



MIGRAINE PROPHYLAXIS

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Migraine is a primary headache disorder that afflicts more than 17% of women and 6% of men in the United States. It may be disabling and incapacitating, with severe pain and associated symptoms including nausea, vomiting, visual aura, and photo- and phonophobia. Missed work and lost productivity secondary to migraine create a significant public burden financially and emotionally. Migraine remains largely under treated and under diagnosed. Migraine prevention is under used and, because it is not outstanding in its efficacy, is often ignored. Most patients have fewer than two headaches per month. When there is a need to reduce the headache frequency to below two per month or when disability is a concern even at one episode a month, prophylaxis may be needed. Migraine-preventative therapy reduces attack frequency, severity, and duration while improving response to acute therapy and restoring function. Preventative therapy should be considered if migraines frequently interfere with daily function, if the acute medications are insufficient or ineffective at controlling the headache, or if there is a specific contraindication to using abortive treatment or acute medication is overused. Intermittent prophylaxis may be considered in long-duration headache (eg, menstrual migraine) [1-3]. Prophylaxis should also be considered in the presence of uncommon migraine conditions (eg, hemiplegic migraine) and when there are attacks with risk of permanent neurologic damage [4].

Although the focus of prophylaxis has been on patients with more than two attacks, some patients with up to eight attacks per month do well on acute care alone. It is suggested that each individual receive tailored treatment that suits their case. Care should be given to note whether the recurring migraines significantly interfere with their daily routine despite receiving acute treatment [5,6].

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Preventive medications should be taken, whether or not a headache is present, in an attempt to reduce the frequency and perhaps the severity and duration of anticipated attacks. Current treatment aims to decrease frequency 50% or more.

Preventive therapy may raise the brain threshold, minimizing migraine activation centrally or peripherally. Preventative drugs could decrease the migraine generator, enhancing central antinociception, raising the threshold for spreading depression, or stabilizing the more sensitive migrainous nervous system by changing sympathetic or serotonergic tone. Preventive drugs most likely work by more than one mechanism. The drugs could, in part, have a peripheral mechanism of action similar to specific acute medications but likely have a central effect as well [5,7].

When considering the patient for preventive treatment, we may provide the therapy episodically, short term, or chronically. Episodic preventive treatment is used when there is a known headache trigger, such as exercise (exertional migraine) or sexual activity (coital migraine). Patients can be instructed to pretreat before the exposure or activity. For example, single doses of indomethacin can be used to prevent exercise-induced migraine. Doses between 25 and 75 mg are beneficial [8]. Short-term prevention is used in patients undergoing a time-limited exposure to a trigger, such as ascent to a high altitude or menstruation. These patients may be treated with daily medication just before and during the exposure. Diamox is commonly considered in doses of 125 mg/d to 250 mg twice daily for altitude-induced headache. Another consideration for short-term prevention is in menstrual migraine. When migraine is refractory to acute therapy during menses, preventing the attack may be beneficial. Menstrual migraine has been reported to occur in 60% to 70% of women with migraine (C.B. Johannes, unpublished data, 1989). When the migraine consistently occurs with menses alone, preventative therapy premenstrually has been beneficial. Antidepressants, β -blockers, Ca-channel blockers, nonsteroidal anti-inflammatory drugs (NSAIDs), ergots, or triptans may decrease the presence of migraine by 50% or more [9,10]. Oral contraceptives (OCs) may prevent menstrual migraine. There are three categories of OC formulations: fixed dose, phasic, and progestin only. First-generation OCs contain estrogen in concentrations ≥ 50 μg ; second-generation OCs have <50 μg of estrogen; and third-generation OCs are formulations with new progestins, desogestrel, norgestimate, and gestodene. Four double-blind, placebo-controlled studies (not necessarily of migraineurs) found no difference in headache incidence between the oral contraceptive group and the placebo group [11,12]. Low-dose estrogen OCs have lower associated headache incidence. Oral contraceptive therapy in migraine is variable. Although OCs can trigger a migraine attack, patients taking OCs report improvement in 3% to 35% of cases, worsening headache in 18% to 50% of cases, and no change in 39% to 65% of cases [14]. OC therapy can be used to maintain persistent estrogen levels for up to 4 months and eliminate menses during that time; with the next menstrual flow, acute care or episodic preventative care with an NSAID or triptan can be considered [7].

Standard, chronic preventive treatment may need to be maintained for months or years. Usually, if a patient is doing well after 6 months, a slow taper may result in the need for occasional acute therapy. It is advisable not to rush to eliminate prophylaxis; rather, spend time restoring healthy behaviors and normal function. The goal is to restore a locus of control where the patient feels they are not dreading their next migraine. Therapy should be initiated with the lowest tolerable dose. Increase the dose slowly (every 4–7 days) until clinical benefits are achieved to minimize adverse events or until the treatment is limited by adverse events. Give each treatment an adequate trial. A clinical benefit may take as long as 2 to 3 months to manifest itself. Most controlled prophylactic trials show a split from placebo around 3 weeks and adequate responses between 6 and 12 weeks. It is not uncommon for patients to take new treatments for 1 to 2 weeks without seeing an effect and then discontinue prematurely, with the physician and patient believing the medication was not effective. Although this is often frustrating, a realistic expectation is imperative. The biggest problem in obtaining adequate outcome with preventions is to avoid pharmacologic or chemical triggers that make outcome doubtful. The most common agent preventing positive outcome is frequent acute medication use. If the patient uses acute medications more than 2 days per week on a regular basis, the preventative is unlikely to be beneficial. Common acute medication and chemical triggers are ergotamine- or caffeine-containing products, analgesics, combination analgesics containing barbiturates, and triptans.

Choosing preventatives may be helped if long-acting formulations are available. They may improve compliance and decrease side effects. Discuss the rationale for a particular treatment with the patient, including when and how to use the treatment and what adverse events are likely. Address and establish patient expectations. Goals must be clear because migraine is a genetic disorder and can only be managed—not cured. Discuss the expected benefits of therapy and how long it will take to achieve them. Create a formal management plan based on patient preferences. Monitor the patient's headache by having them keep a user-friendly diary to measure attack frequency, severity, duration, disability, response to type of treatment, and adverse medication effects. After a period of stability, consider tapering or discontinuing treatment [7].

Take into account the presence of coexisting diseases and behavioral states. Some comorbid conditions are more common in persons with migraine; these include stroke, myocardial infarction, Raynaud phenomenon, epilepsy, affective disorders, depression, and anxiety disorders. Coexisting diseases present treatment opportunities and limitations. Once the coexistent condition has been identified, select a pharmacologic agent that treats both disorders. Establish that the coexistent disease is not a contraindication for the selected migraine therapies (eg, β -blockers are contraindicated in patients with asthma or depression). Ensure that treatments being used for coexistent conditions do not exacerbate migraine. Beware of interactions between pharmacologic agents used for migraine and those used for other conditions. Special attention should be

directed to women who are pregnant or want to become pregnant. Preventive migraine medications may have teratogenic effects [13].

The major medication groups for preventive migraine treatment include (1) cardiovascular agents such as β -adrenergic blockers, Ca-channel antagonists, and angiotensin reuptake inhibitors; (2) antidepressants, including the tricyclic antidepressants and selective serotonin/norepinephrine reuptake inhibitors; (3) antiepileptic agents; (4) serotonin antagonists; (5) NSAIDs and others including riboflavin, minerals, herbs, and botulinum toxin. If preventive medication is indicated, the agent should be preferentially chosen from one of the first-line categories based on the drug's side effect profile and the patient's coexistent and comorbid conditions [7].

EVIDENCE-BASED GUIDELINES

Migraine

Although it would be ideal to treat purely based on evidence-based guidelines, there are many limitations. There are guidelines for migraine that have been developed and published that help guide our choices. Since their publication, a number of agents have been studied and therefore deserve a different position in the guideline [14]. The full texts are available [15–19]. There are other guidelines for migraine published in the Canadian Medical Association Journal by Pryse-Phillips and colleagues [20]. The information presented here is a synopsis taken from these references.

Prophylactic Therapy, Preventative Therapy (Pharmacologic)

These groups are somewhat dated at this point because many trials fulfilling the evidence-based criteria have been completed. Some of these studies are described. Topiramate is now in group 1 because it has recently been approved by the FDA for migraine. Other agents with proven efficacy in placebo-controlled trials include candesartan, gabapentin, and venlafaxine. Methysergide has been removed from the United States market. Preventative efficacy may be judged based on the criteria listed in [Box 1](#).

The major categories are discussed to provide information on the pharmacology, contraindications, interactions, adverse reactions, and administration.

CARDIOVASCULAR AGENTS

β -Blockers

Drug Pharmacology

Adrenergic receptors, to which norepinephrine binds, are classified as α - and β -receptors. These are principally found on peripheral sympathetic

Box 1. Criteria for Efficacy of Pharmacologic Preventative Therapy

Group 1: Proven higher efficacy, mild to moderate adverse events

- Amitriptyline
- Divalproex sodium
- Lisuride (not available in the United States)
- Propranolol
- Timolol

Group 2: Lower efficacy, mild to moderate adverse events

- Aspirin (not including combination products)
- Atenolol
- Fenoprofen
- Feverfew
- Flurbiprofen
- Fluoxetine (racemic)
- Gabapentin
- Guanfacine
- Ketoprofen
- Magnesium
- Mefenamic acid
- Metoprolol
- Nadolol
- Naproxen
- Naproxen sodium
- Nimodipine
- Verapamil
- Vitamin B2

Group 3a: Opinion-based, low adverse events

- Cyproheptadine
- Bupropion
- Diltiazem
- Doxepin
- Fluvoxamine
- Ibuprofen
- Imipramine
- Mirtazapine
- Nortriptyline
- Paroxetine
- Protriptyline
- Sertraline
- Tiagabine
- Topiramate
- Trazodone
- Venlafaxine

Group 3b: Opinion-based, high adverse events

- Methylergonovine (methylergometrine)
- Phenelzine

Group 4: High efficacy, but high adverse event profile

- Methysergide
- Flunarizine (not available in the United States)

- Pizotifen (not available in the United States)
 - TR-DHE (not available in the United States)
- Group 5: Limited or no efficacy
- Acebutolol (not available in the United States)
 - Carbamazepine
 - Clomipramine
 - Clonazepam
 - Clonidine
 - Indomethacin
 - Lamotrigine
 - Nabumetone
 - Nicardipine
 - Nifedipine
 - Pindolol

synapses. β -receptors predominate in the heart (B1) and the arteries, which contain skeletal muscle and bronchi (B2). Their stimulation causes cardiac excitation, vasodilatation, and bronchodilatation. Blockade was thought to decrease vasodilatation, thereby effecting neurovascular pains (migraine); however, there is minimal if any change in cerebral blood flow produced by β -blockers. Additionally, the vascular theory as described by Wolf is no longer considered a primary migraine mechanism. Other proposed mechanisms are platelet aggregation inhibition through decrease in prostaglandin production. The prostaglandins are inhibited secondary to a decrease in lipolysis, which decreases arachidonic acid synthesis. The inhibition of platelet aggregation is also aided through a decrease in catecholamine-induced platelet adhesion.

β -Blockers cross the blood-brain barrier (65%) in a single passage through the brain. It has been postulated that they exert their effect in part secondary to their effect on the serotonin system by inhibiting the noradrenergic system. β -Blockers are absorbed in the gastrointestinal tract and metabolized in the liver. They are also extracted from the plasma by the liver, and therefore hepatic blood flow is an important factor in the blood level.

Contraindications

β -Blockers are generally well tolerated. Care should be paid to the following medical conditions (alternative medication therapies should be considered): congestive heart failure, asthma, insulin-dependent diabetes mellitus (atenolol or metoprolol may be better), pregnancy, and lactation.

Interactions

A list of drugs that may affect β -blocker use is provided with the common interaction effect in [Box 2](#).

Box 2. Drugs That May Affect β -Blocker Use

- Cimetidine: may increase hepatic metabolized β -blockers
- Contraceptives: increase pharmacologic effect of metoprolol
- Phenobarbital: decreases metoprolol and propranolol plasma levels secondary to liver enzyme induction
- NSAIDs: salicylates decrease antihypertensive effects secondary to inhibition of prostaglandin synthesis
- Smoking: reduces plasma levels
- Thyroid hormones: may decrease effects

Adverse Reactions

Generally, β -blockers have minimal adverse reactions. Fatigue and depression are often precipitated. With initial dosing, dreams and nightmares are common but usually subside. Other problems encountered include gastrointestinal distress and hypotension. Plasma levels may be increased in renal failure, in women, and with old age. They may be lower in smokers and blacks. It is felt that plasma levels are not correlated with success.

Administration

The most effective β -blockers for migraine therapy are described in Table 1. Included are the dose ranges and dosing regimen and a suggested dose schedule.

Begin propranolol 20 mg BID and increase by 20 mg every 4 to 7 days. Avoid long-acting preparations. If pain worsens, reduce the dosage or discontinue. Begin atenolol 25 to 50 mg/d and increase in increments of 25 mg/wk. Hold at 100 mg for 1 to 2 weeks before pressing maximum doses. Begin metoprolol 50 mg twice daily and hold for 1 to 2 weeks; if there is no change, increase the dosage by 50 mg and hold for 1 to 2 weeks at a time. Begin timolol at 10 mg twice daily and increase by 10 mg every week. Begin nadolol at 20 mg/d and increase by 20 mg every week. The average dosage is 120 mg/d in three doses.

TABLE 1.
The Most Effective β -Blockers for Migraine Therapy

Generic	Trade Name	Dose (mg/d)	Half-life (h)	Dosing	Onset (wk's)
Atenolol	Tenormin	50–200	6–7	BID	2–4
Metoprolol	Lopressor	50–250	3–4	TID	4–6
Nadolol	Corgard	40–240	20–24	QD	4–6
Propranolol	Inderal	40–320	4–6	TID	4–6
Timolol	Blocadren	10–60	4	TID	2–4

Withdrawal may result in tachycardia, tremulousness, ventricular arrhythmia, angina, and myocardial infarction. The suggested taper is over 14 days.

There have been numerous controlled studies reporting that β -blockers are effective in treating migraine. Between 60% and 85% of patients respond by the end of the trial. Some longitudinal studies report benefit lasting at 1-year follow-up. At this point, it may be prudent to slowly withdraw the β -blocker and determine if therapy can be provided with an abortive alone. Many patients require long-term (continuous) use of a prophylactic medication. There does not seem to be a tolerance that develops.

Ca-Channel Blockers

Drug Pharmacology

Calcium plays a role in specialized muscle cells of the heart. It is involved in the genesis of the action potential. In the contractile cells, it links excitation to contraction. The contraction depends upon the movement of extracellular calcium into the cells through specific ion channels. The Ca-channel blockers stop the movement of Ca, thereby regulating the contraction. They also decrease impulse formation (automaticity) and conduction velocity (Table 2).

Intracellular Ca is also known to regulate some hormones, enzymes, and neurotransmitters. Serotonin release is Ca dependent, and therefore Ca-channel blockers inhibit serotonin release. The original theory was that they affected vasoconstriction and would help migraine. It is now believed that their mechanism involves serotonin modulation.

Contraindications

There are few situations where Ca-channel blockers are to be avoided. Box 3 describes the situations where they are not recommended.

Interactions

Barbiturates are known to decrease verapamil bioavailability. This may be important if they are used in combination to treat migraine or

TABLE 2.
Ca-Channel Blockers

Generic	Trade Name	Dosing
Diltiazem	Cardizem	60–360 QD
Nifedipine	Procardia, Adalat	10–20 TID
Nimodipine	Nimotop	30–60 QID
Verapamil	Calan, Isoptin	80–240 TID

Box 3. Situations where Ca-Channel Blockers Should Be Avoided

- Second- or third-degree AV block
- Hypotension <90 mm Hg systolic
- Diltiazem—acute MI, pulmonary congestion
- Verapamil—ventricular dysfunction
- Duchenne muscular dystrophy
- Increased intracranial pressure
- Age (increases antihypertensive effects)
- Hepatic clearance in patients with hepatic problems
- Rebound angina with rapid withdrawal

cluster. Care should be given to the presence of calcium salts as a supplement because they may decrease the effects of verapamil.

Adverse Reactions

This drug class is well tolerated. The common side effects include hypotension, constipation, aching joints, and, rarely, heart block.

Administration

It takes months for Ca-channel blockers to work. Start slowly with blood pressure monitoring regularly and increase over a 30- to 60-day period. Raskin [21] suggests that Ca-channel blockers may have some specific effects in complicated migraine, Raynaud syndrome, and Prinzmetal angina.

Angiotensin Reuptake Blockers

Although only one drug in this class has been studied and has been shown to be effective compared with placebo, the mode of action is speculative. It may be used in patients requiring antihypertensive therapy where a β -blocker is contraindicated. Candesartan, an angiotensin II inhibitor, has also been effective in migraine prophylaxis compared with placebo [22]. Starting doses are 4 mg at bedtime increasing by 4 mg every 4 to 7 days with a goal of 16 mg at bedtime.

ANTIDEPRESSANTS

Drug Pharmacology

Antidepressants are thought to exert their therapeutic action through changes in monoamine neurotransmitter activity (Table 3). The monoamines

TABLE 3.
Antidepressants

Generic	Trade Name	Dosing
Tricyclic antidepressants		
Amitriptyline	Elavil	10–200
Desipramine	Norpramin	10–200
Doxepin	Sinequan	10–200
Nortriptyline	Pamelor	10–200
Other		
Trazodone	Desyrel	50–300
Selective serotonin reuptake blockers		
Fluoxetine	Prozac	10–60
Paroxetine	Paxil	10–50
Sertraline	Zoloft	50–200
Selective serotonin/norepinephrine reuptake blockers		
Venlafaxine	Effexor	37.5–300
Duloxetine	Cymbalta	30–60
Monoamine oxidase inhibitors		
Isocarboxazid	Marplan	10–30
Phenelzine	Nardil	15–30
Tranlycypromine	Parnate	10–30

involved include norepinephrine and serotonin. This is usually at the synapse; however, central changes in the raphe may be involved. After the neurotransmitter is released into the synaptic cleft, it is taken back into the nerve using a membrane-bound amine pump. The antidepressants interfere with this process, and therefore the amine remains in the synaptic cleft longer, thereby enhancing its action. This process is called reuptake blockade. The role in descending modulation or specific effects on individual 5HT receptors is not well described. Most tricyclic antidepressants (TCAs) are broad in their action and are thought to have numerous functions. The selective serotonin reuptake inhibitors (SSRIs) are more specific, not enhancing norepinephrine as much as serotonin; this may make them less attractive in pain problems. Venlafaxine (Effexor) is described as selective for serotonin and norepinephrine. There is a placebo-controlled trial of venlafaxine that shows its superiority over placebo in migraine prophylaxis [23]. Duloxetine (Cymbalta) is FDA approved for neuropathic pain but has not been studied in migraine.

Antidepressants also exert antimuscarinic effects, which are manifested as the usual side effects of dry mouth, urinary retention, and impaired visual accommodation. In older patients, hypotensive effects are seen as a problem. This has been attributed to the α 1-blocking effects.

TCAs inhibit pain through multiple mechanisms. Some TCAs are potent H₂ receptor blockers and may be effective in patients who have gastric distress requiring medication therapy. Doxepin has the highest H₂-blocking effect. Few TCAs affect the GABA.

In migraine, there is the possibility that serotonin release is defective. This causes intermittent reductions in synaptic serotonin levels and secondary increased dorsal raphe neuronal firing rates. The drugs that are effective (eg, amitriptyline and nortriptyline) are known to block the serotonin receptor centrally and downregulate it and to produce some reuptake blockade. This is contrary to other antidepressant medications, such as Trazodone, which do not downregulate the receptor and do not have a noradrenergic effect and therefore are less effective. The TCAs may also exert their action through enhancing the serotonergic action at spinal terminals of an opioid-mediated intrinsic analgesia system.

Contraindications

Caution should be exercised when using this class of drug. Patients who have respiratory depression, hepatic compromise, or asthma should be carefully followed because the use of TCAs may aggravate these conditions. Patients who have had recent myocardial infarction or arrhythmia should not be given TCAs. In patients who have a history of suicidality, alcoholism or manic depressive disorder the TCA must be used with caution.

Interactions

There is a move to combine therapies for the difficult pain patient. Often the TCA is mixed with SSRIs, anticonvulsants, and analgesics. In drugs metabolized by the P450 cytochrome system, there may be a build-up; therefore, caution should be exercised in combining such drugs. A common problem is seen when SSRIs and TCAs are mixed. Additionally, epinephrine-containing local anesthetics combined with TCAs may cause an arrhythmia. The monoamine oxidase inhibitors are contraindicated with many drugs and food substances.

SSRIs and triptans should be combined with caution. Although rare, a serotonin crisis may occur when the serotonin concentrations are high.

Adverse reactions

Drug overdose is a major concern, with over 500,000 cases in the United States annually. A lethal dose may be 2 g or more. TCAs should not be mixed with alcohol. Patients who have a history of seizure may develop more frequent seizures. Other more common interactions are drowsiness or improved sleep, dry mouth constipation, urinary retention, and prolongation of QT interval and supraventricular tachyarrhythmia.

Administration

Begin all TCAs with low doses and increase every 4 to 7 days. In older patients, take even longer and insist on seeing the patient for encouragement and heart rate checks on a regular basis. Begin with secondary amine

drugs (eg, nortriptyline) and progress to tertiary if greater effect is needed. Consider combining the TCAs and SSRIs for mood modulation if the side effects of the TCA limit their use in antidepressant doses. Care should be taken in combining these drugs because both are metabolized by the cytochrome P450 enzyme. This results in slow elimination and possible toxic reactions. Prozac has been shown to be effective in migraine prophylaxis, but the effect may take over 3 weeks to begin.

ANTIEPILEPTIC AGENTS

Drug Pharmacology

The action of anticonvulsants in pain management is not well understood (Table 4). Some, like carbamazepine, block the use of dependent sodium channels and inhibit sustained repetitive firing. There is also an effect in the spinal cord whereby post-tetanic potentiation of synaptic transmission is reduced. There is a decrease of synaptic transmission in the trigeminal nucleus, which may explain their effectiveness in facial pain. Valproic acid increases brain concentrations of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the central nervous system, and affects sodium channels. The action of phenobarbital is not at the trigeminal nucleus but rather in the brain. It is therefore not known to affect pain associated with trigeminal nerve sensitization or hyperexcitability. Gabapentin may have an effect on the GABA system or the N-methyl-D-aspartate (NMDA) receptors. The mechanism by which topiramate exerts its antiseizure effect is unknown; however, electrophysiologic and biochemical studies of the effects of topiramate on cultured neurons have revealed three properties that may contribute to topiramate's antiepileptic efficacy. First, action potentials elicited by a sustained depolarization of the neurons are blocked by topiramate in a time-dependent manner, suggesting a state-dependent sodium-channel blocking

TABLE 4.
Antiepileptic Agents

Generic	Trade Name	Dosage (mg/d)	Blood Level (µg/mL)	Serum Half-life (hr)
Gabapentin	Neurontin	100–5000	2	5–7
Lamotrigine	Lamictal	50–500	2–5	14–59
Levetiracetam	Keppra	200–2500	—	7–8
Topiramate	Topamax	15–400	—	21
Valproic acid	Depakote	125–2500	50–100	6–16
Pregabalin ^a	Lyrica	25–300		

^a Has not been approved.

action. Second, topiramate increases the frequency at which GABA activates GABA_A receptors and enhances the ability of GABA to induce a flux of chloride ions into neurons, suggesting that topiramate potentiates the activity of this inhibitory neurotransmitter. This effect was not blocked by flumazenil, a benzodiazepine antagonist, nor did topiramate increase the duration of the channel open time, differentiating topiramate from barbiturates that modulate GABA_A receptors. Third, topiramate antagonizes the ability of kainate to activate the kainate/AMPA ([alpha]-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; non-NMDA) subtype of excitatory amino acid (glutamate) receptor but has no apparent effect on the activity of NMDA at the NMDA receptor subtype.

Contraindications

Carbamazepine is contraindicated in patients who have hematologic disease. In rare instances, leukopenia, thrombocytopenia, and aplastic anemia may occur. Cardiac disease may be exacerbated, as can kidney and liver disease. The major concern with valproic acid is hepatotoxicity. It may also inhibit platelet aggregation, thereby causing thrombocytopenia.

Interactions

Because there is an induction of microsomal enzymes, the metabolism of carbamazepine may accelerate the metabolism of numerous medications. Dosage adjustments may be necessary. Valproic acid is also known to potentate the effect of many drugs.

Adverse reactions

Although rare, aplastic anemia, leukopenia, and agranulocytosis are the most feared side effects of carbamazepine. Routine blood monitoring is required when using this drug. More frequent adverse reactions include dizziness, drowsiness, fatigue, and confusion. In addition to the CNS effects seen with this class, phenytoin is known to stimulate connective tissue proliferation, resulting in gingival hyperplasia. The most significant adverse reaction caused by valproic acid is hepatotoxicity, which occurs within the first 6 months of therapy and primarily in children. Other adverse reactions commonly seen are weight gain, diarrhea, tremor, drowsiness, and ataxia. Gabapentin is exceptionally well tolerated with sedation, confusion, and weight gain being rarely reported. Topiramate has been associated with glaucoma and a small increase in kidney stones. The most frequent clinical complaint with topiramate is a paresthesia, which can be minimized using K plus, for example, orange juice once a day.

Administration

Anticonvulsants should be slowly introduced to minimize side effects. It is useful to obtain baseline blood levels so that any changes in blood

profile or liver function can be compared with baseline. Valproic acid and gabapentin have been studied in migraine, and both demonstrate greater efficacy than placebo. Serum blood levels serve a purpose if the patient does not seem to be responding as expected. The blood level indicates if there is a therapeutic level and if not the drug should be further escalated. When ordering the blood level, it is essential to obtain a trough level (ie, have the patient take their evening dose, miss the morning dose, and have the blood drawn in the morning). Topiramate is initiated as a 15 or 25 mg dose a night and increased to a goal of 100 mg at night. Most patients do not need higher doses, but doses of 100 mg BID are not uncommon [24].

SEROTONIN ANTAGONISTS

Drug Pharmacology

Although methysergide and methylergonovine are ergot alkaloids, they have weak vasoconstrictive action (Table 5). Methysergide does not inhibit the reuptake of norepinephrine at nerve endings or produce direct vasoconstrictor effects, as do DHE-45 and ergotamine. Methysergide is a highly competitive serotonin antagonist in the periphery and may be a central serotonin agonist. In the periphery, it inhibits serotonin-mediated platelet aggregation, inflammation, and vasoconstriction. Methylergonovine is a metabolite of methysergide and therefore has a similar mechanism of action.

Cyproheptadine, which is primarily used as an antihistamine, exhibits a potent peripheral anti-serotonin effect. Its mode of action in migraine is not understood.

Contraindications

Because of the vasoconstrictive effects, methysergide and methylergonovine are contraindicated in patients with angina, coronary artery disease, peripheral vascular disease, and uncontrolled hypertension and in those who smoke. They are contraindicated in patients who are using triptans.

TABLE 5.
Serotonin Antagonists

Generic	Trade Name
Cyproheptadine	Periactin
Methylergonovine	Methergine
Methysergide	Sansert

Interactions

There is an interaction with drugs that produce vasoconstriction. Care should be exercised in combining methysergide or methylergonovine with cocaine, epinephrine, and nicotine.

Adverse reactions

There are few side effects when serotonin antagonists are used for short periods of time. Abdominal pain and uterine contraction usually subside in a few days. If angina is present, the drugs should be stopped immediately. Retroperitoneal fibrosis or pulmonary fibrosis may be minimized by limiting the course to less than 6 months. Giving drug holidays is not considered adequate in preventing these serious conditions.

Cyproheptadine may cause sedation, drying of the mucosa, and weight gain. Care should be exercised when using this drug in combination with antidepressants because there may be some competitive inhibition.

Administration

Methysergide is started at 2 mg/d and increased to a maximum of 8 mg/d. The dose should be titrated against pain. Methylergonovine is begun at 0.2 mg three times per day and increase to 0.4 (two tablets) three times per day after 4 days. Both drugs are limited to 6 months continuous use.

Cyproheptadine may be used at doses of 2 to 12 mg/d. For children, start at low doses and use the elixir form. In adults, a 4 mg dose is used as an abortive, and usually 4 mg three times per day is required for prophylaxis.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

NSAIDs are traditionally acute medications and have not been studied long term in migraine. Their role in episodic prophylaxis is well known, especially around menses. With recent information looming about the cardiovascular effects of Cox 2 inhibitors and some Cox 1 inhibitors, NSAIDs should be used with caution.

Indomethacin has a unique role in headache treatment and may be effective at staving off exertional migraine or coital migraine.

HERBAL THERAPIES

Various studies of herbs, minerals, or vitamins have suggested that there may be some effect in preventing migraine. Magnesium dinitrate 600 mg/d and riboflavin 400 mg/d have been shown to be effective in placebo-controlled trials. Although these data are preliminary, these therapies may present a safe alternative without side effects. The herb feverfew has been shown in two small, randomized, placebo-controlled trials to be effective.

There are minimal side effects, such as oral ulceration and contact dermatitis. These avenues may offer alternatives when more traditional therapies are contraindicated or for patients do not wish to use prescription drugs. The long-term side effects of these treatments are not known. Coenzyme Q10 is another agent that has been shown in small uncontrolled trials to be effective in migraine prevention at 300 mg/d. Petadolex has been shown in placebo controlled trials to be beneficial [25].

OTHER

Therapy using naturopathy or homeopathy has not been subjected to sufficient critical study to allow appropriate evaluation. Even if they are safe, they may not afford any specific benefit beyond a placebo approach.

All patients need nonpharmacologic treatment; the extent and type is dependent on the individual patient. Nonpharmacologic approaches for migraine are an adjunct to preventative therapies, but they work alone for migraine prevention. Certain factors steer the clinician to use behavioral techniques. Many patients express a preference for nonpharmacologic intervention, which may be a good indication of potential success. Because motivation is essential for effective behavioral techniques, these patients may have a greater likelihood of success with the nonpharmacologic techniques. Nonpharmacologic treatments may play an important role in patients who are intolerant of medication, for whom abortive and preventative agents are contraindicated, or who have failed to respond to drug therapy. Pregnant women are appropriate candidates for nonpharmacologic treatment because medication raises concerns of injury to the fetus. Analgesic overusers may benefit from alternative strategies to control medication intake. Behavioral techniques may supplement stress-coping skills in patients for whom life stress exacerbates headache [26]. Relaxation training, thermal biofeedback with relaxation training, EMG biofeedback, and cognitive behavioral therapy may be effective. Acupuncture, TENS, cervical manipulation, occlusal adjustment, hyperbaric oxygen, and hypnosis have been shown to be ineffective or inadequately studied to establish efficacy. The benefit of behavioral therapy seems to be additive with pharmacotherapy. Grade A biofeedback interventions, including relaxation training, thermal biofeedback with relaxation training, EMG, and cognitive behavioral training, are considered effective.

PROPHYLAXIS IN PREGNANCY

Nonpharmacologic, behavioral, and physical techniques should be emphasized in the management of headache occurring in pregnancy. Biofeedback, physical therapy, trigger-point injections, and relaxation techniques can be useful. In one study [27], pregnant patients treated with physical therapy, relaxation, and biofeedback had an 81.2% reduction in headache compared with a 32.7% reduction in a control population. Third-party payers that generally do not provide coverage for these methods of

treatment often approve exceptions for pregnant patients in an effort to avoid medication use. In women with identifiable trigger points, local anesthetic infiltration can be safely performed during pregnancy. All of these methods should be considered for use in our case patient. Even if these are incompletely effective, they may provide important augmentative benefits to other therapy.

SUMMARY

Migraine prevention is an art and not a science. Careful attention to triggers, personality traits, and comorbid health issues help guide the choice of medication. Often, multiple agents providing different mechanisms of action may be needed. It is essential that patients use their acute medication even when on prophylaxis but less than two times per week on an ongoing basis. It is imperative to be patient with preventative outcome because it can take weeks to establish. Supportive care and parallel cognitive interventions helps patients not become frustrated. Migraine remains a devastating condition, with a minimal number of appropriate patients receiving preventative therapy.

Key Points

- Migraine is a common disorder and often very disabling.
- Prevention of migraine will lead to less suffering and better qualities of life.
- Prevention is best achieved with a combination of medication, dietary modifications, physical therapy and cognitive behavioral interventions.

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