but it is available in Canada and many other countries.

NONSTEROIDAL ANTIINFLAMMATORY AGENTS

Naproxen and tolfenamic acid are two agents that have been tried for migraine prevention. Clinical efficacy of both is not as good as that of beta-blockers, valproate, topiramate or methysergide. The gastric and renal side effect potential prevents them from being long-term drugs. However, for

short-term prophylaxis, particularly around the menstrual time, agents like naproxen sodium may be very effective.

Nonsteroidal antiinflammatory agents act in multiple ways producing prostaglandin inhibition, reducing neurogenic inflammation perivascularly, and influencing central serotonin neurotransmission. There is no correlation between the degree of platelet inhibition and the prophylactic restrictiveness of nonsteroidal antiinflammatory agents.

MISCELLANEOUS AGENTS

Even though magnesium deficiency in the brain is implicated in the pathophysiology of migraine, there is still no proof that magnesium replacement is of any benefit in migraine prophylaxis. The only double-blind placebo controlled study in patients with migraine without aura (69 patients) reported negative results even though a previous small study in menstrual migraine reported magnesium to be effective. Mauskop et al emphasized the importance of serum ionized magnesium measurements in determining the magnesium state in migraine patients and have used intravenous magnesium in patients found to have low ionized magnesium levels. These observations have not been confirmed, yet.

RIBOFLAVIN

Based on theoretical considerations of possible altered mitochondrial energy metabolism in migraine and the striking link between mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) and migraine, riboflavin 200 mg twice daily was studied in a double-blind placebo controlled trial. Riboflavin reduced the frequency of migraine significantly compared to placebo.

Riboflavin (vitamin B2) is the precursor of flavin mononucleotide and flavin adenine dinucleotide, co-enzymes required for the activity of flavoenzymes in the transfer of electrons in oxidation - reduction reactions. The beneficial clinical response to high dose of riboflavin has been observed in some patients with mitochondrial myopathies and encephalomyopathies associated with mutation of mitochondrial DNA. If deficient mitochondrial

energy metabolism is a casual factor in migraine, logistically, riboflavin might have some beneficial effect. The author has not found riboflavin to be significantly effective in migraine prevention.

CO-ENZYME Q10

Co-enzyme Q10, which acts in a similar fashion influencing mitochondrial oxidative metabolism has been reported to be effective as a prophylactic agent in migraine in a double blind, placebo controlled trial. Further confirmation is needed before it can be recommended as an effective treatment.

NATURAL PRODUCTS

Feverfew (*Tanacetum parthenium*) is a medicinal herb, the effectiveness of which has not been established. Feverfew may be acting through nitric oxide mechanism, which is implicated in the pathophysiology of migraine. Since there is no definite evidence based efficacy determination, feverfew cannot be recommended at the present time.

Petasites hybridus root (butterbur) is a perennial shrub. A standard extract (75 mg twice daily) was effective in a double-blind placebo controlled study. The most common adverse event was belching. Until confirmatory studies are done or extensive clinical experience with this agent is available, it cannot be advocated as an effective preventive treatment for migraine.

ANGIOTENSIN INHIBITORS

An association has been reported between migraine and the angiotensin converting enzyme (ACE) - DD gene. One randomized, double-blind, placebo controlled crossover trial involving 47 patients (60 enrolled) with episodic migraine suggested that lisinopril in doses of 20 mg are effective in reducing hours with headache and headache pain, headache days, migraine days, and severity index by 20 percent, 17 percent, 21 percent and 20 percent respectively, compared with placebo. Cough is one of the main side effects associated with angiotensin converting enzyme inhibitors. Further studies are needed.

ANGIOTENSIN 2 RECEPTOR BLOCKER - CANDESARTAN

In a similar study to the one with lisinopril, the same group demonstrated that 16 mg candesartan led to a reduction in the number of headache days (13.6 vs 18.5 with placebo, $P= 0.001$). This again was a small study involving 60 patients with episodic migraine with two 12 weeks periods. As with lisinopril, further large scale studies are needed before recommendation can be made about the use of angiotensin inhibitors in migraine prophylaxis. In patients with migraine and hypertension who do not tolerate beta-blockers, angiotensin blockers may be considered.

NEUROTOXINS - BOTULINUM TOXIN TYPE A (BoNTA)

BoNTA is a focally acting protein that inhibits the release of the neurotransmitter acetylcholine from presynaptic nerve endings. 57 Preclinical in vitro and in vivo data have demonstrated that BoNTA also blocks the neuronal release of nociceptive mediators such as substance P, glutamate, and calcitonin-gene-related peptide (CGRP) in the periphery, which suggests it may possess peripheral antinociceptive activity. The biological effects of BoNTA are transient and within approximately 3 months normal neuronal signaling is restored. There is no evidence that BoNTA acts directly on centrally sensitized neurons; however, BoNTA inhibition of nociceptive mediators in the periphery may reduce central sensitization, perhaps by inhibiting afferent input to the central nervous system, thereby reducing inflammatory signals to sensitized regions in the brain.

Botulinum toxin has been used in several different headache types. The initial observation was rather serendipitous, when Dr. William Binder, a plastic surgeon, observed that many of his patients who had undergone botox injections for treatment of glabellar lines reported substantial improvement in headache frequency and severity. After making these initial observations, he helped to design and complete a multicenter open label trial of botulinum toxin type A in patients with migraine. Of 77 patients studied, 36 patients with migraine reported complete relief of the headaches. The

mean duration of effect of botox was found to be 4.1 months and 27 of the 77 (38 percent) reported partial response. Site of injections were determined based on particular needs of the patient, but generally included frontalis, temporalis, corrugator, procerus muscles and in a few patients, suboccipital muscles as well. The dose used also varied from patient to patient. Except for brow ptosis, no significant adverse effects were experienced.

The first multicenter double-blind placebo controlled trial involved 123 patients with IHS defined migraine who experienced between two and eight severe migraine headaches in each month. The patients were randomized to one of three groups, placebo, 25 units botox or 75 units botox. Eleven standard injection sites were used including frontalis, temporalis, corrugator and procerus muscles. Bilateral injections were performed. Compared with placebo, patients receiving 25 units of botox A experienced the following effects after botox injection: 1) significantly fewer and less severe migraine headaches each month, 2) reduction in the amount of acute medications used and 3) lower incidence of emesis. There was no difference between those receiving 75 units of botox and those receiving placebo. No adverse events were reported except diplopia in two cases and transient ptosis in 13 cases. Brin et al in a separate study presented the results of a randomized placebo-controlled multicenter study of botox in migraine prophylaxis. In this study, several injection site patterns were used. Those patients who received botox injections in the temporal and frontal regions experienced significantly greater pain relief than placebo group.

In a study of 30 patients with IHS classified migraine headache experiencing between two and eight attacks each month, patients were randomized to receive 50 units or placebo injections. Fifteen injection sites were included temporalis, frontalis, corrugator, procerus, trapezii, and splenius capitis muscles bilaterally. Patients were observed for 90 days. Compared with placebo-treated patients who did not experience any significant change of headache frequency and severity, those who received botox injections had significant reduction of the headache frequency at 90 days, (2.5 vs 5.8) ($P= <0.01$) as well as severity. No significant adverse events were reported.

In an open label study evaluating the effects of botulinum toxin type A on disability in episodic and chronic migraine, treatment with 25 units of botox resulted in decreased migraine associated with disability in 54 percent of patients. In a large prospective study undertaken by Mathew et al, migraine associated disability scale (MIDAS scale) was used. Patients who responded were shown to have significant reduction in their MIDAS scale and the reduction of MIDAS scale was maintained with repeated injections of botox. In that particular study, botulinum toxin type A injections were given up to four years. In addition to reduction in the MIDAS scale, these patients exhibited much less number of headache attacks and reduced use of acute medications such as triptans and nonsteroidals. It was pointed out that botulinum toxin may have a “disease modifying effect” in chronic migraine.

Many of the reports concluded that there may be an increase in benefit experience with repeated treatment with botulinum type A for patients with chronic migraine. These observations although not derived from randomized controlled studies are important to consider because many injectors indicate, some empirically discovered, that for maximum benefit to be realized from botox, the patient may need treatment at least several times.

BoNTA IN CHRONIC DAILY HEADACHE

BoNTA was recently evaluated as prophylactic treatment of chronic daily headache (CDH) in two large, exploratory, multicenter trials involving over 1,000 patients. Patients with any combination of migraines, with or without aura, migraineous/probable migraine, and/or episodic or chronic tension type headache (as defined by IHS 1988 International Classification of Headache Disorders) on more than 15 of 30 days per month were included. The majority of patients in both trials who did have their headaches subclassified had transformed migraine. Both trials incorporated a 30-day baseline screening period, followed by a 30-day (single-blind) placebo run-in period, and a 9-month treatment period encompassing up to 3 treatment cycles with an overall maximal treatment duration for each patient of up to 11 months. At the end of the placebo run-in period, patients in

both trials were classified as placebo responders if they had gone from 16 headache days to < 16 headache days or had a 30 percent decrease from baseline in the number of headache days. All other patients were considered placebo nonresponders. Following the placebo run-in period, patients in each trial were randomized to the first of 3 masked identical BoNTA or placebo treatments at days 0, 90, and 180. Follow-up visits occurred at 30-day intervals following each treatment through day 270.

Patients in the trial conducted by Mathew and colleagues (N=355) were randomized either BoNTA treatment (n=173) or placebo (n=182) using a modified follow-the-pain injection protocol at the investigator’s discretion. The mean (median) total BoNTA dose used for the 3 treatments was 190.8 units (U) (200 U) at day 0, 190.9 U (200 U) at day 90, and 190.5 (200 U) at day 180. Patients in this trial had a mean of 13.1 headache episodes per 30-day period, 11.0 of which were migraine/probable migraine headache episodes.

During the 30-day baseline period, BoNTA patients in the placebo nonresponder group (n=134) had a mean of 5.8 headache-free days and patients in the placebo group (n=145) of the same stratum had 5.5 headache-free days. Although there were no statistically significant differences between BoNTA and placebo patients at any time point in the primary outcome, a significantly higher percentage of BoNTA patients in the placebo nonresponder group compared with placebo patients of the same stratum had at least a 50 percent decrease from baseline in the frequency of headache days per 30-day period at day 180 (P=0.027). Additionally, in the placebo-nonresponder group, statistically significant differences in the mean change from baseline in the frequency of headache episodes per 30 days favoring BoNTA were observed at most time points. A pooled analyses of both strata (placebo responders and placebo nonresponders) indicated statistically significant differences for this outcome favoring BoNTA at day 180 and at all time points except day 90 (figure 3). Also, in a pooled analysis of both strata, the proportion of patients with at least a 50 percent decrease from baseline in the frequency of headache episodes per 30-day period was significantly greater

for BoNTA patients compared with placebo patients at days 180 and 210 ($P = 0.05$).

Treatment-related adverse events were reported for a significantly higher percentage of BoNTA patients compared with placebo patients (50.9 percent [88/173] vs 23.1 percent [42/182]; $P < 0.001$). The majority of treatment-related adverse events were transient, and mild to moderate in severity. Treatment-related adverse events that occurred in significantly more BoNTA patients than placebo patients were muscular weakness (22 percent [38/173] vs 0, $P < 0.001$), neck pain (13.3 percent [23/173] vs 0.5 percent [1/182], $P < 0.001$), skin tightness (4.6 percent [8/173] vs 0, $P = 0.003$), blepharoptosis (6.9 percent [12/173] vs 0.5 percent [1/182], $P = 0.001$), and shoulder/arm pain (4.0 percent [7/173] vs 0.5 percent [1/182], $P = 0.033$). Five patients (1.4 percent [5/355]; four BoNTA, one placebo) discontinued the study due to adverse events.

Silberstein et al, in a similarly designed trial, evaluated BoNTA 225 U, 150 U, and 75 U as prophylactic treatment in CDH patients ($N = 702$) using a standardized fixed-site, fixed-dose paradigm. All treatment groups experienced mean improvements in the primary and secondary outcome measures but did not separate from placebo.

In a subset of patients from Mathew et al trial who were not taking concomitant headache prophylaxis, BoNTA treatment resulted in significant improvements compared with placebo in the frequency of headache episodes and in several additional efficacy measures including headache-free days, usual headache severity, and number of days of acute medication use. In the trial conducted by Silberstein and colleagues, a pooled analysis of both treatment strata (placebo-responders and placebo-nonresponders) revealed significant between-group differences favoring BoNTA over placebo in reduction of the frequency of headache episodes and migraine or probable migraine headache episodes at several time points. Interestingly, the analysis of the pooled populations of both trials revealed a very similar response pattern for the BoNTA treatment groups, but a higher placebo response in the Silberstein trial compared to the Mathew trial. The authors attributed this to the uneven randomization (3:1).

CDH patients, who by definition have a higher mean baseline frequency of migraineous headaches than episodic migraine patients, may be more appropriate candidates for BoNTA treatment as the results of the large, randomized, double-blind, placebo-controlled trials reviewed in this paper suggest. It is perhaps difficult to understand why a more severe “chronic” form of migraine would preferentially respond to BoNTA: an understanding of this phenomenon may inform the pathophysiological divergence between episodic and chronic migraineous disorders, which may be related to peripheral and central sensitization.

Sensitization of peripheral nociceptors during migraine ultimately may lead to central sensitization of second-order nociceptive neurons. There is emerging evidence that patients with transformed migraine experience central sensitization (as defined by the presence of cutaneous allodynia) to a greater degree than episodic migraine patients. It may be that patients with CDH and transformed migraine have a more pronounced response to BoNTA than episodic migraine patients on the basis of the greater degree of sensitization in these patients but considerable further clinical research is needed to clarify this and the potential antinociceptive mechanism of action of BoNTA.

From extensive experience, the author feels that botox has a place in the management of chronic migraine with significant disability who are resistant to prophylactic pharmacotherapy. It is ideal for those migraineurs who have contraindications for triptans and ergotamine and those who have significant adverse events from prophylactic pharmacotherapy. It is also probably a good choice in patients with chronic migraine in the older age group, as it is not associated with any adverse events such as sedation and disorientation. In professionals who require full alertness and quick recall while at work, BoNTA may be more appropriate than agents like topiramate or amitriptyline. Botulinum injections are not recommended for episodic infrequent migraine patients or as a first line therapy.

In those who get adequate response, the headache may start relapsing after 3-4 months and repeat treatments are usually necessary. No long-term adverse events have been reported

except atrophy of the muscles in the anterior areas of the temples.

Stratification of migraine prophylaxis

Migraine prophylaxis could be continuous, intermittent, or episodic.

Continuous daily treatment with prophylactic medications is necessary when migraines are frequent and when migraines are associated with interictal nondescript tension-type headache. Patients with severe menstrual migraine or those who get headaches when visiting high altitudes may require medication for a limited time. Intermittent prophylaxis in menstrual migraine is usually given 2 or 3 days before the menstruation and through the period. Episodic prophylaxis may be instituted when there is a known trigger for headache. For example, exercise-induced headache can be partially prevented by using medications like beta-blockers or indomethacin. The same applies to headache induced by sexual activity where the patient may take a prophylactic agent prior to the event.

The role of comorbidity in prophylactic treatment of migraine

Comorbidity may result in certain therapeutic opportunities. Table 5 shows therapeutic opportunities provided by comorbid conditions. On the other hand, comorbidity may impose therapeutic limitations in using certain medications. Table 6 lists the therapeutic limitations because of comorbidity. Therapeutic limitations due to side effects are also a problem. Table 7 shows the therapeutic limitations as a result of side effects.

A primary antimigraine prophylactic agent can be combined with compatible agents for treating comorbidity (depression, anxiety, panic disorder, hypertension, sleeplessness). As long as the antimigraine drug and the drug used for comorbidity do not interact with each other, it is certainly logical to use combinations. Table 8 shows certain examples of rational copharmacy in migraine.

Drug combinations are commonly used for patients with refractory headache disorders. Some

combinations, such as anti-depressants and beta-blockers, are suggested; others, such as beta-blockers and calcium-channel blockers, should be used with caution; and some, such as monoamine oxidase inhibitor (MAOI) and SSRI, are contraindicated because of potentially lethal interactions (Table 8). Many clinicians find that the combination of an antidepressant (such as a tricyclic antidepressant or SSRI) and a beta-blocker act synergistically. Lance has advocated combining methysergide with a vasodilator such as a calcium channel blocker to decrease side effects. Divalproex or topiramate used in combination with antidepressants, is a logical choice to treat refractory migraine that is complicated by depression or bipolar illness.

Use of abortive medications along with preventive treatment

Even though preventive agents reduce the frequency and severity of migraine attacks, many patients have breakthrough migraine or tension-

TABLE 5. COMORBIDITY AND THERAPEUTIC OPPORTUNITIES.

Disorders	Medication
Migraine + hypertension	Beta-blockers, angiotensin blockers
Migraine + angina	Calcium channel blockers
Migraine + stress, anxiety	Beta-blockers
Migraine + depression	Tricyclic antidepressant (TCA), SNRIs, SSRIs
Migraine + insomnia	TCA
Migraine + underweight	TCA
Migraine + overweight	Topiramate
Migraine + epilepsy	Divalproex, topiramate
Migraine + mania	Divalproex, topiramate

TABLE 6. COMORBIDITY AND THERAPEUTIC LIMITATIONS.

Migraine + epilepsy	Tricyclic antidepressant (TCA)
Migraine + depression	Beta-blockers
Migraine + obesity	TCA, divalproex

type headache while on them. Menstrual migraine is a good example of the breakthrough headache. In general, preventive medications make acute agents more effective.

While using the acute medication, one should make sure that they are not overused. A limit of use two times a week is recommended to prevent secondary failure of preventive treatment.

Table 9 shows the potential drug interactions between abortive and preventive agents.

TABLE 7. THERAPEUTIC LIMITATIONS DUE TO SIDE EFFECTS.

Asthma	AVOID Beta-blockers
Elderly with cardiac disease	Tricyclic antidepressant (TCA)
Congestive failure Heart block	Calcium channel blockers Beta-blockers
Athletes	Beta-blockers
Professions requiring quick recall and sharp cognitive ability	Beta-blockers TCAs, topiramate
Obesity	Valproate, TCAs
Liver dysfunction	Valproate

TABLE 8. RATIONAL COPHARMACY.

Suggested	Antidepressants	+	Beta-blocker calcium channel blocker divalproex, topiramate methysergide
	Methysergide	+	Calcium channel blocker
	Selective serotonin reuptake inhibitor (SSRI)	+	Tricyclic antidepressants
Caution	Beta-blocker	+	Calcium channel blocker Methysergide
	Monoamine oxidase inhibitor (MAOI)	+	Amitriptyline or nortriptyline
Contraindications	MAOI	+	SSRI Most tricyclic antidepressants (except amitriptyline or nortriptyline) Carbamazepine
Rational or strategic copharmacy			

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TABLE 9. CAUTION AND CONTRAINDICATIONS FOR COMBINING ABORTIVE AND PROPHYLACTIC ANTIMIGRAINE THERAPY.

Agent	Caution	Contraindicated
Methysergide	Ergotamine, dihydroergotamine, triptans	
Monoamine oxidase inhibitors rizatriptan	Oral sumatriptan zolmitriptan	Meperidine sympathomimetics (midrin)
Divalproex	Overuse of short-acting barbiturates	
Propranolol	Rizatriptan Zolmitriptan	
Antifungal agents	Eletriptan	

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