PROPHYLACTIC MIGRAINE TREATMENT WITH ANTICONVULSANTS:
AN EDUCATIONAL TOOL

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STATEMENT BY THE AUTHOR

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APPROVAL BY THE REPORT DIRECTOR

This report has been approved on the date shown below:

____________________________________   __________________
Judith Berg, PhD, RNC, WHNP     Date
DEDICATION

I would like to thank my family and all my friends for their love and support throughout my work on this clinical project. I will never be able to convey how much I appreciate the encouragement from my husband, Pete Tees. I truly relied on his patience and understanding through this program. He means everything to me. I also want to thank my editor and daily supporter in all aspects of my life, my mother, Kathleen Buchanan.
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ABSTRACT

Migraines are a significant condition, affecting millions worldwide; however, management of the migraine patient can often be confusing and difficult for the primary care practitioner (PCP). Oftentimes, the PCP will refer the patient to a neurologist for consultation or order a multitude of expensive radiology tests to rule out other conditions affecting the brain. The medications used to treat migraines can also be complicated. The two main categories of medications most often prescribed are prophylactic and abortive. There are multitudes of medications within each of those two classifications. Many practitioners are unsure when to consider prophylactic medications versus abortive medications and which types to use.

The purpose of this clinical project is to review the literature regarding the two most promising anticonvulsants used in migraine prophylaxis, divalproex sodium and topiramate. The literature review will then be used to outline the best practice for these two medications in migraine prophylaxis, including the dosing, the side effect profile, and the expected outcome timeline for treatment effect. It will also outline which type of patient would best benefit from prophylactic medication treatment versus abortive treatment. This will then lead to the development of an educational module for primary health care providers.

Suggestions for future educational modules would be targeted toward other classifications of prophylactic medications and outline an educational module for those, such as common beta-blockers, antidepressants, calcium channel blockers, and even other anticonvulsants. The goal of all of these educational tools would be to increase primary health care providers’ knowledge and familiarity with prophylactic medication for
migraines in order to increase their prescription writing of these for better patient management. This in turn would improve patient outcomes.
CHAPTER 1

INTRODUCTION

In this chapter, the topic of migraine headache is introduced. Background information is provided, followed by a discussion of the problem that is addressed by this project. The purpose of this clinical project is detailed, followed by an outline of its significance to the health of individuals affected by migraine headache, as well as to health care professionals, especially those in nursing.

The purpose of this clinical project is to develop an educational module for primary care clinicians targeting anticonvulsants as prophylaxis for the treatment of migraine in females and to increase the overall understanding of migraine. Headache can be defined in multiple ways; however, the most generic is pain located above the orbitomeatal line of the head (Hickey, 2003). Headaches are further categorized into primary and secondary headaches. Primary headaches are those without an identifiable organic cause, such as migraine, tension-type headaches, and cluster headaches, which are not associated with structural changes or lesions in the brain anatomy. Secondary headaches are related to a specific underlying organic cause, such as a tumor or an aneurysm (Hickey, 2003).

Migraine headaches affect approximately 18% of the women in the United States, with current estimated costs in the millions due to lost work productivity, health care expenses, and the price of medication (Hu, Markson, Lipton, Stewart, & Berger, 1999). The peak incidence of migraines is adolescence with migraines persisting through menopause. The median frequency of migraines is 1.5 per month, lasting an average of twenty-four hours (Goadsby, Lipton, & Ferrari, 2002). Although migraine is increasingly
common and can be incapacitating for the affected, it does not receive adequate attention as a public health issue, because it is underdiagnosed and its effect on society and the patient population is underestimated (Hu et al., 1999).

A migraine by definition is a complex disorder. It is a common, yet disabling, neurovascular disorder, distinguished by attacks of severe headache and associated autonomic nervous system dysfunction, which can affect the entire body (Goadsby et al., 2002). There are three major theories of migraine. One cites blood vessel dilation due to dysfunction of the ganglionic neurovasculature of the brain stem. The second involves dilation of the intracerebral arteries and inflammation. The third theory implicates hyperexcitability of the central nervous system (CNS).

In the first theory, the headache involves a neurovascular disorder in which the major blood vessels of the brain dilate, causing increased blood flow to the brain. There is then further nerve cell activation, which increases the cycle of pain. The center of the dysfunction of the migraine is in the brainstem. It is related to the pathways, which normally regulate sensory input; however, in a migraine, these brainstem ganglionic neurons are not correctly modulated in the trigeminocervical complex. The pathways overlap thus letting in all the sensory input, overactivating the brain. This may account for poor localization of pain during a migraine attack. This has been suggested through brain imaging studies of migraine patients (Goadsby et al., 2002).

The second theory of migraine is based on the pain of migraine which may be related to the dilation of the intracerebral arteries, as well as neurogenic inflammation, although the second aspect has yet to be proven. The trigeminocervical complex is where there is significant overlap in nerves and vessels. This is also where the 5-HT receptor
agonists for serotonin are located, which block electrical activity in response to painful stimulation within the brain. This suggests that the trigeminocervical complex is related to the migraine pathway, as well as serotonin uptake (Welch, Cutrer, & Goadsby, 2003).

The third theory of migraine relates to hyperexcitability of the CNS, which in some way makes the patient susceptible to a migraine. The proposed neuronal hyperexcitability is conceivably related to low levels of \( \gamma \) amino butyric acid (GABA) concentrations (Elkind, 2003). All three theories find advocates in the current migraine literature. However, it is my belief that the process of migraine includes all of the above and more that has yet to be uncovered.

Migraine is typically manifested by a disabling headache, possibly with associated symptoms of nausea, vomiting, and light/noise sensitivity. The pain is described as moderate to severe and unilateral; it is also aggravated by activity. There are multiple types of migraine headache. Migraine with aura is referred to as classic migraine. This type includes a visual or other sensory stimulus predicting the migraine, and this aura relates to the onset of pain. Migraine without aura is referred to as common migraine. It has the same types of symptoms and onset as the classic migraine but does not have a distinctive aura before onset of pain (Elrington, 2002). When left untreated, migraines generally last from four to seventy-two hours (Goadsby et al., 2002). There is a type of migraine referred to as chronic migraine, chronic daily migraine, or transformed migraine. Some neurologists believe this is a migraine out of control due to medication overuse, to the point that the brain can no longer regulate itself.

Because migraines may have multiple causes, including some to be discovered, no single treatment algorithm will work for migraine sufferers, since pain, frequency,
severity, medication tolerance, comorbidities, etc., must all be considered when making a treatment plan for a migraineur (Gelb, 1995). There are two types of management of migraine pain. The first is abortive medication, which is medication given during the acute migraine attack. The second is prophylactic medication, defined as medication taken on a daily basis to prevent migraine attacks.

The goals for any abortive medication are to (a) treat the attack rapidly, without recurrence; (b) restore patient function; (c) minimize the use of additional medications; (d) be cost-effective; and (e) have minimal side effects. Abortive treatment may include pain medication or antimigraine medication, such as those listed below; hydration therapy; and antiemetics. Abortive medications include simple over-the-counter medications, such as aspirin, acetaminophen, naproxen, and ibuprofen. They also encompass ergot derivatives, such as DHE, cafergot, and ergotamine; or they can be combination therapies, such as those with butalbital including Fiorinal® and Fioricet®. There are also a few which do not fit into any specific class, such as Lidocaine® nasal spray, Midrin®, and corticosteroids. Abortive medications also include opiate analgesics, from Percocet® to Toradol® or morphine. However, since the conception of triptans, these are by far more widely used and most effective. Currently, there are seven triptans on the market in various forms for use. Sometimes abortive therapy can also include adjunctive antiemetic treatment for those patients suffering from severe nausea as an associated symptom of migraine (Silberstein, 2000).

A variety of medications have been used in the prophylactic treatment of migraines, including beta-blockers, calcium channel blockers, antidepressants, and anticonvulsants (Rapoport, Sheftell, & Tepper, 2001). A relationship between migraines
and menstrual cycles has been widely reported by approximately 60% of women with migraine, and the higher incidence of migraine in postpuberty-aged women also suggests a hormonal component. In addition, it has been suggested that the decline in the average number of migraines by the suffering migraine patient after age 42 may be due in part to decreasing levels of estrogen (Diamond & Wenzel, 2002). Therefore, using birth control pills to suppress the fluctuation in hormones during the traditional menses cycle can be helpful in preventing migraines; however, that concept is beyond the scope of this paper.

Beta-blockers work by stabilizing the artery wall or preventing the central generator of migraines from firing, both of which create a more stable environment for blood flow through a constantly equally constricted artery. Calcium channel blockers prevent the extracellular calcium from entering certain cells within the brain and muscle, which prevents the blood vessels from dilating, the main trigger in the beginning of the migraine process. Antidepressants increase the amount of circulating serotonin, which is helpful for the chronic migraine, but how this works is unknown pathophysiologically. The most recent literature focuses on anticonvulsants as a prophylactic treatment for migraine, in part due to their ability to modulate the effects of glutamate, sodium ion channels, and GABA, during the aura phase of migraine attacks. However, their complete role in migraine prophylaxis is not fully understood, and each anticonvulsant works in a manner different from other anticonvulsants (Cutrer, 2001).

As many as 30 million Americans suffer from migraine headaches, and these patients can be a challenge not only within the primary care setting but also in the emergency room if not managed correctly (Aukerman, Knutson, & Miser, 2002). The goals of long-term treatment must be addressed on a patient-by-patient basis; however, it
would be useful to have an overall understanding of the types of treatment modalities available. Many patients self-medicate. Others are mismanaged by practitioners and physicians, because neurology is overwhelming and the drug regimen and choices are complicated. The object of prophylactic therapy is to accomplish one or more of the following goals: (a) decrease attack frequency, severity, and duration; (b) improve responsiveness to treatment of acute attacks; and (c) improve function and reduce disability (Hickey, 2003). It has been increasingly noted that young women in this population do not always tolerate the old standard first prophylactic treatment option of beta-blockers, for a multitude of reasons, mainly orthostatic hypotension and bradycardia (Silberstein & Goadsby, 2002). Now, researchers and practitioners have discovered anticonvulsants as an option for migraine prophylaxis. Migraine is becoming a common malady treated in the primary care setting rather than by referral to neurology. Therefore, it is crucial that PCPs understand migraine treatment options.

STATEMENT OF THE PROBLEM

PCPs are often overwhelmed by migraine patients and may not know when to treat with abortive medication and when to treat with prophylactic medication. When PCPs use anticonvulsants, they may be unfamiliar with how to use them as migraine prophylaxis and may not understand the medication profile.

Migraine pain can be debilitating and can affect the patient’s ability to work and function in society or within his or her family. Using prophylactic medications to decrease the severity, the frequency, and the duration of attacks can be the first step in increasing the patient’s well-being and promoting his or her quality of life.
STATEMENT OF THE PURPOSE

The purpose of this clinical project is to educate PCPs about migraine. It is to help them understand the pathophysiology mechanisms and current theories behind migraines, as well as current treatment options for prophylaxis. Mainly, this project will compare the two most commonly used and most promising anticonvulsants currently on the market. Divalproex sodium and topiramate are both well-known anticonvulsants, which have shown promise in other avenues of medicine, including migraine prophylaxis. However, PCPs may not fully understand their usage, titration schedule, side effect profile, or sequence of effectiveness. It is also difficult for PCPs to decide when a patient needs prophylactic medication management, rather than abortive pain management, which will also be part of the educational tool.

SIGNIFICANCE

Overall Significance

Migraines and other headaches are among the most common complaints seen by PCPs; however, all headaches continue to be underdiagnosed, misdiagnosed, and mistreated. The medical community often mismanages headaches, and this leads to self-medication through the use of over-the-counter pain relievers. Better understanding of prophylaxis versus treatment options is critical to better migraine control. Migraine headaches greatly impair quality of life in patients who are affected, but they also affect quality of life for family members and coworkers. Therefore, optimal management of headaches vis-à-vis prophylaxis or abortive therapies is essential.
Significance to Health Providers

Health care practitioners are concerned with migraineurs on multiple levels since they can be difficult patients to manage and because of their frequent use of emergency rooms for pain management. They can also be frightening for practitioners who do not understand the common presentation and do not elicit a full headache history. Since there is not an organic cause or specific test to order, although many practitioners often order computed tomography (CT) scans when they are unneeded, practitioners find migraines difficult to diagnose. With a headache history, a physical exam, and a simple list of the common red flags about which to be concerned, the practitioner should feel comfortable diagnosing and managing the average migraine patient using abortive or prophylactic medications. In the majority of patients, there is no need for further diagnostic workup or emergency transfer (Gelb, 1995). The goal of this project is to increase the health care practitioner’s understanding of migraine prophylactic treatment, such as when to use it and specifically how to use two particular medications. This particular project will be helpful in identifying and outlining the effects of two common anticonvulsants, divalproex sodium and topiramate, used in migraine prophylaxis, including dosing schedules, side effect profile, and expected outcome.

Significance to Nursing

Nursing has been goal oriented to quality of life for patients, and migraines can be significantly painful and disabling. If prophylactic medication can prevent the migraine or decrease the frequency, duration, or severity, then the quality of life for the patient will increase. Nursing will be crucial in helping the patient overcome some of the difficulties in the stigma associated with taking pills daily or having the diagnosis of migraine.
Nurses will also help teach the patient how to use a headache diary, avoid triggers, use their abortive and prophylactic medication appropriately, etc. The significance to nursing is based on patient outcomes and education to prevent frequent emergency room visits for crippling pain. This pain impacts the patient and family, both socially and emotionally, in all interpersonal relationships.

The nursing role would center on education and include a detailed teaching plan for patients with headache. This teaching plan would contain a multitude of items, including (a) what migraines are (and what they are not), (b) helping the patient identify his or her migraine triggers, (c) helping the patient begin a headache diary, and (d) providing a copy of a tyramine-free diet. The nurse would also be instrumental in (a) teaching stress reduction techniques, (b) supplying a medication management/side effect profile, (c) providing comfort measures during an attack, and (d) identifying migraine resources within the community and on the Internet (Hickey, 2003).

The utilization of health care services would diminish as pain and migraine attacks were controlled through abortive and prophylactic medications. Migraines are adding to the current burden in the health care system.

**SUMMARY**

In this chapter, background information was provided on migraine headaches. The various theories of the causes of migraines were outlined. Definitions of migraine types, approaches to treatment and/or prophylaxis, a statement of the problem, and the purpose of this clinical project were detailed. Finally, the significance of this problem and clinical project were discussed related to the overall population and to health care providers, particularly those in nursing.
CHAPTER 2

INTRODUCTION

In this chapter, the theoretical framework for this clinical project is discussed. First, the development of the theory is outlined, followed by an overall discussion of details and their interrelationships. The application of this theoretical view to this clinical project is highlighted. Following the discussion of the theoretical framework is a review of pertinent literature. Finally, this literature is critiqued.

THEORETICAL FRAMEWORK

The Health Belief Model was selected to frame this clinical project, because it embraces proactive health behavior. Rather than passively accepting migraine headache as the fate of affected individuals, the Health Belief Model analyzes personal behaviors which might predict future behaviors with prevention potential, including compliance with medical regimens known to prevent or abort migraine onset (Friedman, 1998).

Development of the Health Belief Model

A group of psychologists, Hochbaum, Rosenstock, Leventhal, and Kegeles, developed the Health Belief Model while they were working in the U.S. Public Health Service during the 1950s. They wrote it to increase public awareness of preventive services, such as immunizations. They assumed the lay public feared disease, and therefore, that would be the motivating factor (Robinson & Kish, 2001). The Model is based on cognitive theory, in that behavior is initiated at least in part to elicit a reward, but it is also connected to the expectation of acquiring a certain outcome. The theory is based largely on the free will of the patient and the patient’s ability to make sound decisions related to his or her own health care needs. Rosenstock later developed the
Model more formally and published it in 1974 when the public health movement began to move toward health promotion and away from acute care symptom management. It was essentially based on a cost analysis plan at the individual level in that the individual must feel the benefits outweigh the perceived costs (Robinson & Kish, 2001). In 1984, Janz and Becker reviewed the Model and found that barriers and susceptibility were the most predictive health actions. However, the Model was not fully developed into an intervention action model, only a theory. In practical application, it has proven to be much more useful in understanding and helping cease negative behaviors than in encouraging positive health behaviors. It is also very helpful as a framework for designing change strategies, especially in persuading people to make healthy decisions (Friedman, 1998). The concept of self-efficacy was added to the Model in the late 1980s after being introduced in 1977 by Bandura to increase explanatory power. It helps explain the power of self will, the ability of people to determine their own outcomes; this is especially critical with long-term lifestyle changes, such as quitting smoking or beginning an exercise program (Robinson & Kish, 2001). Pender revised the health promotion model in 1996 that focuses on enhanced well-being and states that the threat of disease has a minimal motivating factor for most people (Friedman, 1998).

The Health Belief Model makes certain assumptions regarding social interactions and personal development. The first is that individuals act as reasonable people at all times and use information to determine which action should be taken in each individual setting unrelated to previous situations. This also means that people do not take their emotions, fears, denial, etc., into account and do not let that play a factor in how decisions are made. The second is that people can linearly consider the implications of
their actions and determine the detrimental effects of any such action down the road and, therefore, make logical decisions. Third, the theory assumes that all people are long-term thinkers and that all behaviors are goal oriented at that level of thinking. Fourth, it assumes that people make decisions alone without outside family, social, or environmental influences on the decision-making process; this influence was only mentioned in the modifying factor section in deciding whether to make a lifestyle change or not.

Overall, the Health Belief Model is crucial for PCPs to understand since it may identify patients who are willing and able to take prophylactic medicine for migraines. The patient can be identified through the concepts listed above, and the PCP will be better able to target those patients destined for success with prophylactic medication. PCPs should comprehend all the concepts of the Health Belief Model in order to understand and help the patient through those difficult times in adjusting to the new role as a medication-taking person, especially prior to the time he or she sees the positive effects of the medication. The Health Belief Model may allow an increased pattern of communication to occur between the PCP and the patient. The Model is also very helpful in guiding the formulation of a teaching module in order to allow the educational continuum to trickle from the educator to the PCP to the patient.

Critique of the Health Belief Model

The main criticisms of the Health Belief Model stem from the notion that it is impossible to predict human behavior. Each situation has a unique set of circumstances related to that person, in that place, with that history, with those previous life experiences, and with those variables; and therefore, each person has an individual concept of the
perceived threat. There are other factors not mentioned in the Health Belief Model which affect behavior, such as interpersonal factors, institutional and community factors, and public policy (Robinson & Kish, 2001). It is also difficult if not impossible to quantify the implied correlations or outcomes from the Health Belief Model. It is hard to classify relationships in terms of variables and place them into categories.

Overall, the Health Belief Model is very useful in providing certain aspects of helping to plan change, both cessation of risky behaviors and support for certain healthy behaviors. There have been multiple changes, deletions, and renovations to the original Health Belief Model. The Model has been criticized because it has limited applicability. However, Nursing Science is heavily involved with health promotion and disease prevention study, and the Model can have utility in that work.

Summary of the Health Belief Model

The Health Belief Model was one of the first change behavior theories developed. According to this theory, change depends on multiple factors related to whether a particular person will carry out a lifestyle change, especially long term. There are five main factors: (a) perceived severity—the belief that a health problem is serious; (b) perceived threat—the belief that one is susceptible to the problem; (c) perceived benefit—the belief that changing one’s behavior will reduce the threat; (d) perceived barriers—a perception of the obstacles to changing one’s behavior; and (e) self-efficacy—the belief that one has the ability to change one’s behavior (Friedman, 1998). Time can also be a positive or a negative factor, in that the person can feel he or she must make this lifestyle change immediately to affect the rest of his or her life, or the person can feel he or she has the rest of his or her life to make the lifestyle change. The primary
motivating factor is usually the belief in the perceived threat of a certain disease, i.e., migraines.

Health Belief Model Application to the Present Project

Perceived threat and severity of illness are important determinants of a change in behavior. According to the Health Belief Model, perceived severity of illness and prognosis have an affect on the individual trying to make a lifestyle change. In the case of migraine headaches, the perceived severity of illness is intertwined with how frequently the migraines occur and how disabled the individual is during a migraine headache. Perceived threat from migraine headaches includes the very real fear that one is more susceptible to frequent headaches or to other related neurological problems rather than the threat being an abstraction. Otherwise, the affected individual is unlikely to change his or her lifestyle or utilize other preventive measures. Often, the fear of disabling pain is the perceived threat and is the deciding factor for the patient.

Perceived benefit and barriers can also affect change in behavior. The perceived benefit of a change in behavior must be personalized, so that if the patient makes a lifestyle change, the threat of migraines or headache pain would be reduced or negated. Perceived barriers are the obstacles, real or self imposed, that an individual feels stand in the way of making a lifestyle change. Often, the perceived difficulty in taking a daily medication is the possible side effects or the stigmatism of being a “sick person,” who needs medicine every day.

Finally, the concept of self-efficacy is an important element in the Health Belief Model. Self-efficacy relates to the concept of self-power. The person must feel that he or she has the power to elicit change and affect the future. The person must have hope
that he or she can change the outcome of his or her migraines by taking a prophylactic medication.

The Health Belief Model is most pertinent to examining change behavior or potential for change in individuals. However, it is relevant to this clinical project because the educational module developed for clinicians includes elements that prompt change to healthy behavior and prophylactic management of migraine in individuals. In other words, the Health Belief Model is a suitable framework for this clinical project, because it guided the development of a teaching module that ultimately impacts the individual patient affected by migraine.

LITERATURE REVIEW

In this section, literature relating to migraines and their prophylactic treatment will be reviewed and critiqued. Literature reviewed includes treatment protocols, epidemiological facts about migraineurs, and predisposing factors related to migraineurs. Articles were chosen for their potential contribution to establishing the significance of the problem, the target population, and the treatment implications. Food and Drug Administration (FDA) approval has been granted for the use of divalproex sodium in the prophylactic treatment of migraines. Topiramate also shows similar promise in the treatment of migraine with research supporting a significant decline in the number of headaches per month. Each of these medications will be discussed related to the previous research, the current understanding of the medication properties, and common usage.

The review of literature focuses on the two most promising anticonvulsants used in migraine prophylaxis mentioned above, divalproex sodium and topiramate. All the articles reviewed were evaluated for (a) medication use, (b) length of use of the
medication, (c) safety of the medication (side effects), (d) efficacy of the medication as
determined by a decrease in number and severity of migraines during treatment with
migraine prophylactic medication, and (e) length of treatment in order to produce effect.
The two medications will then be reviewed and compared to one another for the above
qualities in order to evaluate the medication properties.

Clinical presentation includes frequent migraine attacks, generally more than
three days of headache-related disability a month, or headaches of significant severity.
Prophylactic treatments may also be needed for patients who have comorbid conditions,
an inability to tolerate standard abortive medications, or contraindications to acute
therapy. Frequent migraine attacks, which indicate the use of prophylactic treatment, are
those that occur on four or more occasions per month (Snowise, 1999). It is necessary to
counsel patients that prophylactic medications are not a cure; and therefore, patients will
still need abortive and/or pain medication for breakthrough migraines. Prophylactic
treatment is not recommended for all patients with migraine; however, it merits use in
certain clinical situations. Prophylactic management has several goals, including
decreasing migraine frequency, severity, and duration; making attacks more responsive to
acute treatments; and improving the quality of life in migraine sufferers (Dodick, 2001).

When starting prophylactic treatment, other comorbid conditions should be
considered in order to choose the most appropriate medication for that patient. Common
comorbid conditions, which may benefit from prophylactic treatment, include cardiac
conditions, such as angina, hypertension, and coronary artery disease, in which beta-
blockers or calcium channel blockers may be used for prophylactic treatment of migraine.
If the patient has an underlying seizure history or essential tremor, an anticonvulsant
would be used. Patients with anxiety disorders, difficulty sleeping, chronic fatigue syndrome, or depression may be tried first on an antidepressant such as a tricyclic antidepressant (TCA) or selective serotonin reuptake inhibitor (SSRI). Monoamine oxidase inhibitors (MAOIs) can also be used for patients who are refractory to other treatments. Birth control pills may also be considered as prophylactic management depending on the timing of the migraines and other related conditions. Reducing the frequency and duration of migraines is the main goal of any prophylactic therapy (Silberstein, Goadsby, & Lipton, 2000). An anticonvulsant may be the first line of treatment in certain cases when other prophylactic medications are contraindicated, such as in asthma when beta-blockers are often not tolerated (Mathew, 2001).

Divalproex Sodium (Depakote®)

Divalproex sodium has been researched for migraine prophylaxis and, as stated previously, has FDA approval for this use. It was approved for the prophylactic treatment of migraine by the FDA in 1996 and is sold under the generic name of divalproex sodium or the brand name Depakote® (Landy, 1998). Several studies have established the effectiveness of divalproex sodium at migraine prophylaxis. Divalproex sodium is absorbed through the gastrointestinal tract, and it then changes into the chemical form, valpoate. This appears to increase GABA by inhibiting GABA transaminase, the enzyme connected with its degradation (Mathew, 2001). This inhibitory neurotransmitter is generally depressed in migraine patients (Diamond et al., 1997). An alternative explanation of action relates to the blood flow theory in which migraines are caused by increased blood flow to a certain area of the brainstem. This increased blood flow persists even after pain relief, which may suggest an imbalance in
the activity between the brainstem nerves and blood vessels. Because divalproex sodium increases the inhibitory brain proteins and decreases the excitatory brain proteins, it has the potential to turn off or modulate the chemical reactions leading to migraine (Landy, 1998).

The long-term safety of divalproex sodium has been demonstrated in a variety of studies, with the longest use up to 63 months (Diamond et al., 1997). The general treatment protocol in the research articles for divalproex sodium was to start the participants on a minimum of 125 mg three times per day and titrate that dose upward every five to seven days based on the side effect tolerance and headache profile. Mean dose was generally between 1000-2000 mg per day in divided doses. After 3000 mg per day without significant decline in headaches per month and/or severity, it was concluded that the medication was not effective for that individual, and the medication was discontinued. It is not considered necessary to check medication levels because it does not correlate with clinical effectiveness in this particular disease process. However, it is general practice to perform baseline complete blood counts (CBCs) and liver function tests (LFTs) and then check again after one week, then four weeks, and then every six months (Klapper, 1996). The side effect profile for divalproex sodium includes (a) asthenia, (b) nonspecific back pain and other generalized nonspecific pain, (c) infection, (d) dyspepsia, (e) diarrhea, (f) nausea, (g) tremor, and (h) somnolence (Mathew, 2001). Increased appetite and weight gain was reported in the majority of the studies (Jensen, Brinck, and Olesen, 1994).

Klapper (1996) reviewed significant studies on migraine treatment using divalproex sodium. This review focused on four studies utilizing this medication for
migraine prophylaxis. In a study by Sorensen (1988), 22 participants received an average
dose of 600 mg twice per day (bid). Sixty-one percent responded favorably to the
medication regimen, with 11 becoming completely headache free while on the
medication. Hering and Kuritzky (1992) gave a divalproex sodium dose of 400 mg bid to
29 participants in a randomized, double-blind study. There was a decrease in frequency
of attacks and severity of migraine. Overall, 86% responded positively to the medication
treatment. Jensen, Brinck, and Olesen (1994) studied 43 participants who were given
divalproex sodium 500 mg bid over a 12-week treatment period plus a 4-week washout
period of placebos. Fifty percent of the participants had at least a 50% reduction in
migraine frequency. A large multicenter, randomized, placebo-controlled, double-blind
study was conducted by Mathew, Saper et al. (1995) with 107 participants over 12 weeks
using an average dose of divalproex sodium of 1087 mg per day, slowly titrated up from
250 mg per day every third day until effective. Overall, 48% experienced at least a 50% 
reduction in migraine frequency when compared to the placebo group. They also
reported less use of abortive medications, fewer functional restrictions during their
headaches, and fewer associated symptoms (nausea, vomiting, and photophobia) with
their migraines (Mathew, Saper et al., 1995).

A study on divalproex sodium was published in 1999 with 53 participants
completing the study from multiple centers around the country (Silberstein & Collins,
1999). The average dose was based on how long each participant was involved in the
study, with a minimum beginning dose of 500 mg per day and averaging 950 mg per day,
titrated based on their headache diary, tolerance, and side effects. The side effect profile
presented in this study concurred with Mathew, Saper et al. (1995) but added minor
infection and dyspepsia. Results supported divalproex sodium as an effective prophylactic treatment of migraine with increased efficacy for longer use. The greatest decrease in headache frequency began after day 541 on the medication. This is a crucial piece of information for practice, as this medication continues to improve up to day 1080 of use. No change in the mean severity of experienced headaches or the functional ability of the participants was noted. However, overall use of other symptomatic medication decreased in proportion as the number of migraines decreased. This study’s major contribution was to establish that the long-term effectiveness of divalproex sodium was proven through research. Practitioners and patients must adequately test the efficacy of divalproex sodium prior to changing to another medication by lengthening the trial period. Critique of the study centers on its lack of control subjects and multiple sites that had no standardized practice (Silberstein & Collins, 1999).

A large double-blind, randomized, placebo-controlled, parallel-group study focused on extended release divalproex sodium tablets in migraine prophylaxis (Freitag et al., 2002). The trial lasted 17 weeks and included a 4-week baseline phase, a 12-week experimental phase, and a 1-week termination phase. The study upheld classification criteria from the International Headache Society (IHS) for clinical trials on migraine. The aim of the study was to test a once-a-day treatment regimen to increase compliance and, therefore, increase the effectiveness. The first two weeks of the experimental phase were used to titrate the medication and manage dosage-related side effects, the average dosage being 871 mg per day. The results were significant for the 202 participants who completed the study. The treatment group experienced a mean reduction in migraine headaches by 1.5 per week in each of the four-week trial periods. The placebo group did
not have a statistically significant decrease in mean number of headaches. The greatest reduction in the treatment group was noted in the last four-week period. This confirmed earlier findings about time to maximal treatment effect. However, divalproex sodium did not appear to change the severity of a migraine when one did occur. Side effects were consistent with those in the placebo group in number of participants experiencing them and types of side effects noted. Weight gain was noted in both groups but was higher in the treatment group. The once-a-day formulation and convenience was attributed to some of the success (Freitag et al., 2002).

Topiramate (Topamax®)

Topiramate or the brand name Topamax® has shown potential for use in migraine prophylaxis, although it does not currently have FDA approval for this use. It has shown significant promise in early clinical trials for the prophylactic treatment of migraine, as well as chronic migraine, daily headache, and chronic cluster headache (Freitag, 2001). Topiramate is a broad-spectrum anticonvulsant with multiple mechanisms of action. Enhancing GABA neurotransmission, blocking voltage-sensitive sodium-ion channels, and blocking glutamate action is how topiramate works (Mathew, 2001). Being a weak inhibitor of some isoenzymes of carbonic anhydrase is an additional action mechanism (Mathew, Hulihan, & Rothrock, 2003). Side effects are related to CNS effects, such as (a) overall changes in concentration, (b) language/speech problems, (c) psychomotor slowing, (d) memory impairment, (e) somnolence, and (f) fatigue. Extremity paresthesias are also common and may be dose related. This may be attributable to the effect of topiramate as a weak carbonic anhydrase inhibitor (Storey, Calder, Hart, & Potter, 2001). Patients occasionally complained of diarrhea. However, the most noted side effect was
decreased appetite and otherwise unspecified weight loss. Most side effects were reported as mild, and the medication was well tolerated in all of the reported studies (Mathew, Hulihan et al., 2003).

Trials of topiramate note that the medication was generally well tolerated, reduced body weight, and significantly reduced migraine frequency, as well as reduced the number of days acute (abortive) medications were needed. Trials using topiramate doses of 100-200 mg per day demonstrated that this drug was significantly more effective than placebo in reducing the frequency of migraine, the overall number of migraine days per month, and the need for abortive medication. In addition, it had a higher response rate when compared with placebo (Dodick, Neto, Schmitt, Jacobs, & Raritan, 2003; Mathew, Schmitt, Jacobs, Neto, & Raritan, 2003). Similar findings were reported by Brandes, Jacobs, Neto, Bhattacharaya, & Raritan (2003). These researchers concluded that slow titration and a target dose of at least 100 mg per day in a divided dosage regimen increased efficacy and tolerability (Poole, 2003).

Multiple studies have been conducted to assess the effectiveness of topiramate in migraine prophylaxis. In 2001, prophylactic therapy with topiramate significantly reduced migraine frequency (Storey et al., 2001) in a sample of 40 participants ranging in age from 19 to 62 years. These participants were randomly assigned to the placebo or the topiramate group and then followed over the course of eight weeks as the drug was titrated upward to goal dosage. The participants were then monitored for an additional eight-week maintenance phase during which both the frequency and severity of migraines were monitored over each 28-day period. The effect of the medication was monitored through self-report daily headache logs for occurrences, severity, and associated
symptoms. Migraines were ranked by the participants on a scale of 1 - 3 (1 = mild, 2 = moderate, and 3 = severe). Mean dose was 125 mg/day with a range of 25-200 mg/day. Topiramate reduced the incidence of migraine, but it had no effect on the severity of the migraines that occurred. Few side effects were reported (Storey et al., 2001).

In a retrospective chart review of 69 patients, who had a previous diagnosis of migraine treated with topiramate, the most common side effects were paresthesias and drowsiness (Von Seggern, Mannix, & Adelman, 2002). The mean dose was 100 mg/day with a range of 25-500 mg day. The 500 mg per day was for a patient with a seizure disorder who was using topiramate to manage both disease processes. There were substantial benefits of topiramate in prophylaxis of migraine, especially for those with moderate or severe migraines who did not respond well to other treatment options. Many patients in this chart review had failed multiple other treatment modalities and medications.

In another retrospective chart analysis, three types of patients participated, those with transformed migraine, episodic migraine, or cluster headache (Mathew, Kailasam, & Meadors, 2002). A total of 178 patients were started on 25 mg of topiramate per day and were titrated by 25 mg per week based on their headache and side effect profile. The average dose was 87.5 mg per day with a range of 25-300 mg per day. The most common side effects were paresthesias and cognitive (CNS) effects. Notably, 12% of those in the study lost more than five pounds during the treatment. Topiramate appears to work as a monotherapy in patients with episodic migraine and as adjunctive therapy with abortive treatment in patients with transformed migraine. Patients with transformed migraine took fewer doses of abortive medication and expressed overall improvement in
multiple areas of lifestyle quality. The results implicate topiramate as achieving significant reduction in migraine frequency, migraine severity, and number of headache days per month, as well as reducing the use of abortive medications. Topiramate was well tolerated by participants (Mathew, Kailasam et al., 2002).

In another study, 74 chronic or episodic migraine patients, who were treated with topiramate for over six weeks, decreased their headache occurrence from 20.6 to 13.6 days/month (Mathew, Schmitt et al., 2003). The average dosage was 200 mg per day. All participants exhibited more than a 50% reduction in monthly migraine frequency compared to the patients taking placebos, with the most statistically significant portion being those patients treated with 200 mg. per day. A statistically significant reduction in the frequency of headache occurred within the first month of treatment (Mathew, Schmitt et al., 2003). The study also involved patients with comorbid conditions, mainly depression, and identified their results separately. Side effect profile supported previous research. Paresthesias and cognitive (CNS) difficulties were the most common. Weight loss was also common though not a complaint. Dose did not correlate with weight loss, although duration of treatment and higher weight at baseline did correlate with higher reported weight loss. In this study, topiramate was effective in reducing the severity, duration, and frequency of headaches. It was especially useful for those patients with psychiatric comorbidity issues. Of note, previous failed migraine treatment did not predict either topiramate failure or future effectiveness (Young, Hopkins, Shechter, & Silberstein, 2002).
Comparison

Both divalproex sodium and topiramate were generally well tolerated by patients and showed significant reduction in the mean number of headaches per month. Although both divalproex sodium and topiramate have been used as prophylactic medication for migraine, the dosages, length of use, titration of dose, side effect profile, and efficacy varies between the two drugs. The time to efficacy also varies between the two medications. In fact, even the effective dose used varies between studies. The most important note is to start at a low dose and titrate based on patient profile.

The most obvious difference is in the side effect profile, the most apparent being weight. Divalproex sodium caused patients to gain weight, while topiramate caused most patients to lose weight. Since most migraineurs are women, this is a significant discovery and important to note when prescribing. The complaints about divalproex sodium were all vague and included (a) gastrointestinal upset, (b) generalized pain, (c) asthenia, and (d) somnolence. However, it did produce rare increases in LFTs and caused some cases of pancreatitis. The main complaints for topiramate were related to the CNS effects, including (a) memory impairment, (b) psychomotor slowing, (c) dizziness, (d) language problems, (e) difficulty with concentration, and (f) fatigue. Another problematic complaint was extremity paresthesias, which were often transient and dose related. However, although topiramate is more costly than divalproex sodium and has the above-mentioned side effects, it is conceivable that women may prefer topiramate since the end outcome on headache improvement was similar and there was the added benefit of weight loss. Diarrhea was the only side effect that was common to both medications. Overall, divalproex sodium took longer to work effectively although the end outcome
was just as, if not more, effective than topiramate. However, the efficacy of divalproex sodium was not usually apparent until three months after beginning treatment as opposed to topiramate which began to have effects after one month.

The expense of migraine treatment is a concern in this cost-conscious health care society. However, if anticonvulsants can prove their effectiveness at limiting migraine attacks and decreasing severity, such as in the studies listed above, they could be a cost saving measure. Abortive and pain medications for the treatment of migraines in the acute phase are expensive, as is a trip to the emergency room when the migraine is out of control or undiagnosed. Prophylactic migraine management is not necessary for everyone. The U.S. Headache Consortium Evidence-Based Guidelines suggest that prophylactic medication should be considered when migraine significantly interferes with a patient’s daily routine despite acute care treatment, in cases where acute-care treatment is not tolerated or is contraindicated or where the frequency of migraine attacks is such that the reliance on acute care medication would increase the potential for medication-overuse (rebound) headache (Silberstein, 2000). However, the expense of anticonvulsants does not compare favorably with other prophylactic migraine medications, especially the beta-blockers (Adelman, Adelman, & Von Seggern, 2002). It is also necessary to weigh the adverse reactions of the anticonvulsant and its long-term safety. However, the PCP prescribing medication for the migraineur must consider the savings to the patient in terms of pain management, fewer lost workdays, etc., if the migraine prophylaxis proved successful. Patient suffering and even adverse reactions are indirect costs and, therefore, impossible to measure. There are multitudes of aspects to consider including cost effectiveness when prescribing an anticonvulsant for use in this
manner. They are really only applicable in certain situations, such as in those patients with comorbid conditions or patients with significant frequency of migraine (Adelman et al., 2002).

SUMMARY

It is important to be cautious in prescribing any medication to any patient and to monitor the patient for (a) tolerance, (b) safety, (c) adverse effects, (d) efficacy, and (e) compliance. With both divalproex sodium and topiramate, the PCP should start at the lowest possible dose and make changes based solely on patient tolerance and need, per headache profile. Each patient may need a different dosage based on his or her pharmacokinetics and headache profile; therefore, each therapy should be individualized. Patient education at the beginning of medication administration and throughout the process is crucial for patient compliance and to allow the patient to own his or her condition and take part in its management. It is also important to continue to have consistent follow up with patients in order to monitor both their tolerance to the medication and the effectiveness of the prophylactic treatment. Side effects can be the main reason patients stop prophylactic treatment, so those should be discussed prior to the initiation of any new medication regimen. Weight loss can occur with topiramate, and weight gain can occur with divalproex sodium; this is a noted difference and an important one. As with any medication regimen, compliance can be an issue; and therefore, the patient must recognize that the treatment plan is not abortive therapy; it is therapy to prevent migraines from beginning. As per the Health Belief Model, the patient must own the process of having migraines and be willing to take an active role in their prevention by taking medication daily to prevent the acute pain of a migraine attack.
CHAPTER 3
INTRODUCTION

In this chapter, the clinical project will be detailed. The project is an educational module for primary health care providers intended to increase their knowledge of anticonvulsants used for the prophylactic treatment of migraine in women. The module is detailed in this chapter and includes a brief description of the (a) theories of migraine, (b) types of migraines, (c) approaches to treatment, and (d) goals of prophylactic medication management, as well as a discussion of which patients are best suited for this type of treatment regimen. Two main prophylactic anticonvulsant medications are reviewed, divalproex sodium and topiramate, and compared. A plan for evaluation of the presentation and its impact on practice is included.

CLINICAL PRESENTATION TO PRIMARY CARE PRACTITIONERS

The purpose of this educational module is to increase PCPs’ overall knowledge of migraines and, more importantly, their understanding of the use of the anticonvulsants divalproex sodium and topiramate in the treatment and prevention of migraine. The module is designed as a short, concise presentation for PCPs during a lunch break. This strategy was adopted, because PCPs are accustomed to obtaining medical updates at lunch meetings. The module as outlined should take approximately 30 minutes or less to present. This gives busy professionals the opportunity to access current knowledge without attending a clinical conference that is expensive and time consuming. The short presentation allows time for questions and answers, and this opportunity is often the most educational aspect of a presentation. The teaching module includes (a) a simple handout emphasizing the two main medications discussed, (b) the medication profile of each, (c)
the side effects, (d) the special important properties/tests, and (e) the common dosing regimens. The module handout also includes a brief section on when to consider prophylactic migraine treatment and which patients would best benefit from such treatment. The developed handout can be found in the Appendix.

PROJECT DESCRIPTION

Current research-based knowledge on the use of anticonvulsant medication for prophylactic treatment of migraine was outlined in Chapter Two. From that literature review, two anticonvulsants were selected to be included in this educational module. Divalproex sodium and topiramate were selected, because the first has FDA approval for use with migraine and the second is expected to be approved for migraine prophylaxis in 2004. A secondary reason for selecting these two drugs was that they have dichotomous secondary effects on body weight and time to efficacy.

Following is an outline of the educational module:

I. Introduction to migraine.
   A. Epidemiology of migraine.
   B. Pathophysiology – theories of migraine.

II. Diagnosing migraine.
   A. Diagnostic criteria.
   B. Treatment protocols.

III. Medications.
   A. Abortive treatment.
   B. Prophylactic treatment.
      1. Who qualifies.
2. Types of medications used.
   
a) divalproex sodium.

b) topiramate.

The educational module was developed from a review of the literature. To measure the effect of the presentation, both a pretest and posttest will be administered. The pretest and posttest design is commonly used in education and in research to measure immediate learning (Polit & Hungler, 1993).

Pretest

1. Women who develop migraines are overemotional; it is just a normal headache, but they have a low pain tolerance. True ___ False ___

2. Which of the following are options for prophylactic treatment of migraine? Circle all that apply.
   a. Beta-blockers
   b. Daily NSAIDs
   c. Vioxx
   d. Anticonvulsants

3. You should start prophylactic medication for anyone who asks for it. True ___ False ___

4. Anticonvulsants have more than antiseizure properties. True ___ False ___

5. Migraines are easily understood in terms of the pathophysiology of what causes the pain to start and persist. True ___ False ___

6. Which of the following occurs in migraine headaches (more than one may be correct): Circle all that apply.
a. The vessels in the brain constrict causing pain.

b. The vessels in the brain dilate causing pain.

c. There is low serotonin uptake in the trigeminocervical complex.

d. There is increased dopamine uptake in the neurovasculature of the brainstem.

7. Common migraine, tension headache, and classic migraine are all the same. True ___ False ___

8. All three of the above types of headache are treated similarly. True ___ False ___

Explanation of Clinical Presentation

The first topic to be discussed will be the nature of migraines and headaches in general. The focus of this portion of the presentation will be to accurately define each type of headache. There will be an epidemiology review, including statistics regarding the scope of migraines in the adult population of women in the U.S. Pathophysiology of migraine, including the various working theories of migraine pain, will be briefly reviewed. There will be a short discussion of the diagnostic difficulties in assessing migraine, as well as the diagnostic criteria currently used to assess migraine. There will also be an overview concerning treatment options and an explanation of the difference between abortive pain management and prophylactic pain management for migraine relief. Then two medications, divalproex sodium and topiramate, will be outlined for use in prophylactic migraine management.

Posttest

This will be administered once the presentation is finished. It is the same questionnaire as provided in the pretest, and the results will be compared to determine the effectiveness of the educational module.
Evaluation of Clinical Presentation

Six months after the educational module, the health care providers would be asked to evaluate the effectiveness of the module and rank their perceived knowledge of the migraine patient. They would also be asked about their current prescription practices, whether prescribing or considering prescribing prophylactic medication for migraine patients, versus their practices prior to attending the educational module. This will assess whether or not they have increased their rates of prescribing or considering prescribing prophylactic medications.

Evaluation:

1. Did you attend the migraine educational module?
   Yes ____ No _____

2. If you attended, did you find it useful in increasing your overall knowledge of migraines?
   Yes ____ No ____
   Please explain either way ________________________________________________
   ______________________________________________________________________

3. Do you prescribe or consider prescribing migraine prophylactic medications more now than prior to the educational module?
   Yes ____ No ____

4. Do you now refer fewer migraine patients to neurologists and other specialists and more often manage these patients yourself?
   Yes ____ No ____
5. Do you prefer anticonvulsants as a first line prophylactic migraine medication? If not, what is your preference?
   Yes ____ No ____, prefer __________________________

6. Do you feel all anticonvulsants are difficult to manage, mainly due to the frequent lab testing required?
   Yes ____ No ____

7. Do you believe all anticonvulsants cause weight gain and multiple significant side effects?
   Yes ____ No ____

8. Would you be interested in attending more of these miniature educational modules?
   Yes ____ No ____

DETAILED EDUCATIONAL MODULE

The educational module is detailed in this section. It follows the outline as presented above.

Introduction to Migraine

Migraine remains one of the more underdiagnosed and undertreated disorders despite recent advances not only in the understanding of the pathophysiology but also the treatment of migraine using the newest pharmacotherapeutics (Cady & Dodick, 2002). One of the most difficult parts of dealing with migraine patients may be making the initial diagnosis. Since migraine patients rarely need diagnostic testing or imaging, the diagnosing is based solely on the history and physical. The IHS developed classification tools and diagnostic criteria to help define the types of headache suffered by patients and when to use diagnostic testing. The most basic definition is of the migraine without aura,
common migraine, which when left untreated could last four to seventy-two hours and include one or more of the following associated symptoms: (a) nausea and/or vomiting, (b) photophobia, or (c) phonophobia. It is also associated with at least two of the following pain characteristics: (a) unilateral location, (b) throbbing quality, (c) moderate to severe intensity, and/or (d) aggravation by routine activity. Generally, this is not diagnosed as migraine until the patient has had the type of headache that meets the above criteria at least five times per patient history. There are slight differences in the definition of the other types of migraine, such as classic migraine, etc. (Evans & Olesen, 2003).

Epidemiology of Migraine

It is estimated that over 28 million Americans suffer from migraines; that means that 12.6% of the U.S. population has been diagnosed with the condition. Eighteen percent of the women in the U.S. have migraines. The peak prevalence of migraine is among persons aged 25-55. Females outnumber men with the diagnosis at all ages after puberty (Lipton, Stewart, Diamond, Diamond, & Reed, 2001). Migraine takes a toll on the patients who have this diagnosis. It disrupts the patient’s life, causes missed work days, costs money due to medical expenses, and causes pain and discomfort. Based on a study done in 1998, the average number of attacks for women age 20-64 years was 34 per year. Younger patients were more likely to be bedridden, but those older patients who were bedridden stayed in bed longer. On average, all women stayed in bed at least six hours. Women with migraines missed an average of 5.6 days of work per year due to migraines. The medical costs were related to physician expenses (60%), medications (30%), and emergency visits (1%) (Hu et al., 1999). However, managing the treatment plan for any migraineur can be a challenge.
Pathophysiology – Theories of Migraine

The pathophysiology of migraine has multiple theories and is still being researched. There are three main accepted theories regarding the source of migraine development and the associated pain. One of the original theories of migraine relates to intracranial vasoconstriction and extracranial vasodilation. This causes increased blood flow to the major blood vessels of the brain, essentially a neurovascular disorder. This cycle of pain is repeated as more nerve cells are activated by the expanding vessels. The center of the dysfunction is the brainstem, which should shut down the overloading sensory nerve stimulation in the trigeminocervical complex; however, in a migraine, these brainstem ganglionic neurons are not correctly modulated and do not work correctly. They are too open and overload the brain (Goadsby et al., 2002). There is another theory related to neurogenic inflammation based on the pain of migraine. This theory is based on the fact that the trigeminocervical complex is where there are millions of nerves and vessels overlapping and where the 5-HT receptor agonists for serotonin are located. Serotonin is a chemical involved in vasoconstriction, which can also block electrical activity in response to painful stimulation within the brain. However, during migraine attacks, serotonin is depleted as well as the mechanism regulating serotonin uptake (Welch et al., 2003). There is another possibility that migraine is related to the hyperexcitability of the CNS, which may be due to low levels of GABA; however, this is only an emerging theory and is still being researched (Elkind, 2003). More realistically, migraine is a complex disorder, which is triggered by a multitude of pathophysiologic causes, some of which have not yet even been discovered.
Diagnosing Migraine

The differential diagnoses considered in migraine represent a large portion of neurological conditions, mainly other types of headaches; however, they can also include (a) seizures, (b) stroke, (c) transient ischemic attacks, (d) brain cancer, (e) cranial neuralgias, and (f) other structural abnormalities, which may increase intracranial pressure causing pain. Part of diagnosing migraine is to determine if the headache is of primary or secondary classification. The diagnosis of primary headache is made through a thorough history and physical exam, including a detailed neurological examination. A secondary headache is one due to an underlying medical condition, such as an organic process. These are often identified through common red flags, such as (a) the new onset of headaches after age 40, (b) the onset of a new headache type, (c) a new level of pain, (d) a change in headache intensity or frequency, (e) a headache that interrupts sleep, (f) a headache initiated with Valsalva maneuver, (g) a headache associated with neurological changes, or (h) a headache in patients with known underlying malignancy or human immunodeficiency virus (Cady & Dodick, 2002). For any of these common red flags, a further workup is necessary, possibly including neuroimaging, lab testing, or neurology consult.

The spectrum of headache included in the diagnosis of primary headache is also vast. It includes all types of migraines and tension-type headaches. Generally, the accepted, although not widely used, criteria to diagnose each type of primary headache are the IHS criteria. The IHS criteria spell out the definition of each type of headache and include the standards each patient must fulfill in order to meet that diagnosis (Cady & Dodick, 2002).
The presence of comorbidities is another important factor in the migraine diagnosis and treatment plan. Migraine sufferers have greater relative risks for suffering from a multitude of medical conditions, such as (a) asthma, (b) familial tremor, (c) irritable bowel syndrome, (d) epilepsy, and (e) stroke. They also have a high incidence of comorbidity with depression and anxiety disorders, including associated sleep disturbance problems (Finkel, 2002).

Migraine remains a difficult diagnosis for the PCP to determine since the migraine sufferer rarely presents during an acute attack, and there are no definitive diagnostic tests to outline the diagnosis. Approximately half of the migraine sufferers have not received a medical diagnosis of migraine (Lipton, Diamond, Reed, Diamond, & Stewart, 2001). The majority of migraineurs treat their headache pain with over-the-counter pain medication rather than prescription medication, since only 41% of the diagnosed migraine population actually receives prescription drug treatment (Lipton, Diamond et al., 2001).

The process of diagnosing migraine should include most importantly a thorough patient history. Often, it is necessary to obtain a headache diary (calendar) from the patient, which includes (a) a detailed log of when the pain occurred; (b) the time of month the pain occurred; (c) the aggravating/relieving factors; (d) any associated symptoms; (e) the type of pain, including the duration and severity; (f) the presence of aura; (g) the location of the pain (unilateral or bilateral); and (h) the recurrence of pain. The patient should also try to identify any common triggers that may set off his or her migraines, such as (a) food, (b) alcohol, (c) sleep deprivation, (d) hunger, (e) flashing
lights, etc. The diagnosis of migraine is based on the IHS diagnostic criteria, which state the patient must have a history of at least five attacks fulfilling the criteria listed above.

**Diagnostic Criteria**

Neuroimaging can be another source of concern for PCPs; it can be difficult to determine whether a patient needs a CT scan or magnetic resonance imaging (MRI) performed. The American Academy of Neurology suggests that neuroimaging is only necessary in patients with migraine who also have atypical headache patterns or other neurological signs; therefore, in general, the U.S. Headache Consortium does not recommend neuroimaging unless the patient meets specific criteria that were developed by the Consortium (Auckerman et al., 2002). The American Academy of Neurology’s guidelines regarding neuroimaging are very similar to the U.S. Headache Consortium guidelines and its suggestions for patients who should receive a CT scan or an MRI. In fact, the only common abnormalities noted in migraine patients with neuroimaging studies were white matter abnormalities, and it has yet to be determined why this occurs in migraineurs (Evans & Olesen, 2003). At times, clinicians have also used electroencephalography (EEG) to diagnose migraine; however, the main purpose of an EEG is to exclude an underlying structural lesion, such as a tumor, in which case a CT or MRI is preferred (Evans & Olesen, 2003).

**Treatment Protocols**

There are a multitude of reasons a treatment protocol for migraine patients would not work in all settings, mainly due to the severity of the illness, the need for prophylactic medication management versus only abortive pain management, and the patient’s other comorbid conditions. The condition is ever evolving and complex in all patients, each
with unique associated symptoms, which necessitate individualized treatment and patient education (Diamond & Wenzel, 2002). This is why treatment protocols are not widely accepted; however, there are a few available, of which some parts of the protocol can be used successfully. The first part of any protocol is to establish a diagnosis based on the IHS criteria, as listed above, and rule out other neurological conditions, including other forms of headache. Once the diagnosis of migraine has been established, the PCP must decide if the patient has the headaches often enough to merit needing prophylactic medication based on criteria outlined below. Adjunctive non-pharmacologic treatment, such as relaxation therapy, biofeedback, and cognitive-behavioral therapy, can also be considered at any point (Silberstein & Lipton, 2003).

Whenever a treatment plan is discussed with a patient, the first order should be to mutually decide on achievable goals of treatment. In order to set these goals, the PCP should elicit triggers, frequency, severity, time to peak, prior response to abortive and prophylactic treatment (including side effects), and patient preference to treatment plan. Often the PCP and the patient will need to establish a similar vocabulary to discuss the headache in a concrete manner. This should include a brief explanation by the PCP of migraine pathophysiology in order to better inform the patient how to determine the best treatment option for him or her (Finkel, 2002).

Patients need to hear the diagnosis once and for all. They need to understand that there is a specific diagnosis; the testing is over; and that there is a treatment plan. Patients should be actively involved in the treatment decisions and should not be placed on prophylactic medications without their desire to take that route of treatment. Patients also want to understand (a) the natural history of the disease, (b) that it is a lifelong
condition, (c) that there may be complications, and (d) the long-term prognosis (Finkel, 2002). Once a treatment plan has been mutually established by the patient and the PCP, both abortive and prophylactic medications should be explained, if both are options for that particular patient.

The most basic of treatment plans is a stratified care approach with three tiers of treatment. The low need patient is started on abortive treatment with over-the-counter products, such as nonsteroidal anti-inflammatory drugs (NSAIDs); however, if the patient fails the plan, he or she then tries combination analgesics until treatment is effective. The moderate need patient is also given combination analgesics plus a triptan if the pain is not controlled within the beginning part of the attack. The high need patient is given only triptans. All patients are taught to (a) establish goals, (b) keep a headache diary and treatment diary, (c) use relaxation therapy, (d) avoid triggers, and (e) adjust their lifestyle, including decreasing stressors (Roger & Dodick, 2002). One of the main detractions of this stratified approach is that prophylactic treatment is not specifically outlined within the plan, although it could easily be added as part of the design.

Medications

Abortive Treatment

Abortive treatment has five basic principles developed by the U.S. Headache Consortium, which include (a) educating patients with migraine about their illness and treatment plan while encouraging them to participate in their own management; (b) using migraine specific agents in patients with severe migraine and those who respond poorly to NSAIDs or combination agents; (c) selecting a non-oral route for those patients with associated symptoms of vomiting or nausea; (d) considering the use of a self-
administered rescue medicine for patients who fail other treatments; and (e) guarding against medication overuse, in order to prevent rebound headache. The exact medication used for abortive therapy depends on the severity of the migraine, the coexisting conditions, the associated symptoms, and the length of the migraine (Morey, 2000). Abortive therapy includes a large variety of medications and comes in a multitude of routes, including (a) oral, (b) nasal, (c) intramuscular injection, (d) intravenous injection, and (e) subcutaneous injection (Diamond & Wenzel, 2002). The most widely used abortive agents are the triptans; however, NSAIDs, ergot alkaloids and derivatives, opioid analgesics, barbiturate hypnotics, plus combinations and antimemetics, are all commonly prescribed.

Prophylactic Treatment

Who Qualifies

The next difficult decision in patient management is when to move from basic defense in abortive treatment to offense in prophylactic treatment of migraines. Prophylactic treatment can be considered for a variety of reasons; it is most often used for patients with frequent or severe migraine attacks. Prophylactic treatment should be considered if (a) a patient has two or more migraines per month, especially those producing significant disability, lasting 2-3 days; (b) there is a failure or inability to tolerate abortive treatment; (c) there is a rising pattern of headaches of more than two per week, especially if there is increasing dependence on abortive treatment which can lead to rebound headache; or (d) there are special circumstances related to comorbid conditions or other neurologic concerns. It can also be considered if the patient prefers it (Silberstein & Goadsby, 2002). The object of prophylactic therapy is to accomplish one
or more of the following goals: (a) decrease attack frequency, severity, and duration; (b) improve responsiveness to treatment of acute attacks; and/or (c) improve function and reduce disability (Hickey, 2003). The prophylactic treatment success has variable definitions; however, the standard goal is to have a reduction in migraine frequency of at least 50% (Snowise, 1999). The length of use of prophylactic medication is variable. Some patients find that six months is enough time to improve the headache cycle to a more controllable degree, which can then be managed with abortive medications. Other patients may use the medication for a few years, such as during a known difficult or stressful time, for example attending graduate school. Then these patients will be weaned off the medication as the stress subsides. Once the headache frequency decreases, they manage the migraines with abortive medications. Unfortunately, there are also select patients who remain on the prophylactic medications for a significant amount of time. These patients often take medication hiatuses in order to monitor the migraine severity and frequency, checking to determine if they still need the medication. The standard of care in migraine prophylaxis is that after a three to six month period of headache control the PCP should consider tapering off or discontinuing the treatment at least to reevaluate the need for therapy (Silberstein, 2000). Often, women in the childbearing years stay on prophylactic medication if they have severe migraines until the migraines dissipate as the menses cycle changes in frequency, although this does not occur for all women either. However, the overall course of the prophylactic medication therapy is dependent on the clinical course and may be influenced by other coexistent conditions (Ward, 2000).
Types of Medications Used

Medications used in the prophylactic management of migraine headache include a variety of subcategories and within those categories are a variety of efficacy rates. The common subcategories for the prophylactic management of migraine include (a) beta-blockers; (b) antidepressants, mainly including TCAs and SSRIs; (c) calcium channel blockers; and (d) anticonvulsants (Silberstein & Goadsby, 2002). Anticonvulsants are increasingly found to be as effective as other prophylactic medication options based on recent double-blind, placebo-controlled studies which have proven their effectiveness. More and more, anticonvulsants are being researched for use in this manner, although at this time, only divalproex sodium has FDA approval for migraine prophylaxis (Silberstein & Goadsby, 2002).

Divalproex sodium. Divalproex sodium is generally started at 125 mg three times per day TID with a goal dose of 1000-2000 mg per day in a divided TID dosing schedule (Diamond et al., 1997). Another option for a starting dose is 250 mg BID titrating up the dosage as needed from there (Mathew, Saper et al., 1995). Many of the researchers found that lower doses of divalproex sodium had just as positive an outcome in reducing the mean number of headaches per month as found by Diamond et al. Hering and Kuritzky used 400 mg BID in 1992 with positive effect on patient outcomes, as did Sorensen in 1988 using 600 mg BID. Since there is no standard treatment, it is crucial to look at each patient individually and titrate the medication as needed. The effective dose will be unique to each patient from 800 mg per day to 2000 mg per day in divided doses. However, once a dose of 3000 mg is reached per day without improvement in migraines, it is considered a failure, and a new prophylactic medication should be initiated.
Migraine Treatment

(Diamond et al., 1997). It should be standard treatment to check baseline CBCs and LFTs and then check again after one week, then four weeks, and then every six months (Klapper, 1996).

The side effect profile for divalproex sodium includes (a) asthenia, (b) nonspecific back pain and generalized nonspecific pain, (c) infection, (d) dyspepsia, (e) diarrhea, (f) nausea, (g) tremor, and (h) somnolence (Mathew, 2001). Increased appetite and weight gain were reported in the majority of the studies (Jensen et al., 1994).

Topiramate. Topiramate has shown significant promise in early clinical trials for the prophylactic treatment of migraine, as well as chronic migraine, daily headache, and chronic cluster headache (Freitag, 2001). Mean dose was 125 mg/day with a range of 25-200 mg/day. The mean dose in another study was 100 mg per day with a range of 25 mg to 500 mg per day; the 500 mg per day was for one patient with a comorbid seizure condition using topiramate for both disease processes (Von Seggern et al., 2002). There were substantial benefits to topiramate in prophylaxis of migraine, especially for those with moderate or severe migraines who did not respond well to other treatment options (Von Seggern et al., 2002). Topiramate reduced the incidence of migraine, but it had no effect on the severity of the migraines that occurred (Storey et al., 2001). Mathew, Kailsam, and Meadors found in 2002 that starting patients on 25 mg per day of topiramate and titrating up by 25 mg per week, based on their headache profile and headache diary, worked well to manage side effects and decrease the overall incidence of migraines. They ended with the average topiramate dose as 87.5 mg per day and a range of 25-300 mg per day.
Few side effects were reported with topiramate (Storey et al., 2001). Side effects were related to CNS effects, such as (a) overall changes in concentration, (b) language/speech problems, (c) psychomotor slowing, (d) memory impairment, (e) somnolence, and (f) fatigue. Extremity paresthesias were also common and may be dose related (Storey et al., 2001). However, the most noted side effects were decreased appetite and otherwise unspecified weight loss (Mathew, Hulihan et al., 2003).

The main point to note with both medications is to start at the lowest possible dose and make changes based solely on patient tolerance and need, per headache profile. It is also important to continue to have consistent follow-up with patients in order to monitor their tolerance to the medication and the effectiveness of the prophylactic treatment. Side effects can be the main reason patients stop prophylactic treatment, so those should be discussed prior to the initiation of any new medication regimen. Weight loss can occur with topiramate, and weight gain can occur with divalproex sodium; this is a noted difference and an important one. As with any medication regimen, compliance can be an issue. Therefore, the patient must recognize that the treatment plan is not abortive therapy; it is therapy to prevent migraines from beginning. The patient must be willing to take part in a daily process of taking medication to improve his or her overall life in dealing with migraines.

SUMMARY

A teaching module was developed for PCPs in order to increase their knowledge about and understanding of migraines. The module may also increase the use of prophylactic medication prescriptions written by these PCPs and, therefore, improve patient outcomes. In order to monitor the effectiveness of the educational module, a
pretest and posttest were administered, and these tests were scored to determine learning immediately after the educational tool was implemented. Ideally, PCPs would be evaluated as described six months after the module was given to identify any further educational needs and any change in their practice. The module was designed for all PCPs since migraine management is increasingly becoming a primary care disease, not one to be readily referred to neurologists or other specialists.
CHAPTER 4

INTRODUCTION

The purpose of this chapter is to discuss the educational module in terms of its benefits and limitations for teaching health care providers in need of the knowledge it presented. The primary thrust of the module was to introduce the idea of using anticonvulsants for migraine prophylaxis. After considering the strengths and limitations of the project, suggestions for future educational projects will be highlighted. The long-term goal is to educate primary health care providers on the pathophysiology of migraines and the use of anticonvulsant medication for migraine prophylaxis.

BENEFITS OF THE EDUCATIONAL MODULE

This educational module was based upon state-of-the-art medical management gleaned from the research-based literature. This is a strength. Often, management decisions are based upon tradition rather than being evidence-based. The module developed here included careful consideration of data about migraine prophylaxis. This is a strong benefit, as PCPs are often too busy to peruse the latest research findings for use in practice. They most often rely upon periodic updates at conferences which are broad spectrum and may not include specific updates on practice guidelines or pharmaceutics for prophylaxis of migraine.

Another benefit of this educational module is that it can teach a large group of PCPs in a short amount of time and give them a take-away handout on migraine and migraine prophylactic medications. The educational module includes a brief review of the pathophysiology of migraine and the treatment options, but mainly, it identifies those patients ideally suited for prophylactic migraine treatment. This handout is a reference
tool to which the PCP can refer while in consultation with patients. The handout also has a reference section that can enrich knowledge for the interested practitioner. It has the ability to reach a large number of PCPs in the area and, because of the short-term nature of the educational module, keep the interest of the PCPs as they learn. The module can be administered during a lunch meeting or other short session, so that busy professionals can have access to knowledge within the context of their hectic schedules.

LIMITATIONS OF THE EDUCATIONAL MODULE

One limitation of the educational module is that, unless it becomes more widely disseminated, only those within my geographic area can have access to it. However, this limitation could be reduced by publishing the module in a clinical journal. Then, all interested professionals could access the information. Furthermore, professional journals offer continuing education opportunities, and this educational module could be utilized in this manner.

Another limitation is that only two anticonvulsants for use in migraine prophylaxis were reviewed and outlined. There are multiple other anticonvulsants and even multiple other drug classes available for migraine prophylaxis. The abortive medication section is limited in that the types of medications used are not outlined; however, abortive treatment remains the mainstay of migraine treatment. As more educational modules are developed, these and other classes of drugs can be included.

FUTURE RESEARCH AND PROJECT SUGGESTIONS

Future educational modules for clinicians are essential, as new information about migraine prevention, prophylaxis, and treatment are illuminated. This process suggests constant review and outline of other anticonvulsants and other medications with potential
for migraine prophylaxis. Since the field is constantly changing, each medication must be detailed regarding use, dosage, side effect profile, and other diagnostics that may need to be monitored. Research is needed on patient education and outcome that measures their understanding and ability to manage their own symptomatology. Patients must be coached to enable them to recognize onset, then institute management strategies early on with the most effective drug, thereby maximizing the chance for quick resolution (Diamond & Wenzel, 2002). It is hypothesized that related research could establish patient-centered outcomes and patient participation in treatment plans thus decreasing pain and disability.

Future research also needs to assist the PCP in defining the migraine patient and developing an exact headache diary outline for patients to follow during the beginning of their care for medication management. Research must find the true pathophysiology of migraine in order to understand the causes and direct treatment. Migraine must also be distinguished from other types of headaches, if in fact there are other types of headaches. Obviously, research must continue on specific medications for abortive treatment, such as triptans, and for prophylactic treatment. Neurology in general is still a very open field in terms of the migraine research arena and will continue to be so as more medications, diagnostics, and outcomes are studied.

CONCLUSION

This clinical project holds potential for expanding the knowledge of PCPs concerning migraine management, particularly the use of two specific anticonvulsants for migraine prophylaxis. The strengths are that the educational module was developed from the evidence-based literature, and it was approached from a theoretical framework that
embraces health promotion. This is a proactive approach to migraine management. The module can be accessed by PCPs in a group setting; it takes little time to present; and it measures immediate knowledge acquisition. Since migraine is a significant health problem for millions of individuals, new knowledge acquisition by PCPs is a logical way to reduce impact on the health care delivery system. More educational modules of this type are essential for PCPs to impart increased knowledge to their patients, which is a first step toward better migraine management. Better migraine management is highly likely to decrease the burden on the health care delivery system.

This project was only the first part in a series of educational projects needed to outline the use of a variety of medications for prophylactic treatment of migraine. This project has the potential for immeasurable impact in the area of primary care for the patients of nurse practitioners (NPs). This will enable NPs to better understand the role anticonvulsants play in migraine prophylaxis and allow the NP more choices in the treatment plan. The two anticonvulsants discussed, divalproex sodium and topiramate, both have minimal side effects and are considered very effective in reducing the number of migraines. More research may still be necessary to compare all the anticonvulsant medications available as migraine prophylaxis, and even more studies are needed on the comparison of all migraine prophylactic-type medications in general, even though they work in different mechanisms. A study could be conducted to evaluate the efficacy and safety profile comparison between the types. As future research is completed, anticonvulsants may become the main prophylactic used in migraine treatment, especially as more is learned about the relationship between the brain’s neurotransmitters and migraine, similar to epilepsy. The theory of epilepsy and migraine being related is
currently in the hypothesis stage; however, this theory could prove true, which would completely change the use of anticonvulsants in the treatment of migraines.

The secondary research completed could be used to develop an algorithm or treatment protocol for using anticonvulsant medication in women with migraine symptoms without any comorbid conditions per the U.S. Headache Consortium guidelines; or if the stratified approach to migraine is adopted by PCPs, this type of research may be crucial in proving the prophylactic treatment component in migraine management and adding that arm to the treatment design in the stratified approach outlined by Roger and Dodick in 2002. This is especially essential as migraines are increasingly being managed in the primary care setting and less by neurologists.

As discussed, migraines are often underdiagnosed and undertreated; the short-term goal would be to increase the clinician’s understanding of migraine. By increasing the NP’s understanding of migraine and the process of diagnosing migraine, he or she may feel more comfortable making that diagnosis and not refer those patients to specialists. The long-term goal would be to change the prescribing practices or at least open the minds of PCPs in southern Arizona to prophylactic migraine treatment, mainly anticonvulsants. It would include helping them understand the role of anticonvulsants in prophylactic treatment of migraine, which patients should receive this therapy option, and how to use the medication appropriately. Ideally, anticonvulsants would become one of the first medication options in the prophylactic treatment plan.
APPENDIX

PROPHYLACTIC MIGRAINE TREATMENT

WITH ANTICONVULSANTS PAMPHLET
REFERENCES


MEDICATIONS

DIVALPROEX SODIUM

Uses: Migraine; daily headache.

Doses: Mean 1000 mg/day.

Start at 250 mg BID and titrate to range of 1000-2000 mg/day on TID schedule.

Failure: No improvement at 3000 mg/day.*
*Takes 3 months for efficacy to begin.

Labs: Check baseline CBC and LFTs after one week, after four weeks, and again every six months.

Side Effects: Asthenia, generalized pain (including back pain), dyspepsia, diarrhea, nausea, tremor, somnolence, rare infection, increased appetite, and weight gain.

TOPIRAMATE

Uses: Migraine; daily headache; chronic cluster headache.

Doses: Mean dose is 125 mg/day.

If patient has comorbid seizure condition, range can increase to 500 mg/day.

Start at 25 mg/day and titrate up; once past 100 mg/day, divide into BID doses with a range of 25 to 300 mg/day on BID schedule.

Failure: No improvement at 300 mg/day.*
*Faster onset of efficacy than divalproex sodium.

Labs: Some PCPS check baseline renal function; otherwise none required.

Side Effects: Change in concentration, language/speech problems, psychomotor slowing, fatigue, somnolence, extremity paresthesias, decreased appetite, and weight loss.

REFERENCES
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PROPHYLACTIC MIGRAINE TREATMENT WITH ANTIConvULSANTS

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**INTRODUCTION TO MIGRAINE**

**PATHOPHYSIOLOGY**

Migraine is caused by a variety of factors, which are still being researched; some of the theories include:

- Dilatation of vessels causing increased blood flow which overactivates the ganglionic neurons causing pain.
- Neurogenic inflammation of the meninges which relates to the trigemino-cervical complex and serotonin activation/uptake. Serotonin is involved with vasoconstriction.
- Hyperexcitability of the CNS due to low levels of GABA and poor sensory input modulation.

**EPIDEMIOLOGY**

Migraines are suffered by:

- 28 million Americans
- 12.6% of the U.S. population
- 18% of the women in the U.S.

**DIAGNOSIS OF MIGRAINE**

**IHS CRITERIA**

Diagnosing common migraine without aura is a difficult process. The headache when left untreated could last 4-72 hours and include one or more of the following symptoms:

- Nausea or vomiting,
- Photophobia, and/or
- Phonophobia.

It is also associated with at least two of the following pain characteristics:

- Unilateral location,
- Throbbing quality,
- Moderate to severe intensity, and/or
- Aggravation by routine activity.

**COMMON RED FLAGS**

- A new onset of headaches after age 40,
- A new headache type or new type of pain,
- A change in headache intensity or frequency,
- A headache that interrupts sleep,
- A headache initiated with Valsalva maneuver, and/or
- A headache with neuro changes.

**PROPHYLACTIC TREATMENT**

**PATIENT PROFILE**

Treatment should be considered when:

- A patient has two or more migraines per month, especially those producing significant disability, lasting 2-3 days;
- There is a failure or inability to tolerate abortive treatment;
- There is a rising pattern of headaches of more than two per week, especially if there is increasing dependence on abortive treatment which can lead to rebound headache;
- There are special circumstances related to comorbid conditions or other neurologic concerns; or
- The patient prefers this treatment regimen.

**GOALS OF PROPHYLACTIC TREATMENT**

- Decrease attack frequency, severity, and duration;
- Improve responsiveness to treatment of acute attacks; and/or
- Improve function and reduce disability.
- Overall success is defined as a reduction in migraine frequency by 50%.