Management and Treatment of Migraine with the Available Market Preparations of Bangladesh

A Research paper submitted to the
Department of Pharmacy, East West University
in conformity with the requirements for
the degree of Bachelor of Pharmacy

Submitted by:
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June 1, 2011

This Research paper is dedicated to my

Parents

Management and Treatment of Migraine with the Available Market Preparations of Bangladesh

Certificate

This is to certify that the research work on **"Management and Treatment of Migraine with the Available Market Preparations of Bangladesh "** submitted to the Department of Pharmacy, East West University, Mohakhali C/A Dhaka-1212, in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (B.Pharm) was carried out by Md. Anisur Rahman (ID: 2006-2-70-108) under our guidance and supervision and that no part of the thesis has been submitted for any other degree. We further certify that all the sources of information and facilities availed of this connection are duly acknowledged.

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Sufia Islam 30.06.09

Dr. Sufia Islam, Ph.D.

Chairperson

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Aim of the Study:

The objective of this study are-

- Investigate the different types of migraine those are present in Bangladesh.
- Observe the most common form of migraine in Bangladesh.
- Analyze the management option of migraine.
- Which types of migraine are treated by particular Antihistamine.
- Whether the use of Antihistamine is rational.
- Except the Antihistamine other treatment option of migraine.
- The prevalence of migraine in Bangladesh.

Abstract

"Migraine is a familial disorder characterized by recurrent attacks of headache widely variable in intensity, frequency and duration. Attacks are commonly unilateral and are usually associated with anorexia, nausea and vomiting".A subtype of vascular headaches characterized by periodic unilateral pulsatile headaches which begin in childhood, adolescence, or early adult life and recur with diminishing frequency during advancing years. The two major subtypes are classic migraine (i.e., migraine with aura) and common migraine (i.e., migraine without aura). Migrainous episodes may be associated with alterations in cerebral blood flow. Migraine is most likely a heterogeneous disorder and has trigger factors and multiple physiologic causes like fatigue or emotional stress, Secondary to brain dysfunction, Specific foods or alcohol etc. Symptoms of migraines are the result of a constriction and dilation or widening of arteries in the brain. This process results in the classic symptoms of migraine, which include a severe, throbbing persistent headache that increases in intensity. The first step in getting correct treatment is to get a correct diagnosis. Differential diagnosis of migraine may include medical history, headache diary, migraine triggers, investigations (only to exclude secondary causes), EEG, CT Brain etc. Advances in our understanding of the pathophysiology of migraine have resulted in important breakthroughs in treatment. For example, understanding of the role of serotonin in the cerebrovascular circulation has led to the development of triptans for the acute relief of migraine headaches, and the identification of cortical spreading depression as an early central event associated with migraine has brought renewed interest in antiepileptic drugs for migraine prophylaxis. However, migraine still remains

inadequately treated. Indeed, it is apparent that migraine is not a single disease but rather a syndrome that can manifest itself in a variety of pathological conditions. The consequences of this may be that treatment needs to be matched to particular patients. The management approach of migraine is to reducing the attack frequency and severity, avoiding escalation of headache medication, educating and enabling the patient to manage the disorder, improving the patient's quality of life. Clinical research needs to be devoted to identifying which sort of patients benefit best from which treatments, particularly in the field of prophylaxis. We propose four patterns of precipitating factors (adrenergic, serotoninergic, menstrual, and muscular) which may be used to structure migraine prophylaxis. Finally, little is known about long-term outcome in treated migraine. It is possible that appropriate early prophylaxis may modify the long-term course of the disease and avoid late complications.

Keywords : Migraine,Subtypes,Causes,Symptoms,Diagnosis,Prophylaxis,Treatment, Management, etc.

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Chapter One

1. Introduction:

According to the 'World Federation of Neurology'- "Migraine is a familial disorder characterized by recurrent attacks of headache widely variable in intensity, frequency and duration. Attacks are commonly unilateral and are usually associated with anorexia, nausea and vomiting". The pain of a migraine headache is often described as an intense pulsing or throbbing pain in one area of the head. It is often accompanied by extreme sensitivity to light and sound, nausea, and vomiting. Migraine is three times more common in women than in men. Some individuals can predict the onset of a migraine because it is preceded by an "aura," visual disturbances that appear as flashing lights, zig-zag lines or a temporary loss of vision. People with migraine tend to have recurring attacks triggered by a lack of food or sleep, exposure to light, or hormonal irregularities (only in women). Anxiety, stress, or relaxation after stress can also be triggers. Fo33r many years, scientists believed that migraines were linked to the dilation and constriction of blood vessels in the head. Investigators now believe that migraine is caused by inherited abnormalities in genes that control the activities of certain cell populations in the brain. There are two ways to approach the treatment of migraine headache with drugs: prevent the attacks, or relieve the symptoms during the attacks. Many people with migraine use both approaches by taking medications originally developed for epilepsy and depression to prevent future attacks, and treating attacks when they happen with drugs called triptans that relieve pain and restore function. Stress management strategies, such as exercise, relaxation, biofeedback, and other therapies designed to help limit discomfort, may also reduce the occurrence and severity of migraine attacks.

1.1 A Brief History Of Migraines:

Migraines were described in detail in Babylonian writings dating back to 3000 BC, and papyrus scrolls dated from around 1550 BC that were found buried alongside a mummy in Thebes contain even more detailed accounts that are remarkably similar to what modern migraine sufferers describe. Even the Father of Medicine himself. Hippocrates, described what are clearly migraines in 460 BC, when he described a shining light that was typically seen in one eye and followed by severe pain that started in temples and worked its way to encompass the rest of the head and down into the neck. Hippocrates was also well ahead of his time by being the first to correlate head pain with exercise and seven sexual intercourse. Of course, Hippocrates also attributed migraines to vapors making their way up to the head from stomach and thought that the headache pain could be relieved by throwing up.

The Ebers Papyrus, named after George Ebers who obtained it, dates back to at least 1200 BC is an encyclopedic compilation of various prescriptions and medical treatments, including one for shooting pains in the head consistent with modern day migraine headaches. According to the instructions on the papyrus, Egyptians were to use a strip of linen to tie a clay crocodile holding grain in its mouth to the head of the patient. On the linen were written the names of those gods that the Egyptians believed could cure their ailments. As in so many things, the Egyptians may have been preternaturally aware of modern techniques because it is believed that this procedure could possibly have brought relief to the headache sufferer by compressing the scalp and collapsing the blood vessels that were causing the pain.

At the very least it made more sense than the previous Egyptian cure for head pain, which was to simply rub a fried fish on afflicted side of the head.

Plato is considered one of the all-time great thinkers the world has ever produced, up there in the pantheon of great philosophers. And yet he seems to have been so wrong about so many things, including migraines. As far as Plato was concerned, head pain was caused by people paying too much attention to the body. In fact, Plato seems to be in that camp that thinks migraine sufferers are a bunch of whiners and that it's all in their heads, but not in their expanding and constricting blood vessels. It may be time to start second-guessing this whole idea of Plato being really, really smart.

Hua T'o was a Chinese surgeon in the second century who is given credit for the invention of anaesthetic drugs among other things. He was also perhaps the first to take to acupuncture needles to cure migraines. In one particularly infamous and, hopefully, quite rare case, when Hua used a needle to carve a tumor out of patient suffering from pain between his eyes a canary flew out. The man not only lived, but was cured of his pain.

Hildegard of Bingen was a medieval nun and mystic who began experiencing visions at an early age. Her visions eventually led her to write several books on health and medicine and natural remedies. Both her written accounts and the illustrations she drew that reflected her visions have led the belief that those visions may have been the result of migraine auras. Her visions were detailed and vivid, as were her descriptions and she has built a significant following who consider her to be the first migraine-inspired artist. The typical treatment of migraines during Hildegard's time during the

Middle Ages basically consisted of opium and vinegar solutions applied to the skull, with the vinegar thought to have been used to open the pores of the scalp so that the opium would be more quickly absorbed. Centuries, if not millennia, from now people may be reading a history of migraine treatment and shake their head when they reach the 21st century.[1]

1.2 Theory Behind Migraine Emerges:

Cortical Spreading Depression (Depolarization Theory):

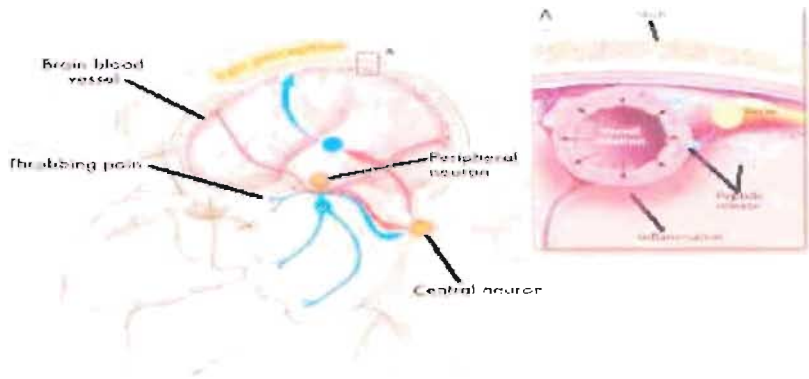

Figure: Cortical Spreading Depression.

One of proponents of the new theory is Richard Kraig, a migraine researcher at the University of Chicago. Kraig argues that a seizurelike phenomenon in the brain known as cortical spreading depression (CSD) is the underlying cause of both migraine auras and migraine pain. CSD, explains Kraig, "is a spreading wave of electrical silence in which cortical neurons go quiet. There's no firing at all." First described in 1944 in the brain of a rabbit, CSD only recently has begun to yield up its secrets. In a 2005 study, Kraig and his colleagues found that CSD can be triggered when the normal flow of electric currents within and around brain cells is somehow reversed.

If a sufficiently large group of cells is affected all at once, the reversal may spread outward through the cortex—"like a ripple on a pond," says Kraig—with a flurry of abnormal brain-cell activity at the wavefront and temporarily exhausted, electrically "depolarized" cells in its wake. CSD frequently begins in the visual or somatosensory cortex, which explains why the aura is commonly experienced visually or as a tactile tingling.

"The scintillating lights you often see in the leading edge are likely to be from that flurry of neural activity" at the CSD wavefront," Kraig says. Direct study of CSD in humans has been rare. "It has been difficult to find somebody who can reliably evoke their migraine aura," explains Michael Moskowitz, a migraine researcher at Harvard. But in 2001 Moskowitz and his colleagues reported finding one such subject, an engineer who was able to trigger his auras by playing 80 minutes of basketball beforehand. Moskowitz's team used functional MRI to track cortical spreading depression in this subject and two others, definitively showing the link between CSD and auras. Only 20 to 30 percent of migraine sufferers report auras. But Moskowitz suspects that CSD can cause migraines without the sufferer noticing an aura or connecting it to the headache. Moskowitz cites 1994 research in which researchers at UCLA studied a young woman who developed a migraine-like headache while she lay in a positron emission tomography (PET) scanner for an unrelated project. "She didn't really describe any aura or other aura-like symptoms," Moskowitz relates. "But when they looked at the blood flow measurements they saw a phenomenon that resembled cortical spreading depression."

1.3 How Can CSD Cause Pain?

The sensory disturbances of the aura are not painful; the pain typically comes minutes to hours later. But Moskowitz and Kraig reported in 1993 that when CSD was evoked in the brain of a rat, it caused the activation of the pain-transmitting "trigeminal" nerve system in the meninges, the sensitive membranes that cover the brain. Kraig and Moskowitz believe that when neurons and other cells experience the electrical surge of the passing CSD wavefront, they abnormally spurt nerve-irritating chemicals into the brain. "Neurotransmitters and potassium and hydrogen ions and all sorts of bad actors get released into the extracellular space," says Moskowitz, "and we think they accumulate at the surface where the meningeal tissues lie and the trigeminal nerve endings travel." Moskowitz points out another link between CSD and migraine pain, reported in a study conducted by his lab in 2006: "We found out that if you chronically administer to experimental animals the most commonly used migraine prophylactic drugs, you can significantly raise the threshold for evoking cortical spreading depression."

At the same time, he notes, "when mutated genes that have been identified in certain families with migraine are 'knocked in' to a mouse model, the mouse is pretty normal except it has a much higher susceptibility for evoking cortical spreading depression." The idea that CSD is the ultimate cause of migraine is still controversial. Some researchers argue that migraine pain can be caused instead by abnormal functioning of pain-processing neurons in the brain stem. Others suggest a blend of both concepts. "I think that CSD is one part of it, and I think that brain stem modulation is another," says Stephen Silberstein, a professor of neurology at Jefferson University in

Philadelphia and an author of several textbooks on migraines. "But I do believe with Dr. Moskowitz that cortical spreading depression is a big part of the picture. And I think his work is very elegant, clearly showing the link between the aura of migraine and the headache." .[2]

1.4 Various Theories for causes of Migraine:

1.5 Vascular theory:

Migraines can begin when blood vessels in the brain contract and expand inappropriately. This may start in the occipital lobe, in the back of the brain, as arteries spasm. The reduced flow of blood from the occipital lobe triggers the aura that some individuals who have migraines experience because the visual cortex is in the occipital area. When the constriction stops and the blood vessels dilate, they become too wide. The once solid walls of the blood vessels become permeable and some fluid leaks out. This leakage is recognized by pain receptors in the blood vessels of surrounding tissue. In response, the body supplies the area with chemicals which cause inflammation. With each heart beat, blood passes through this sensitive area causing a throb of pain. The vascular theory of migraines is now seen as secondary to brain dysfunction. .[3]

1.6 Serotonin theory:

Serotonin is a type of neurotransmitter, or "communication chemical" which passes messages between nerve cells. It helps to control mood, pain sensation, sexual behaviour, sleep, as well as dilation and constriction of the blood vessels among other things. Low serotonin levels in the brain may lead to a process of constriction and dilation of the blood vessels which trigger a migraine. Triptans activate serotonin receptors to stop a migraine attack.

A role for serotonin in migraine has been supported by changes in circulating levels of serotonin and its metabolites during the phases of a migraine attack, along with the ability of serotonin-releasing agents to induce migraine-like symptoms. The development of serotonin receptor agonists with efficacy in the clinic for the alleviation of migraine pain further implicates serotonin as a key molecule in migraine. Several theories regarding the etiology of migraine have been proposed. The vasodilatory theory of migraine suggested that extracranial arterial dilation during an attack was related to migraine pain; a theory supported when vasoconstrictors such as sumatriptan alleviated migraine pain. The neurological theory of migraine proposed that migraine resulted from abnormal firing in brain neurons. Cortical spreading depression, one facet of the neurological theory, could explain the prodrome of migraine. The neurogenic dural inflammation theory of migraine supposed that the dural membrane surrounding the brain became inflamed and hypersensitive due to release of neuropeptides from primary sensory nerve terminals. Substance P, calcitonin gene related peptide and nitric oxide are all though to play a role in the

dural inflammatory cascade. Animal models of migraine have been utilized to study the physiology of migraine and develop new pharmaceutical therapies. One model measures the shunting of blood to arteriovenous anastomoses based on a proposal that migraine primarily involves cranial arteriovenous vasodilation. Another model utilizes electrical stimulation of the trigeminal ganglion to induce neurogenic dural inflammation quantified by the resulting extravasation of proteins. Pharmacological agents such as meta-chlorophenylpiperazine (mCPP) and nitroglycerin have also been used to induce dural extravasation in animals. Both compounds also induce migraine attacks in individuals with a history of migraine. In addition, Fos, a protein produced by activation of the c-fos gene, has been measured as an index of migraine-like pain transmission to the CNS following chemical or electrical stimulation of the trigeminal nerve. A role for serotonin in migraine is further supported by the efficacy of serotonin receptor ligands. Sumatriptan is an agonist at 5-HT1D and 5-HT1B receptor subtypes, and effective in treating migraine pain and associated symptoms. Recently, selective 5-HT1F agonists have been proposed for the treatment of migraine, without the side effects associated with the present 5-HT1D and 5-HT1B receptor agonists. A role for 5-HT2B receptors has also been suggested the initiation of migraine, supporting use of selective 5-HT2B receptor antagonists in migraine. Thus, agents that modulate 5-HT1B, 5-HT1D, 5-HT1F and 5-HT2B receptors either have or may have clinical utility in the therapy of migraine headache.[4]

1.7 Neural theory:

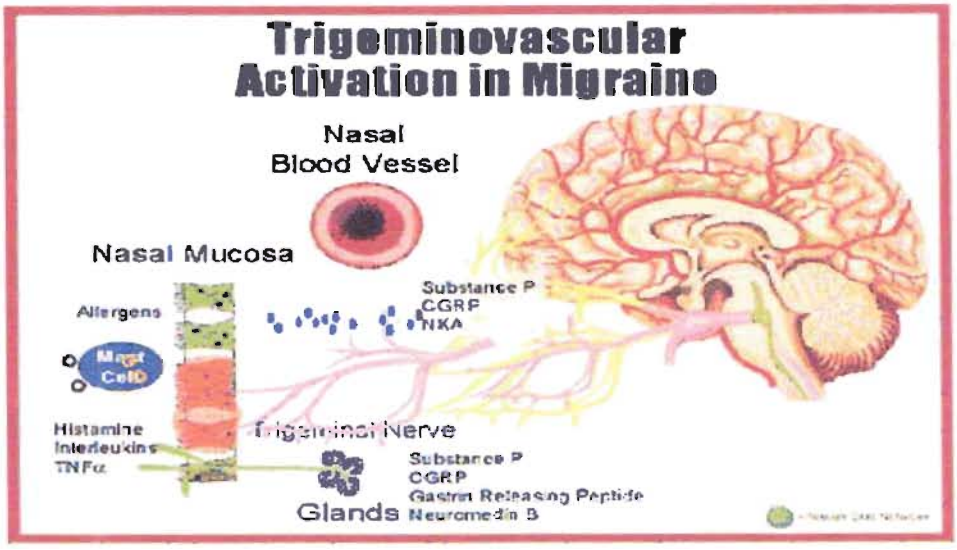

Figure: The Trigeminovascular System.

When certain nerves or an area in the brain stem become irritated, a migraine begins. In response to the irritation, the body releases chemicals which cause inflammation of the blood vessels. These chemicals cause further irritation of the nerves and blood vessels and results in pain. Substance P is one of the substances released with first irritation. Pain then increases because substance P aids in sending pain signals to the brain.[5]

1.8 The Integrated Hypothesis:

According to this theory, triggers such as stress, glare, noise, the patient's internal clock, the dilation of the internal or external carotid arteries, or other factors may activate specific centers in the brain stem. One such center, the locus ceruleus, causes changes in epinephrine levels. Another center, the dorsal raphe nucleus, affects

serotonin levels in the brain. Constriction of cerebral blood vessels may cause a localized deficiency in blood flow, provoking CSD, which may, in turn, stimulate trigeminovascular fibers, eliciting neurogenic inflammation and headache pain. Nerve fibers from the locus ceruleus, the dorsal raphe nucleus, and the trigeminal nerve cause a stimulation of cranial nerves that dilate both cerebral and extracranial blood vessels. The dilation of meningeal vessels contributes to pain generation. The locus ceruleus also sends fibers to higher centers of the cerebral cortex, where it influences a person's state of arousal and awareness, and descending projections interact with the body's pain control mechanisms. Likewise, the dorsal raphe nucleus sends multiple fibers to blood vessels and upward toward the cerebral cortex. These serotonin-secreting fibers help regulate sleep and neuroendocrine functions.

Other connections are made with lower brain stem areas and with the hypothalamus. A disruption in the normal function of the hypothalamus may be responsible for prodromal signs and symptoms of migraine such as mood changes, food cravings, drowsiness, thirst, and yawning. These signs and symptoms may occur several hours, or even as long as 1 day, before headache pain begins.[6]

1.9 Different phases of migraine:

The signs and symptoms of migraine vary among patients. Therefore, what a patient experiences before, during and after an attack cannot be defined exactly. The five phases of a migraine attack listed below are common but not necessarily experienced by all migraine sufferers. Additionally, the phases experienced and the symptoms experienced during them can vary from one migraine attack to another in the same migraineur:

1. The prodrome, which occurs hours or days before the headache.
2. The aura, which immediately precedes the headache.
3. The pain phase, also known as headache phase.
4. The postdrome.
5. Termination Phase

1. Prodrome phase:

Prodromal symptoms occur in 40–60% of migraine sufferers. This phase may consist of altered mood, irritability, depression or euphoria, fatigue, yawning, excessive sleepiness, craving for certain food (e.g. chocolate), stiff muscles (e.g. especially in the neck), hot ears, constipation or diarrhea, increased urination, and other visceral symptoms. These symptoms usually precede the headache phase of the migraine attack by several hours or days, and experience teaches the patient or observant family how to detect that a migraine attack is near.[7]

2. Aura phase:

For the 20–30% of migraine sufferers who experience migraine with aura, this aura comprises focal neurological phenomena that precede or accompany the attack. They appear gradually over 5 to 20 minutes and generally last fewer than 60 minutes.[8]

The headache phase of the migraine attack usually begins within 60 minutes of the end of the aura phase, but it is sometimes delayed up to several hours, and it can be missing entirely. Symptoms of migraine aura can be visual, sensory, or motor in nature.[9]

Visual aura is the most common of the neurological events. There is a disturbance of vision consisting usually of unformed flashes of white and/or black or rarely of multicolored lights (photopsia) or formations of dazzling zigzag lines (scintillating scotoma; often arranged like the battlements of a castle, hence the alternative terms "fortification spectra" or "teichopsia").[10]

Some patients complain of blurred or shimmering or cloudy vision, as though they were looking through thick or smoked glass, or, in some cases, tunnel vision and hemianopsia. The somatosensory aura of migraine consists of digitolingual or cheiro-oral paresthesias, a feeling of pins-and-needles experienced in the hand and arm as well as in the nose-mouth area on the same side. Paresthesia migrate up the arm and then extend to involve the face, lips and tongue.

Other symptoms of the aura phase can include auditory, gustatory or olfactory hallucinations, temporary dysphasia, vertigo, tingling or numbness of the face and extremities, and hypersensitivity to touch. Oliver Sacks's book *Migraine* describes "migrainous deliria" as a result of such intense migraine aura that it is indistinguishable from "free-wheeling states of hallucinosis, illusion, or dreaming."

3. Pain phase:

The typical migraine headache is unilateral, throbbing, and moderate to severe and can be aggravated by physical activity. Not all these features are necessary. The pain may be bilateral at the onset or start on one side and become generalized, and usually it alternates sides from one attack to the next. The onset is usually gradual. The pain peaks and then subsides and usually lasts 4 to 72 hours in adults and 1 to 48 hours in children. The frequency of attacks is extremely variable, from a few in a lifetime to several a week, and the average migraineur experiences one to three headaches a month. The head pain varies greatly in intensity.

The pain of migraine is invariably accompanied by other features. Nausea occurs in almost 90 percent of patients, and vomiting occurs in about one third of patients. Many patients experience sensory hyperexcitability manifested by photophobia, phonophobia, and osmophobia and seek a dark and quiet room. Blurred vision, delirium, nasal stuffiness, diarrhea, polyuria, pallor, or sweating may be noted during the headache phase. There may be localized edema of the scalp or face, scalp tenderness, prominence of a vein or artery in the temple, or stiffness and tenderness of the neck. Impairment of concentration and mood are common.

The extremities tend to feel cold and moist. Vertigo may be experienced; a variation of the typical migraine, called vestibular migraine, has also been described. Lightheadedness, rather than true vertigo, and a feeling of faintness may occur.

4. Postdrome phase:

The patient may feel tired or "hungover" and have head pain, cognitive difficulties, gastrointestinal symptoms, mood changes, and weakness. According to one summary, "Some people feel unusually refreshed or euphoric after an attack, whereas others note depression and malaise." .[11]

5. Termination Phase

In this phase, pain relief occurs. The pain gradually decreases in intensity over a period of several hours, leaving most people with fatigue and irritability. In many people, vomiting or falling asleep signals the end of an attack.[12]

1.10 Classification:

The International Headache Society (IHS) Classification of Migraine

1. Migraine

1.1 Migraine without aura

1.2 Migraine with aura

a. Migraine with typical aura

b. Migraine with prolonged aura

c. Familial hemiplegic migraine

d. Basilar migraine

e. Migraine aura without headache

f. Migraine with acute onset aura

1.3 Ophthalmoplegic migraine

1.4 Retinal migraine

1.5 Childhood periodic syndromes that may be precursors to or associated with migraine

a. Benign paroxysmal vertigo of childhood

b. Alternating hemiplegia of childhood

1.6 Complications of migraine

a. Status migrainosus

b. Migrainous infarction

1.7 Migrainous disorder not fulfilling above criteria

2. Tension-type headache

2.1 Episodic tension-type headache

a. Episodic tension-type headache associated with disorder of pericranial muscles

b. Episodic tension-type headache unassociated with disorder of pericranial muscles

2.2 Chronic tension-type headache.

a. Chronic tension-type headache associated with disorder of pericranial muscles

b. Chronic tension-type headache unassociated with disorder of pericranial muscles

2.3 Headache of the tension-type not fulfilling above criteria.

3. Cluster headache and chronic paroxysmal hemicrania.

3.1 Cluster headache.

3.1.1 Cluster headache periodicity undetermined.

3.1.2 Episodic cluster headache.

3.1.3 Chronic cluster headache.

3.1.3.1 Unremitting from onset.

3.1.3.2 Evolved from episodic.

3.2 Chronic paroxysmal hemicrania.

3.3 Cluster headache like disorder not fulfilling above criteria.

4. Miscellaneous headaches unassociated with structural lesion.

4.1 Idiopathic stabbing headache.

4.2 External compressing headache.

4.3 Cold stimulus headache.

4.3.1 External application of a cold stimulus.

4.3.2 Ingested of a cold stimulus.

4.4 Benign cough headache.

4.5 Benign exertional headache.

4.6 Headache associated with sexual activity.

4.6.1 Dull type.

4.6.2 Explosive type.

4.6.3 Postural type.

5. Headache associated with head trauma.

5.1 Acute post traumatic headache.

5.1.1 With significant head trauma and/or confirmatory signs.

5.1.2 With minor head trauma and no confirmatory signs.

5.2 Chronic post-traumatic headache.

5.2.1 With significant head trauma and/or confirmatory signs.

5.2.2 With minor head trauma and no confirmatory signs.

6. Headache associated with vascular disorders.

6.1 Acute ischemic cerebrovascular diseases.

6.1.1 Transient ischemic attack.

6.1.2 Thromboembolic stroke.

6.2 Intracranial hematoma.

6.2.1 Intracerebral hematoma.

6.2.2 Subdural hematoma.

6.2.3 Epidural hematoma.

6.3 Subarachnoid hemorrhage.

6.4 Unruptured vascular malformation.

6.4.1 Arteriovenous malformation.

6.4.2 Saccular aneurysm.

6.5 Arteries.

6.5.1 Giant cell arteries

6.5.2 Other system arteritides.

6.5.3 Primary intracranial arteries.

6.6 Carotid or vertebral artery pain.

6.6.1 Carotid or vertebral dissection.

6.6.2 Corotidynia (Idiopathic).

6.6.3 Post endarterectomy headache.

6.7 Venous thrombosis.

6.8 Arterial hypertension.

6.8.1 Acute pressor response to exogenous agent.

6.8.2 Pheochromocytoma.

6.8.3 Malignant (accelerated) hypertension.

6.8.4 Pre-eclampsia and eclampsia.

6.9 Headache associated with other vascular disorder.

7. Headache associated with non-vascular intracranial disorder.

7.1 High cerebrospinal fluid pressure.

7.1.1 Benign intracranial hypertension.

7.1.2 High pressure hydrocephalus.

7.2 Low cerebrospinal fluid pressure.

7.2.1 Post-lumber puncture headache.

7.2.2 Cerebrospinal fluid fistula headache.

7.3 Intracranial infection.

7.4 Intracranial sarcoidosis and other non-infectious inflammatory diseases.

7.5 Headache related to intrathecal injection.

7.5.1 Direct effect.

7.5.2 Due to chemical meningitis.

7.6 Intracranial neoplasm.

7.7 Headache associated with other intracranial disorder.

8. Headache associated with substances or their withdrawal.

8.1 Headache induced by acute substance use or exposure.

8.1.1 Nitrate/ Nitrite induced headache.

8.1.2 Monosodium glutamate induced headache.

8.1.3 Carbon monoxide induced headache.

8.1.4 Alcohol induced headache.

8.1.5 Other substances.

8.2 Headache induced by chronic substances use or exposure.

8.2.1 Ergotamine induced headache.

8.2.2 Analgesic abuse headache.

8.2.3 Other substances.

8.3 Headache from substances withdrawal (acute use).

8.3.1 Alcohol withdrawal headache (hangover).

8.3.2 Other substances.

8.4 Headache from substances withdrawal (Chronic use).

8.4.1 Ergotamine withdrawal headache.

8.4.2 Caffeine withdrawal headache.

8.4.3 Narcotics abstinence headache

8.4.4 Other substances.

8.5 Headache associated with substances but with uncertain mechanism.

8.5.1 Birth control pills or estrogens.

8.5.2 Other substances.

9. Headache associated with non-cephalic infection.

9.1 Vital infection

9.1.1 Focal non-cephalic.

9.1.2 Systemic.

9.2 Bacterial infection.

9.2.1 Focal non cephalic.

9.2.2 Systemic (septicemia).

9.3 Headache related to other infection.

10. Headache associated with metabolic disorder.

10.1 Hypoxia

10.1.1 High altitude headache.

10.1.2 Hypoxic headache.

10.1.3 Sleep apnoea headache.

10.2 Hypercapnia.

10.3 Mixed and hypoxia hypercapnia.

10.4 Hypoglycemia.

10.5 Dialysis.

10.6 Headache related to other metabolic abnormalities.

11. Headache or facial pain associated with disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures.

11.1 Cranial bone.

11.2 Neck

11.2.1 Cervical spine.

11.2.2 Retropharyngeal tendinitis.

11.3 Eyes

11.3.1 Acute glaucoma.

11.3.2 Refractive errors.

11.3.3 Heterophoria.

11.4 Ears.

11.5 Nose and sinuses

11.5.1 Acute sinus headache.

11.5.2 Other diseases of nose or sinuses.

11.6 Teeth, Jaws and related structures.

11.7 Temporomandibular joint diseases. .[13]

1.11 Causes of Migraine :

Following is a list of causes or underlying conditions that could possibly cause Migraine includes:

- Genetic causes - autosomal dominance
- Secondary to brain dysfunction
- Depolarization theory
- Vascular theory
- Family history of migraine headaches (70-80%)
- Medications (ie, birth control pills, vasodilators)
- Fatigue or emotional stress
- Specific foods or alcohol
- Exertion
- The exact cause of migraine is unknown. Migraine is most likely a heterogeneous disorder and has trigger factors and multiple physiologic causes
- Birth control pills as well as hormone replacement therapy during menopause
- Allergic tension-fatigue syndrome - migraine
- Antiphospholipid syndrome - migraine
- Aortic dilatation- joint hypermobility- arterial tortuosity - migraine
- Cadasil - migraine
- Centrotemporal epilepsy - migraine
- Chemical allergy - migraine
- Episodic ataxia, type 2 - migraine

- Food Additive Adverse reaction -- amines - migraine
- Food Additive Adverse reaction -- chocolate - migraine
- Food Additive Adverse reaction -- food additives - migraine
- Food Additive Adverse reaction -- salicylate - migraine
- Food Additive Adverse reaction -- sulfite - migraine
- Food Additive Adverse reaction -- sulphite - migraine
- Hereditary paroxysmal cerebral ataxia - migraine
- Hereditary vascular retinopathie -- Raynaud phenomenon -- migraine - migraine
- Idiopathic
- Non-Food Allergy -- Amylcinnamic alcohol - migraine
- Non-Food Allergy -- Anisyl alcohol - migraine
- Non-Food Allergy -- Benzyl alcohol - migraine
- Non-Food Allergy -- Benzyl salicylate - migraine
- Non-Food Allergy -- Cinnamic alcohol - migraine
- Non-Food Allergy -- Cinnamic aldehyde - migraine
- Non-Food Allergy -- Coumarin - migraine
- Non-Food Allergy -- Eugenol - migraine
- Non-Food Allergy -- Geraniol - migraine
- Non-Food Allergy -- Hydroxycitronellal - migraine
- Non-Food Allergy -- Isoeugenol - migraine
- Non-Food Allergy -- Musk ambrette - migraine

- Non-Food Allergy -- Oak moss absolute - migraine
- Non-Food Allergy -- perfume - migraine
- Non-Food Allergy -- Sandalwood oil - migraine
- Non-Food Allergy -- Wood tar - migraine
- Parry Romberg Syndrome - migraine
- Pregnancy - Migraine
- Sensory ataxic neuropathy, dysarthria, and ophthalmoparesis - migraine .[14]

1.12 Symptoms of Migraine:

The list of sign and symptoms are mentioned in the listed below:

- Severe headache - one-sided or both sides of the head
- One-sided headache
- Frontal headache
- Nausea
- Vomiting
- Weakness
- Vision disturbance
- Light sensitivity
- Sound sensitivity
- Throbbing headache
- Pain over one eye
- Sound sensitivity
- Aura - visual, olfactory - announcing the headache
    - Flashing lights
    - Seeing zigzag lines

- Temporary vision loss
- Speech difficulty
- Arm tingling
- Arm weakness
- Leg weakness
- Tingling face
- Tingling hands
- Confusion
- Giddiness
- Noise sensitivity

- Headache is unilateral and pulsating lasting from 4 to 72 hours
- Nausea, vomiting, photophobia
- Hyperacusis
- Seeing flashing lights
- Other visual hallucinations
- Temporary blind spots
- Sensitivity to bright light
- Blurred vision
- Eye pain
- A person who has ophthalmoplegic migraine has specific symptoms involving the eyes. These symptoms may differ from person to person but most likely include the following:
    - Double vision
    - Ptosis
    - Eye paralysis
    - Other types of visual changes
    - Severe headache pain
    - Headache attack is continuous forover 72 hours
    - Patients usually have a preexisting migraine history
    - Severe vomiting, nausea. .[15]

1.13 Risk factors:

Several factors make you more prone to having migraines.

- **Having a family history.** Many people with migraines have a family history of migraine. If one or both of your parents have migraines, there's a good chance you will too.
- **Being younger than 40.** Half the people who suffer from migraines started getting them before they were 20 and migraines are most common in people who are between 30 and 39 years old.
- **Being female.** Women are three times as likely to have migraines as men are. Headaches tend to affect boys more than girls during childhood, but by the time of puberty, more girls are affected.
- **Experiencing hormonal changes.** If you're a woman with migraines, you may find that your headaches begin just before or shortly after onset of menstruation. They may also change during pregnancy or menopause. Some women report that their migraines got worse during the first trimester of a pregnancy. Though for many, the migraines improved during later stages in the pregnancy.

Complications:

Sometimes your efforts to control your pain cause problems.

- **Abdominal problems.** Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen (Advil, Motrin, others) and aspirin, may cause abdominal pain, bleeding and ulcers — especially if taken in large doses or for a long period of time.

- **Rebound headaches.** In addition, if you take over-the-counter or prescription headache medications more than nine days per month or in high doses, you may be setting yourself up for a serious complication known as rebound headaches. Rebound headaches occur when medications not only stop relieving pain, but actually begin to cause headaches. You then use more pain medication, which traps you in a vicious cycle.

- **Serotonin syndrome.** This potentially life-threatening drug interaction can occur if you take migraine medicines called triptans, such as sumatriptan (Imitrex) or zolmitriptan (Zomig), along with antidepressants known as selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs). Some common SSRIs include Zoloft, Prozac and Paxil. SNRIs include Cymbalta and Effexor. Fortunately, serotonin syndrome is rare.

1.14 Tests and diagnosis

If you have typical migraines or a family history of migraines, your doctor will likely diagnose the condition on the basis of your medical history and a physical exam. But if your headaches are unusual, severe or sudden, your doctor may recommend a variety of tests to rule out other possible causes for your pain.

- **Computerized Tomography (CT).** This imaging procedure uses a series of computer-directed X-rays that provides a cross-sectional view of your brain. This helps doctors diagnose tumors, infections and other possible medical problems that may be causing your headaches.
- **Magnetic Resonance Imaging (MRI).** MRIs use radio waves and a powerful magnet to produce very detailed cross-sectional views of your brain. MRI scans help doctors diagnose tumors, strokes, aneurysms, neurological diseases and other brain abnormalities. An MRI can also be used to examine the blood vessels that supply the brain.
- **Spinal Tap (lumbar puncture).** If your doctor suspects an underlying condition, such as meningitis — an inflammation of the membranes (meninges) and cerebrospinal fluid surrounding your brain and spinal cord — he or she may recommend a spinal tap (lumbar puncture). In this procedure, a thin needle is inserted between two vertebrae in your lower back to extract a sample of cerebrospinal fluid (CSF) for laboratory analysis. .[16]

1.15 Treatment of Migraine:

Migraine is a mysterious disorder characterized by pulsating headache, usually restricted to one side, which comes in attacks lasting 4-48 hours and is often associated with nausea, vomiting, sensitivity to light and sound, flash of light, vertigo, loose motions and other symptoms. Two major types are- migraine with aura(classical migraine) in which headache is preceded by visual or other neurological symptoms, migraine without aura(common migraine). Pulsatile dilation of certain large cranial vessels is the immediate cause of pain. The pathogenic mechanisms are not well understood. The vascular theory holds that initial vasoconstriction or shunting of blood through carotid arterio-venous anastomoses produces cerebral ischaemia and starts the attacks.

The neurological theory considers it to be a spreading depressing of cortical electrical activity followed by vascular phenomena. Some triggering events appears to produce neurogenic inflammation of the affected blood vessel wall which is amplified by retrograde transmission in the afferent nerves and release of mediators like 5-HT, neurokinin, substance P, calcitonin gene related peptide(CGRP), nitric oxide, etc.

Changes in blood/urinary levels of 5-HT and its metabolites during migraine attack, its precipitation by 5-HT releasers and efficacy of drugs having actions in the serotonergic system to prevent/abort/terminate migraine attacks suggests a pivotal role of 5-HT in this disorder. Drug therapy of migraine has to be individualized: severity and frequency of attacks and response of individual patients to drugs used earlier determine the choice. The strategy mostly adopted in the following:

Mild Migraine, Cases having fewer than one attack per month of throbbing but tolerable headache lasting upto8 hours which does not incapacitate the individual may be classified as mild migraine.

(i)Simple analgesics, Like paracetamol (0.5-1g) or aspirin (300-600mg) taken at the first indication of an attack and repeated 4-6 hourly abort and suppress most mild attacks.

(ii)Non-steroidal anti-inflammatory drugs (NSAIDs) and their combinations drugs, like ibuprofen (400-800 mg 8 hourly), naproxen (500 mg followed by 250 mg 8 hourly), diclofenac (50 mg 8 hourly), mephenamic acid (500 mg 8 hourly), indomethacin (50 mg 6-8 hourly), either alone or combined with paracetamol/codeine/diazepam or other sedative /diphenhydramine or another antihistamine/caffeine are found more satisfactory by some patients. These drugs are more effective in migraine without aura, but certain patients of migraine with aura also prefer them over ergot alkaloids. Drugs are taken only till the attack passes off. Taken in the prodromal stage they also have a prophylactic effect, but long term treatment on a regular schedule to ward off migraine attacks is not advised.

(iii)Antiemetics, Gastric stasis occurs during migraine which delays absorption of oral drugs. Metoclopramide (10 mg oral/i.m) is frequently used: relieves nausea, vomiting and gastric stasis. Domperidone (10-20 mg oral) and prochlorperazine (10-25 mg oral/i.m) are also effective. Diphenhydramine or promethazine exert sedation as well as antiemetic action.

Moderate Migraine, Migraine may be labeled as moderate when the throbbing headache is more intense, lasts for 6-24 hours nausea/vomiting and other features are more prominent and the patients is functionally impaired. One or more attacks occur per month. Simple analgesic are not more usually effective, but stronger NSAID or their combination mentioned above are beneficial in many cases. The remaining are treated with an ergot preparation or sumatriptan. Antiemetics are almost regularly needed. Prophylactic therapy is advised only when attacks are more frequent than 2-3 per month.

Severe Migraine, These patients suffer 2-3 or more attacks per month of severe throbbing headache lasting 12-48 hours, often accompanied by vertigo, vomiting and other symptoms; the subject is grossly incapacitated during the attack.

Analgesic/NSAID and their combinations usually do not afford adequate relief- specific drugs like ergot alkaloids/sumatriptan have to be prescribed along with antiemetics. Prophylactic regimens lasting 6 months or more are recommended.

Ergotamine, It is the most effective ergot alkaloid for migraine. Give early in attack, relief is often dramatic and lower doses suffice, but when pain has become severe- larger doses is needed and control may be achieved only after few hours. Oral sublingual route is preferred,1 mg is given at half hour intervals till relief is attained or a total of 6 mg is given. Parenteral administration, though rapid in action is more hazardous.

Ergotamine acts by constricting the dilated cranial vessels and/or by specific constriction of carotid A-V shunt channels. Ergotamine and DHE have also been shown to reduce neurogenic inflammation and leakage of plasma in duramater that's occurs due to retrograde stimulation of perivascular afferent nerves. These actions appear to be mediated through partial agonism at 5-HT receptor in and around cranial vessels.

Dihydroergotamine (DHE), It is nearly as effective as ergotamine and preferred for parenteral administration because injected DHE is less hazardous.

Because of erratic oral absorption, frequent side effects, especially nausea and vomiting, and availability of triptans, ergot preparations are not preferred now, except for considerations of cost. Ergot alkaloids have no prophylatic value: regular use is not justified- may itself produce a dull background headache and an attack may be precipitated on discontinuation. Caffeine 100 mg taken with ergotamine enhances its absorption from oral and rectal routes and adds to the cranial vasoconstriction action. Many combination preparations are available.

Migranil, Ergotamine 1 mg, caffeine 100 mg, belladonna dry ext 10 mg, paracetamol 250 mg, tab.

Migril, Ergotamine 2 mg, caffeine 100 mg, cyclizine 50 mg tab.

Vasograin, Ergotamine 1 mg, caffeine 100 mg, paracetamol 250 mg, prochlorperazine 2.5 mg tab.

Ergophen, Ergotamine 0.3 mg, belladonna dry ext 10 mg, phenobarbitone 20 mg tab.

Selective 5-HT agonist:

These are a new class of antimigraine drugs that selectively activated 5-HT receptors, and are called 'triptans'. Currently, they are preferred drugs for patients who fail to respond to analgesics .Ergot alkaloids are now required only in few cases. Because these drugs have been designed to act on the same subtype of 5-HT receptor Pharmacodynamic differences among them are minor, but there are significant pharmacokinetic differences .All have higher oral bioavailability than sumatriptan. Fewer headache recurrences in an attack are reported with naratriptan and frovatriptan due to there longer $t_{1/2}$, but may be slower in affording initial pain relief.

Sumatription, It is the first selective 5-HT receptor agonist ; activates only at very high concentrations, and does not intract with 5-HT2 , 5-HT3 , 5-HT4-7, α or β adrenergic, dopamineragic ,cholinergic or GABA receptors. Administered at the onset of an attack of migraine, sumatripatn is as effective and better tolerated than ergotamine. About ¾ patients obtain complete/significant relief within 2-3 hours. However, recurrence of headache within 24 hours has been noted in 20-40% patients, probably due to short $t_{1/2}$ of sumatriptan. It tends to suppress nausea and vomiting of migraine, while ergotamine accentuates these symptoms.

The anti-migraine activity of sumatriptans has been ascribed to 5-HT receptor mediated constriction of dilated cranial extracerebral blood vessels, especially the arterio-venous shunts in the carotid artery which express 5-HT receptors. Dilation of these shunt vessel during migraine attack is believed to divert blood flow away from brain parenchyma. In addition it can reduce 5-HT and inflammation neuropeptide release around the affected vessels as well as extravasation of plasma proteins across dural vessels. Like ergotamine, the triptans has been found to suppress neurogenic inflammation of cranial vessels. Suppression of impulse transmission in the trigeminovascular syaem has also been implemented.

Prophylaxis of Migraine:

Regular medication to reduce to frequency and/or severity of attacks is recommended for moderate-to severe migraine when 2-3 or more attacks occur per month. Diverse classes of drugs are used but none is effected in all cases, and none abolishes the attacks totally. It may be prudent to discontinue prophylaxis every 6 months to check whether its continuation is need or not. It is important to avoid the precipitating factors.

(i)β-adnergic blockers, Propranolol is the most commonly used drugs; reduces frequency as well as severity of attacks in upto 70% patients. Effect is generally seen in 4 weeks and is sustained during prolonged therapy. The starting dose is 40 mg BD, which may be increased upto 160 mg if required. The mechanism of action is not clear; that it is due to β-adnergic blockade has been questioned. Other nonselective (timolol) and β_1 selective (metoprolol, atenolol) agents are also effective, but pindolol and others having intrinsic sympathomimetic action are not useful.

(ii)Tricyclic antidepressants, Many tricyclic compounds of which amitriptyline has been most extensively tried (25-50 mg at bed time) reduce migraine attacks. It is effective in many patients but produce many side effects than propranolol. It is not known whether its 5-HT and other monoamine uptake blocking property is causally related to the prophylactic effect. The anti-migraine effects is independent of antidepressant property, but this class of drugs are better suited for patients who also suffer from depression

(iii)Calcium channel blockers, Verapamil was found to reduce to migraine attacks, but was judged inferior to propranolol. Flunarizine is a relatively weak Ca^{2+} channel blockers that also inhibit Na+ channels. It is claimed to be as effective as propranolol, but convincing proof is lacking. Frequency of attacks is often reduced, but effort on intensity and duration of attacks is less well documented. It is claimed to be a cerebro-selective Ca^{2+} channel blockers; may benefit migraine by reducing intracellular Ca^{2+} overload due to brain hypoxia and other causes. Side effects are sedation, constipation, dry mouth, gypotension, flushing, weight gain, and rarely extrapyramidal symptoms.

(iv)Anticonvulsants, Valproic acid (400-1200 mg/day) and gabapentin (300-1200 mg/day) have some prophylactic effect in migraine. The newer drug topiramate has recently been approved for migraine prophylaxis. A 50% reduction in the number of attacks in half of the patients was noted in 2 randomized trails. Start with 25 mg OD or BD. Efficacy of anticonvulsants in migraine is lower than that of β blockers. They are indicated in patients refractory to other drugs or when propranolol is contraindicated.

(v)5-HT agonist, The prophylactic effect of methysergide and cyproheptadine is less impressive than β blockers. They are seldom used now for migraine. .[17]

1.16 General Principles of Management

The following consensus-based (not evidence-based) principles of care will enhance the success of preventive treatment. Additional success could be achieved when considering patient preference (formulations, cost, dosing schedules, and tolerability). Consideration of nonpharmacological therapies are reviewed in the Evidenced-Based Guidelines for Migraine

1. Medication use:

A. Initiate therapy with the lowest effective dose. Begin with a low dose of the chosen pharmacological agent and increase the dose slowly until clinical benefits are achieved in the absence of adverse events or until limited by adverse events.

B. Give each treatment an adequate trial. A clinical benefit may take as long as two to three months to manifest itself.

C. Avoid interfering medications (e.g., overuse of certain acute medications such as ergotamine).

D. Use of a long-acting formulation may improve compliance.

2. Patient education:

A. Maximize compliance. Discuss with the patient the rationale for a particular treatment, when and how to use it, and what adverse events are likely.

B. Address patient expectations. Discuss with the patient the expected benefits of therapy and how long it will take to achieve them.

C. Create a formal management plan.

3. Evaluation:

A. Monitor the patients' headaches by having them keep headache diaries. Diaries help to track headache and related symptoms from one clinic visit to another. By consensus, they are considered the "gold standard" in headache attack evaluation. Diaries should be user-friendly and should measure attack frequency, severity, duration, disability, response to type of treatment, and adverse effects of medication.

B. Re-evaluate therapy. After a period of stability, consider tapering or discontinuing treatment.

4. Coexisting (comorbid) conditions:

Some conditions are more common in persons with migraine. Take into account the presence of coexisting diseases. These include stroke, myocardial infarction, Raynaud`s phenomenon, epilepsy, affective disorders, and anxiety disorders. Coexisting diseases present both treatment opportunities and limitations. For example:

A. Once the coexisting condition has been identified, select a pharmacological agent that will treat both disorders.

B. Establish that the coexisting condition is not a contraindication for the selected migraine therapies (e.g., beta-blockers are contraindicated in patients with asthma).

C. Establish that the treatments being used for coexisting conditions do not exacerbate migraine.

D. Beware of interactions between pharmacological agents used for migraine and those used for other conditions.

E. Direct special attention to women who are pregnant or want to become pregnant. Preventive medications may have teratogenic effects. If treatment is absolutely necessary, select a treatment with the lowest risk of adverse effects to the fetus. .[18]

Prevention

Whether or not you take preventive medications, you may benefit from lifestyle changes that can help reduce the number and severity of migraines. One or more of these suggestions may be helpful for you:

- **Avoid triggers.** If certain foods seem to have triggered your headaches in the past, avoid those foods. If certain scents are a problem, try to avoid them. In general, establish a daily routine with regular sleep patterns and regular meals. In addition, try to control stress.

- **Exercise regularly.** Regular aerobic exercise reduces tension and can help prevent migraines. If your doctor agrees, choose any aerobic exercise you enjoy, including walking, swimming and cycling. Warm up slowly, however, because sudden, intense exercise can cause headaches. Obesity is also thought to be a factor in migraines, and regular exercise can help you keep your weight down.

- **Reduce the effects of estrogen.** If you're a woman with migraines and estrogen seems to trigger or make your headaches worse, you may want to avoid or reduce the amount of medications you take that contain estrogen. These medications include birth control pills and hormone replacement therapy. Talk with your doctor about the best alternatives or dosages for you. .[19]

Chapter Two

2. Literature Review

In 2010 famous scientist Contag SA, Bushnell C. has worked on migraine during pregnancy and they have found that beta blocker and calcium channel blocker can prevent migraine during pregnancy .[20]

Oedegaard KJ, Riise T and et.al., in 2010 have worked on the migraine associated with the antidepressants medication. They have found that those prescription contain both medication for migraine and antidepressants give positive and satisfactory result but give risk alertness for teenage girls .[21].

Holroyd KA, Cottrell CK and et.al., in 2010 have worked on the effect of beta blocker in migraine patient. They have found that the patient of frequent migraine is cured when beta blocker is used with other antimigraine medication. But alone beta blocker will not give any positive effects .[22].

In 2010 the most two famous scientist Esposito M, Carotenuto M., Ginkgolide B, have worked on the antimigraine medication on the a herbal constituent extract from Ginkgo biloba tree leaves, was considered as a promising pharmacological aid for the treatment of migraine in adult patients because of its modulation of the glutamatergic transmission in the CNS and on antiplatelet activating factor (PAF) .[23].

In 2010 scientist Weatherall MW, Telzerow AJ and et.al., have worked on the patient of headache with the intravenous acetyl salicylate. It also named as lysine acetyl salicylate. After giving this medication they have found IV aspirin is safe, effective, and useful in the inpatient management of headache .[24].

Flupirtine is a centrally acting, non-opioid analgesic that is available in a number of European countries for the treatment of a variety of pain states. The therapeutic benefits seen with flupirtine relate to its unique pharmacological properties. Flupirtine displays indirect NDMA receptor antagonism via activation of potassium channels and is the first representative of a pharmacological class denoted the 'selective neuronal potassium channel openers'. The generation of the M-current is facilitated by flupirtine via the opening of neuronal Kv7 potassium channels. The opening of these channels inhibits exaggerated neuronal action potential generation and controls neuronal excitability. Neuronal hyperexcitability is a physiological component of many pain states such as chronic pain, migraine and neurogenic pain. Although large-scale clinical trials are lacking, the clinical trial database available to date from smaller-scale studies, together with extensive clinical experience, indicate that flupirtine effectively reduces chronic musculoskeletal pain, migraine and neuralgias, amongst other types of pain .[25].

Chapter Three

3. Methodology:

In this study I am going to concerned Anticholinergic drugs that are prescribed for symptomatic relief of migraine. For doing that I observed some prescriptions of migraine patients.

Place of the study: This study was accomplished among the patients of Physical Medicine Department of Dhaka Medical Hospital. The main reason of choosing Dhaka Medical Hospital is that it is the biggest hospital in the country. Different types of patients from different places of the country come here. Emergency unit of this hospital open all the time. Most of the expertise doctors of the country work here. So patients of different social and economic classes come here. As a result this hospital represents the whole Bangladesh's migraine patient situation.

Survey Duration: The survey was continued for one and half months.

Sample selection criteria: The sample was selected according to indication. Here patients age, gender, social classes were not considered though all the patients that I have got are between 25 to 65 years.

Sample size: 100 patients of migraine were count as sample.

Mode of sample collection: For collecting data I was the outdoor of physical medicine department and was standing here to collect the data. I made questionnaires previously for write down the data. When a patient came from doctor, I saw the prescription and noted down the prescribed Anticholinergic drugs generic name and brand name also in my questionnaire.

Data Interpretation and Result: Microsoft Excel is used to interpret the collected data and made conclusion.

Chapter Four

4. Result & Discussion

Pharma Market of Bangladesh

Pharmaceutical sector is one of the largest sectors of Bangladesh. According to the **IMS 2009/2Q** the size of this sector is BDT 511878, 55,873 with growth rate of 18.22%.

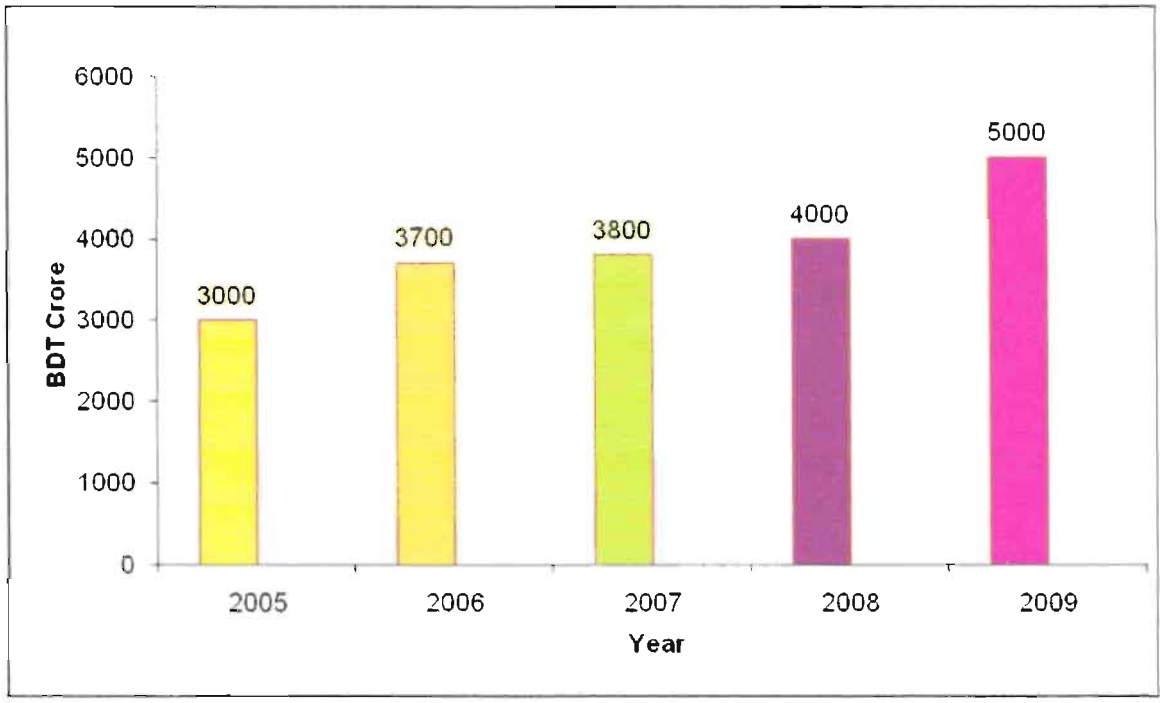

Figure 01: Growth trend of Banglabesh Pharma market from the year 2005 to 2009.

The above graph shows the growth trend of Bangladesh pharmaceutical market from the year 2005 to 2009. The most significant feature is that the market is expanding in every year. So, Bangladesh pharma market is maintaining a upward positive trend.

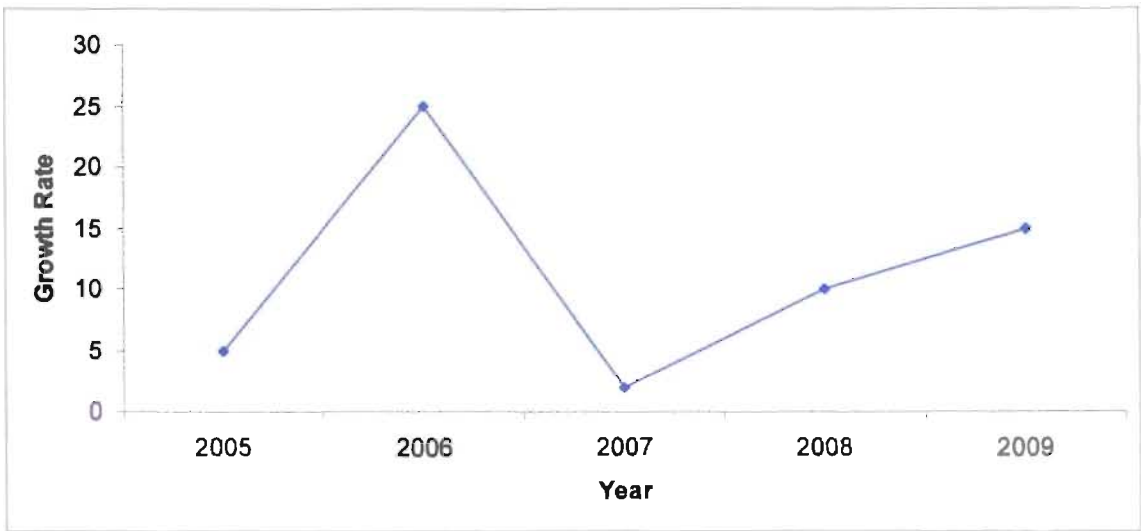

Figure 02: Growth rate of Bangladesh Pharma Market from the year 2005 to 2009.

The above graph shows the growth rate of Bangladesh pharmaceutical market from the year 2005 to 2009. In 2005 the growth rate was 6.18% and in 2009 the rate was 16.91%. In the year 2007 a reduction was occurred.

Market condition of Anticholinergic Drugs

Market scenario of Anticholinergic Drugs in Bangladesh:

The market of Anticholinergic Drugs, in the year 2009, was BDT 21333, 09,753 with growth rate of 17% and sharing 3.89% of total pharmaceutical market.

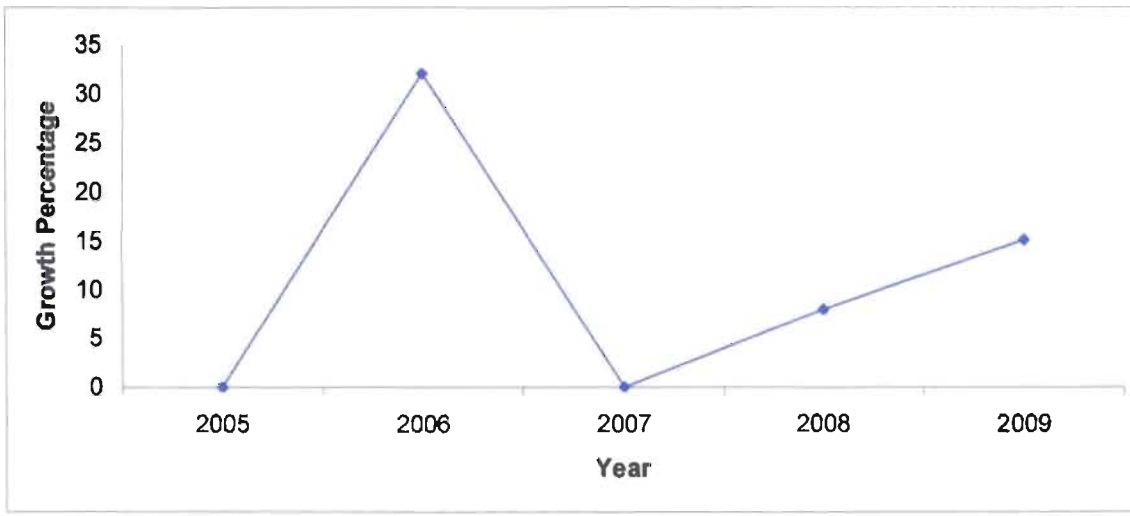

Figure 03: Annual growth rate of Anticholinergic Drugs from year the year 2005 to 2009 **(sources- IMS 2009/2Q)**

The above graph shows the annual growth rate of anticholinergic drugs market in Bangladesh. It is observed that except in 2007, the anticholinergic drugs market has always kept a positive growth. Last year (in 2009) its growth rate was 17%. After a great fluctuation, in last two years the curve of growth rate is showing a good positive trend.

The total market size of anticholinergic drugs in Bangladesh was about 21333, 09,753 BDT in the year 2009. The annual sales of migranil and its competitors in the last year (2009) have shown in figure 04 **(sources- IMS 2009/2Q)**

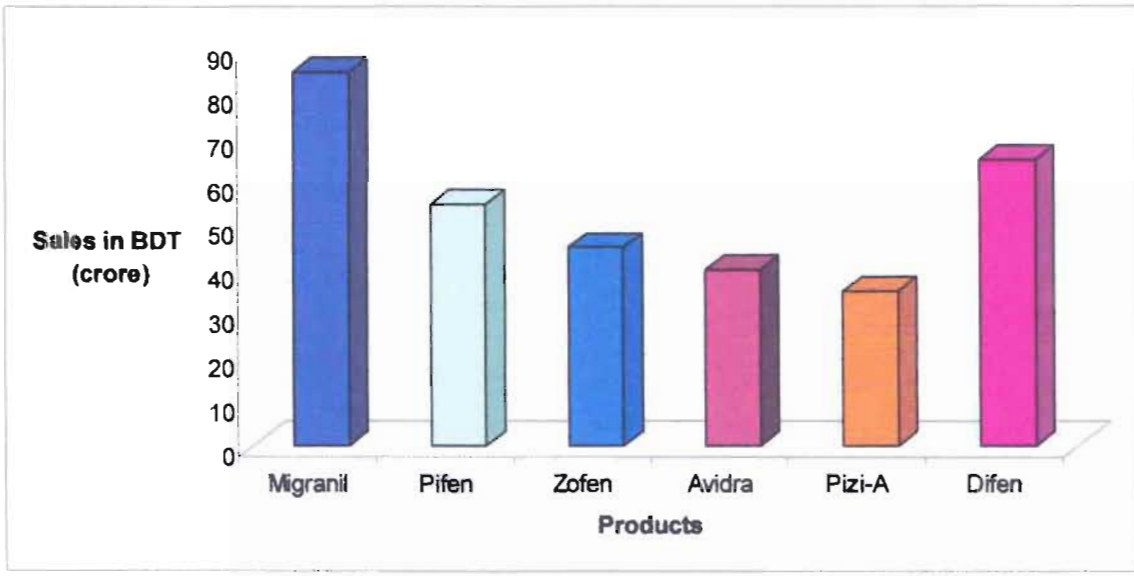

Figure 04: Annual sales of anticholinergic drugs by the year – 2009.

So, we can see that Migranil is in First position in total anticholinergic drugs market according to annual sales of the year-2009. Difen is in second position. Pifen is in third position . Comparing with these three molecules, others are in very low level.

Migranil:

Migranil® contains Pizotifen BP (as Malate) which is a tri-cyclic compound possessing structural similarities to cyproheptadine and tri-cyclic antidepressants. It is given orally for the prophylaxis of migraine and for the prevention of headache attacks during cluster periods. It is not effective in acute attacks of migraine. In the sequence of events leading to migraine attack, depletion of plasma serotonin contributes to loss of tone of extracranial vessels. Pizotifen inhibits serotonin re-uptake by the platelets, thus maintaining plasma serotonin and preventing the loss of tone and passive diffusion of the extracranial arteries. Migranil is the leading Anticholinergic Drugs in Bangladesh market. If we see the yearly growth rate of Migranil, we will find that it always fluctuates and last year it earns a growth rate of 12.51% and annual sale was about BDT 89, 74, 82,431.

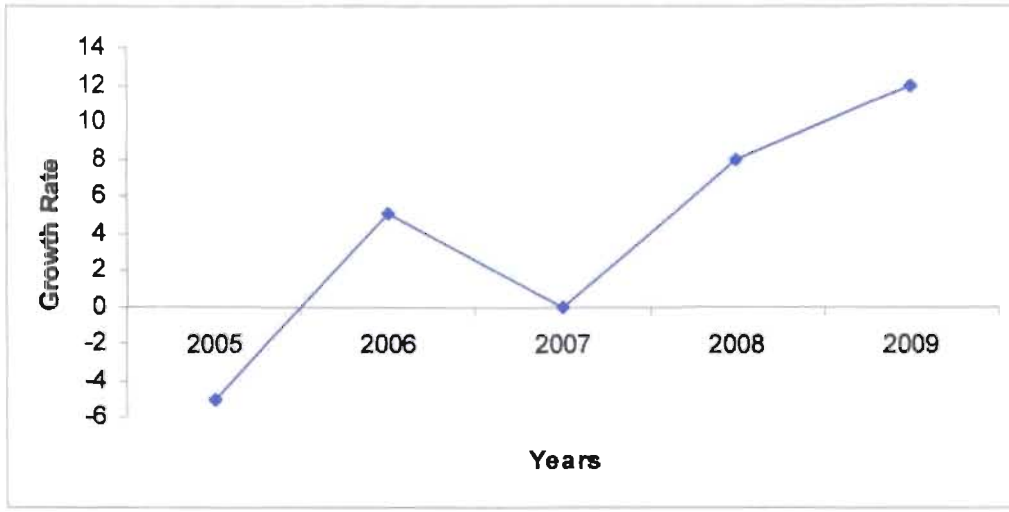

Figure 05: Yearly growth rate of Migranil from the year 2005 to 2009 **(sources- IMS 2009/2Q)**

The growth of The growth of Migranil was very low in the year-2005, but after a fluctuation now it has increased positively in 2009. In last year its growth was 12.51% which is significant.

Pifen:

Pifen is generally prescribed for headache-related inflammatory pains or severe toothaches that result in the inflammation of the gums. Pifen can also be used for treatment of some pain, especially ear pain like post-herpetic neuralgia and referred pain for radiculopathy.

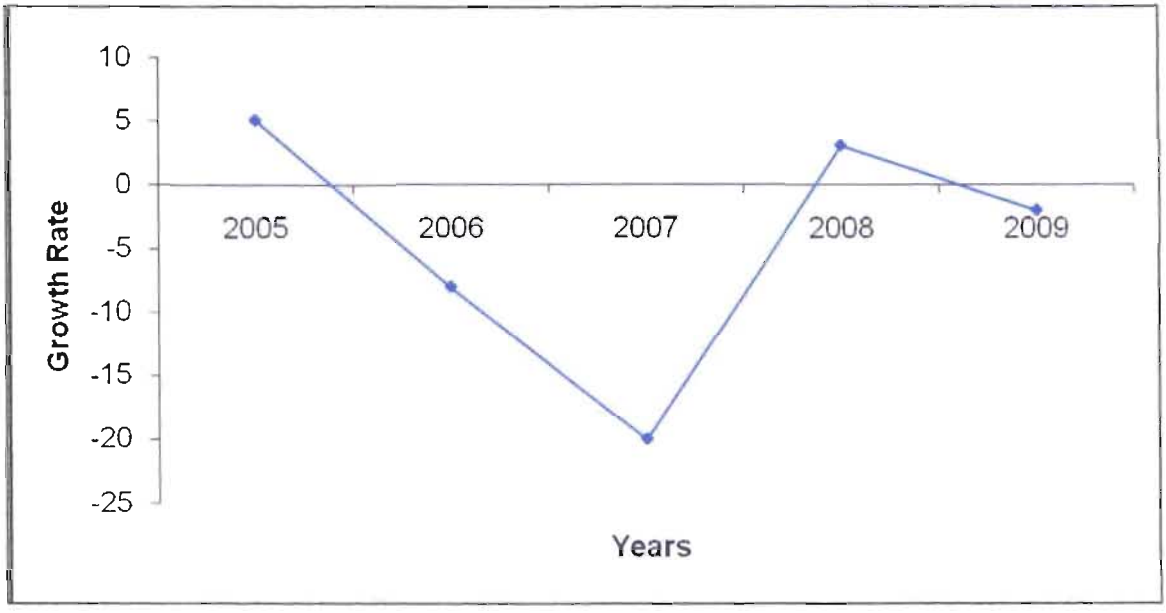

Figure 06: Yearly growth rate of Pifen from the year 2005 to 2009 **(sources- IMS 2009/2Q)**

The growth of Pifen was low in last few years, but in 2008 it was increased. In last year its growth was -2.57% with total sales of about BDT 10.69 crores.

Zofen:

It is a non-steroidal anti-inflammatory drug commonly used to reduce fever, pain, stiffness, and swelling. In the graph we can see that this drug has got always positive growth. Last year it earns 18.68% growth rate and the total sales was about BDT 8.54 crores.

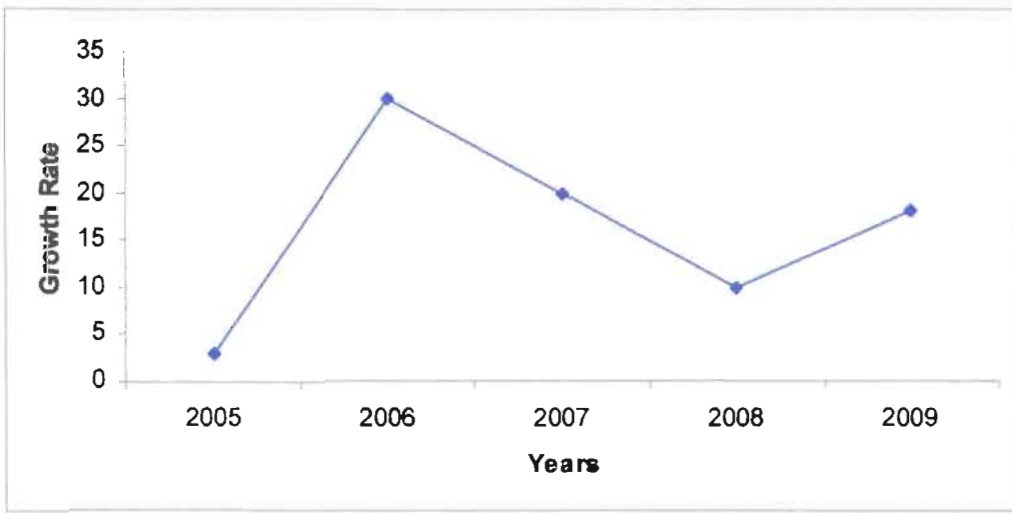

Figure 07: Yearly growth rate of Zofen from the year 2005 to 2009 **(sources- IMS 2009/2Q)**

The growth of Zofen was low in the year 2005, but it was rapidly increased in 2006.After some fluctuations, in 2009 it was increased. In last year its growth was 18.68%.

Avidro:

Avidro is the brand name of pizotifen, which is a tricyclic compound having antiserotonergic and antihistamine effects together with a weah anticholinergic action.It is used as prophylactic treatment of vascular headache of the migraine types, such as classical migraine, common migraine, and cluster headache.

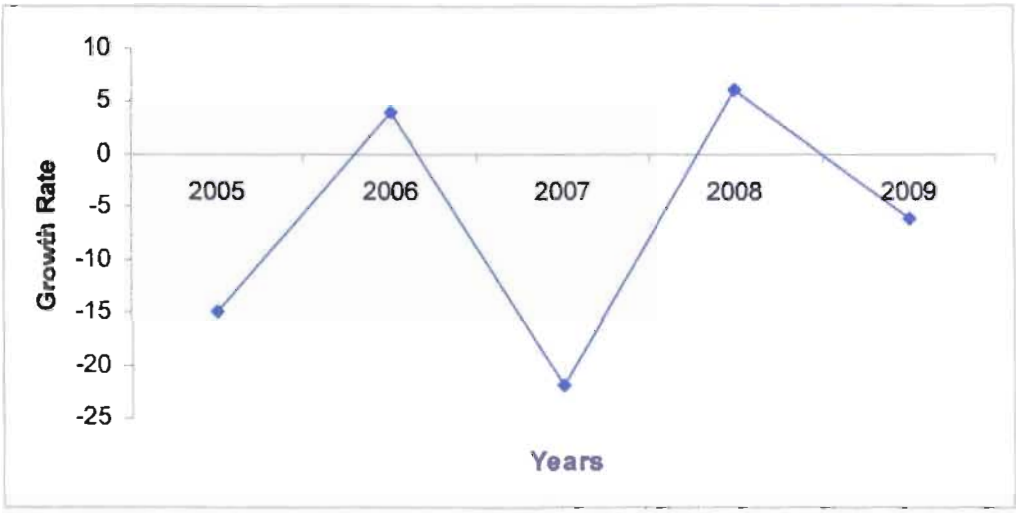

Figure 08: Yearly growth rate of Avidro from the year 2005 to 2009 **(sources- IMS 2009/2Q)**

The growth of Avidro was very low in the year 2005, but it was rapidly increased in 2006. After some great fluctuations, in 2008 it was increased. In last year (2009) its growth was -6.22%.

Pizo-A:

Pizo-A is used in the patients those are complain of blurred or shimmering or cloudy vision, as though they were looking through thick or smoked glass, or, in some cases, tunnel vision and hemianopsia. The somatosensory aura of migraine consists of digitolingual or cheiro-oral paresthesias, a feeling of pins-and-needles experienced in the hand and arm as well as in the nose-mouth area on the same side. Paresthesia migrate up the arm and then extend to involve the face, lips and tongue.

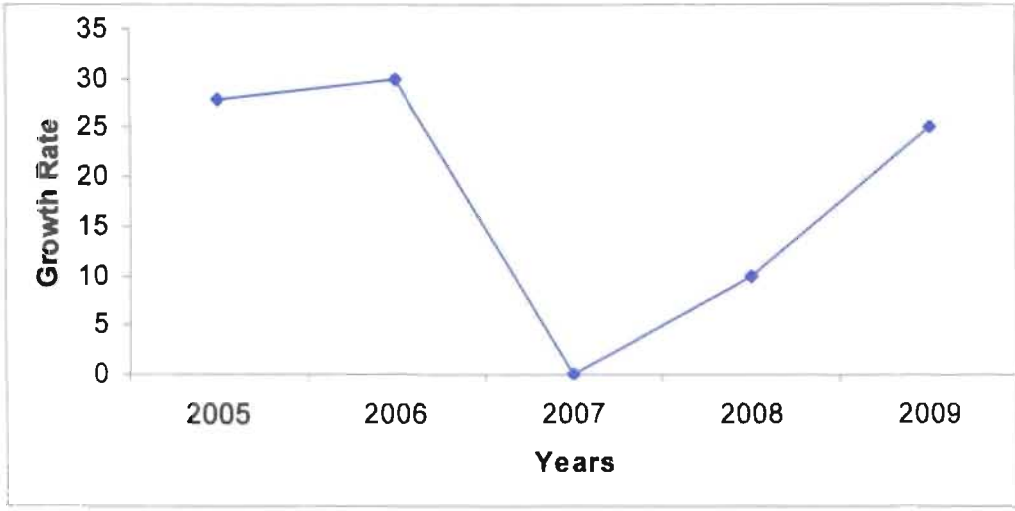

Figure 09: Yearly growth rate of Pizo-A from the year 2005 to 2009 **(sources- IMS 2009/2Q)**

The growth of Pizo-A was very high in the year 2005, but it was decreased in 2006 till 1st half of 2007. From 2nd half of 2007 to 2009 its growth rate increased significantly. In last year (2009) its growth was 24.64%.

Illustration of Pizotifen market growth

Migranil is one of the leading anticholinergic in Bangladesh market in terms of sales and growth. In last year the sales of pifen exceeded 33 crores BDT (exact value: 33, 41, 87,771 BDT) and took the 0.65% share of total market. The graph of yearly sales of migranil (from the year 2005 to 2009) is given below:

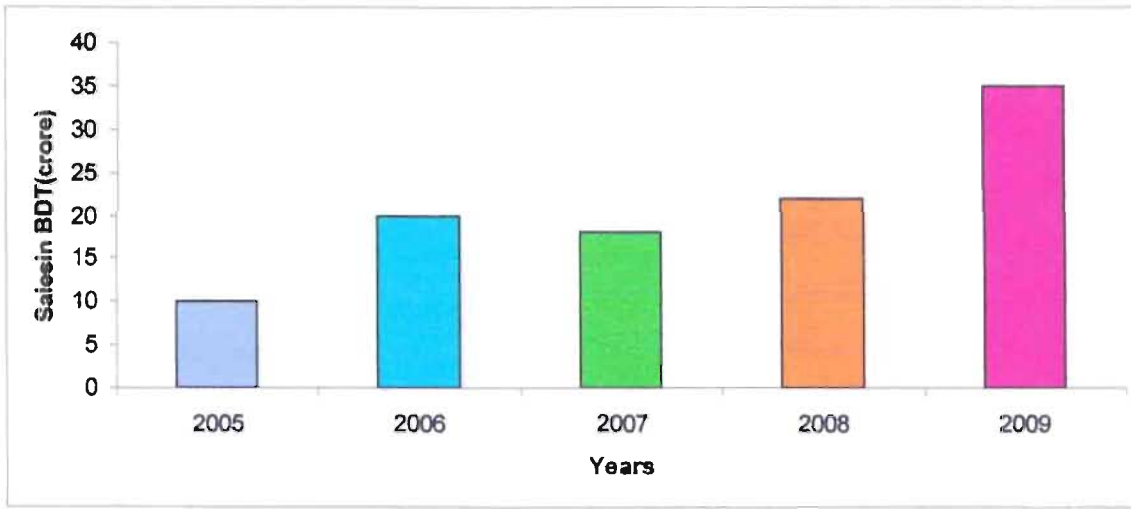

Figure 10: Year wise sales graph of pizotifen **(sources- IMS 2009/2Q)**

The growth of Pizotifen is quite good from its entering in the market. In the year 2005 it earned an enormous growth of 578.11%. From then it has kept a good record of growing. Only exception was year 2007. In that year market of pizotifen fall a little bit. The yearly growth of aceclofenac is shown below:

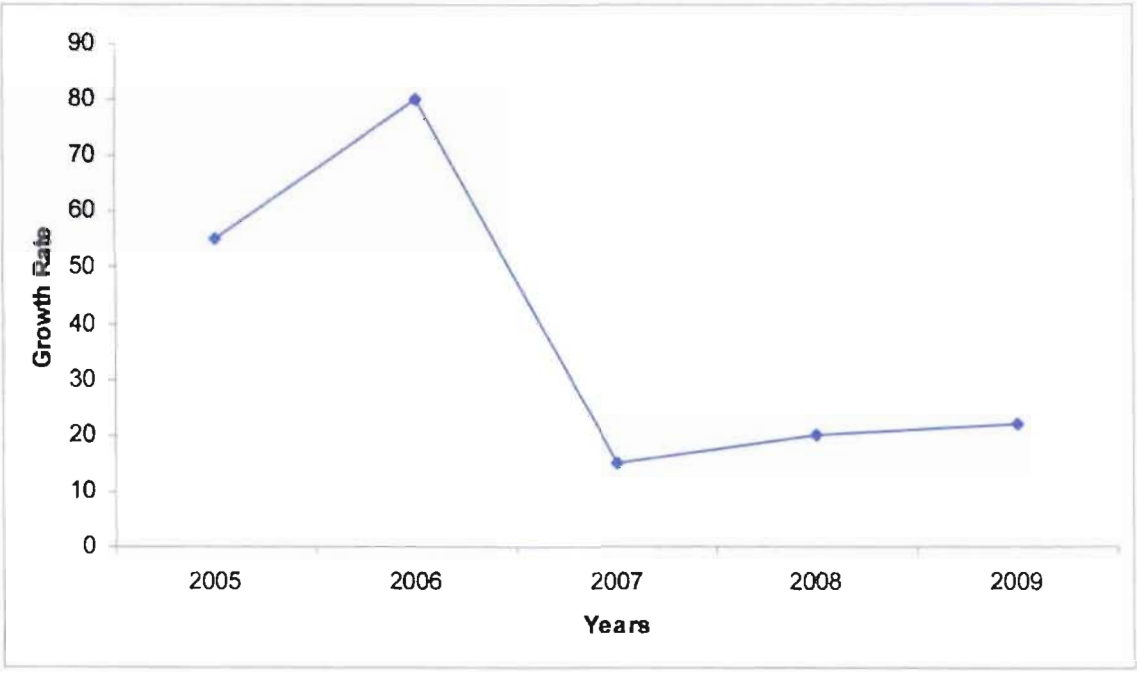

Figure 11: Yearly growth rate of Pizotifen from the year 2005 to 2009 **(sources- IMS 2009/2Q)**

6. Conclusion

Migraine is the most common cause of severe, recurring headache. The unquantifiable amount of human suffering is obviously enormous. However, migraine can be effectively treated, and sometimes even prevented. Migrainous triggers may not always be apparent, even with compilation of a meticulous headache diary by the patient, nor preventable even when identified. Similarly, neither a particular abortive nor prophylactic migraine therapy is universally efficacious. Thus, combined treatment and prevention approaches are most likely to succeed. Moreover, heightened patient awareness of migraine's pervasiveness and core features, coupled with greater diagnostic acumen and therapeutic knowledge of migraine among all physicians, are essential to significantly diminish migraine's deleterious effects.

Limitation:

For a particular type of migraine, particular brand of Anticholinergic is prescribed. It does not mean that this brand is the market leader.

The sample size could be determined by using statistical tools but the study covered only 100 patients which may not be representative of whole population of our country.

Since the time was obstacle, we had to run the study with that specified sample size. The study could cover the opinion of the prescribers. These opinions of the prescribers could explain the logics of their prescribing habit of migraine. This might reveal the relationship between the outcome of the prescriptions and the logics of prescribers.

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APPENDIX

Title: Questionnaire

Types of migraine:

Opthalmoplegic migraine

Retinal migraine

Basilar migraine

Cold stimulus headache

Familial hemiplegic migraine

Episodic tension-type headache

Other types

Anticholinergic is given

☐Yes ☐No

If yes then

Brand name of Anticholinergic:

Generic name of Anticholinergic:

Any Antihistamine drug is given:

☐Yes ☐No

If yes then

Brand name of Antihistamine:

Generic name of Antihistamine:

Other prescribed drugs (Except Anticholinergic)

☐Yes ☐No

If yes then

Brand name of the drugs:

Generic name of the drugs: