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ROLE OF POLYPHARMACY IN THE MANAGEMENT OF MIGRAINE: EXPERIENCE AT A TERTIARY CARE CENTRE

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ABSTRACT

Introduction: Migraine is a common headache disorder characterized by recurrent attacks. It is the most common type of headache diagnosed in neurological practice and is among the top 10 most disabling disorders worldwide. The aim of the study is to assess the role of pharmacological therapy in the patients diagnosed with migraine. **Material and methods:** Patients were selected randomly over a period of 30 days. All of them were evaluated, diagnosed and treated by neurospecialists. Patients included in the study were more than 16 years of age with a history of chronic head ache for more than 1 year. Follow up assessment was done based on the documentary evidence in the OPD cards. **Result and conclusion:** The acute attacks of migraine showed significant relief with non steroidal anti -inflammatory drugs (NSAID) namely naproxen sodium, triptans like sumatriptan and combination of ergotamine and caffeine. Preventive therapy was more complex and included polypharmacotherapy from the antidepressant group, antiepileptic drugs, anti anxiety and sedative drugs.

KEYWORDS: Migraine, pharmacotherapy.

INTRODUCTION

Migraine is one of the most common health disorders worldwide. It is the most common type of headache diagnosed in women (approximately 85 %).[1] Worldwide, migraines affect nearly 15% or approximately one billion people. Migraine is defined as a moderate to severe recurrent headache lasting between four and 72 hours, usually unilateral and pulsatile in quality. It is often accompanied by nausea or vomiting and is aggravated by routine activities,

light and noise.[2] There is a wide lacunae in the knowledge of the causative factors of migraine. However, many theories have been propounded with respect to its pathophysiology. It is widely believed that migrainous pain is caused by the activation of nerve fibers that reside within the wall of brain blood vessels travelling within the meninges. Migraine is usually diagnosed on the basis of signs and symptoms.[3] Neuro imaging is not mandatory but may be required to rule out secondary causes of head ache like cerebral tumors, trauma, infections and stroke. Treatment of migraine includes lifestyle management, trigger avoidance, biofeedback, acute treatment of attacks and preventive treatment for reducing frequency.

Multiple pharmaceutical agents have been shown to reduce the acute effects and the chronic frequencies of the migrainous attacks. The aim of this study is to assess the variation and effect of poly pharmacy in the management of migraine.

MATERIAL AND METHODS

The study is a retrospective observational study conducted in the Institute of Medical Sciences, Banaras Hindu University, and Varanasi. Patients were randomly selected from the out patient department of neurology and neurosurgery over a period of 30 days in January 2018. All the patients were diagnosed with chronic migraine by the concerned neurospecialists.

The patient documents were studied and the various demographic, clinical and treatment variables were tabulated.

The diagnosis of migraine without aura, according to the International Headache Society (IHS), was made according to the following criteria, the **"**5, 4, 3, 2, 1 criteria**"**.[4]

- **Five** or more attacks—for migraine with aura, two attacks are sufficient for diagnosis.
- **Four** hours to **three** days in duration
- ***Two*** *or more of the following:*
  - *Unilateral (affecting half the head);*
  - *Pulsating;*
  - *Moderate or severe pain intensity;*
  - *Worsened by or causing avoidance of routine physical activity*
- ***One*** *or more of the following:*
  - *Nausea and/or vomiting;*

- *Sensitivity to both light (photophobia) and sound (phonophobia)*

If someone experiences two of the following: photophobia, nausea, or inability to work or study for a day, the diagnosis is more likely.[5]

RESULT

The study included 39 patients with recurrent attacks of migraine being managed by neurospecialists. It was more common in females as compared to males (79% vs21%). The common presenting symptoms included throbbing head ache radiating from one part to whole head. The head ache was associated with nausea, noise intolerance, photophobia and was relieved with vomiting and /or sleeping. Associated features included anxiety, giddiness and depression. Mostly there were triggers which potentiated and precipitated the attacks. Most common triggers were generalised anxiety, exposure to sunlight, hunger, lack of sleep, menstruation, alcohol use and excess exercises.

Migraine is more common in age between twenty eight to thirty five years. Most of a time the headache typically started in one part of the head and gradually involved whole head over duration of hours and many times headache present at half of head [Table.1]. Treatment of migraine included drugs for the management of acute attacks and drugs for decreasing the frequency of attacks in patients with chronic complaints (preventive therapy). Acute attacks were controlled with the use of naproxen in all the patients. Combination tablets of ergotamine, paracetamol and caffeine were prescribed in 51 % patients. Sumatriptan was advised in ten patients. Trigger symptoms like anxiety and depression were treated with clonazepam, amitriptyline, escitalopram and chlordiazepoxide. Prochlorpromazine was given in 80% patients for the associated complaint of vomiting and for improving the absorption of co-administered analgesics. Betahistine were prescribed for giddiness or vertigo patients [Table 1].

Most commonly used drug for prophylaxis was propranolol (80%) followed by flunnarizine (51%) and divalproex sodium, a congener of valproate (51%). Amitriptyline was also one of the common drugs used for prophylaxis in this study.Yoga and exercises were advised to all patients [Table 2].

Most common side effects noticed with the use of amitriptyline were dryness of mouth, excessive thirst and limb oedema. Patients were advised to drink lot of fluids and wear stockings. Divalproex sodium was stopped in 5 patients due to rapid weight gain. Dose

reduction was done in patients complaining of excessive daytime sleepiness with the use of chlordiazepoxide and clonazepam [Table 3].

Table 1: Demographic and clinic-pharmacological variables in patients with migraine.

Patient variables		**Number of patients (%) N=39**
Sex	Females	31
	Males	8
Associated symptoms	Headache	39 (100%)
	Nausea	35 (90%)
	Noise intolerance	35 (90%)
	Photophobia	31 (80%)
	Anxiety	25 (64%)
	Depression	20 (51%)
	Vomiting	18 (46%)
	Vertigo	15 (39%)
Duration of Symptoms	≥ 3 months	25 (64%)
	1 to 3 months	8 (21%)
	< 1 month	6 (15%)
Nature of headache	Radiating from one part to whole head	25 (64%)
	Throbbing	17 (44%)
	Ache in one half of head	15 (39%)
	Light headedness	8 (21%)
	Band like	6 (15.38%)
	Scalp tenderness	4 (10.26%)
	Neck pain	4 (10.26%)
Headache triggers	Anxiety and stress	29 (74%)
	Exposure to bright light	27 (69%)
	Hunger and empty stomach	25 (64%)
	Lack of sleep	22 (57%)
	Menstruation	12 (31%)
	Alcohol	6 (15%)
	Excess exercises	4 (10%)

Table 2: Drugs used for Pharmacological management of migraine.

Clinical condition	**Drugs (standalone or in combination)**	**Group of drug**	**Number of patients (%) N=39**	**Common adverse effects**
Prophylaxis	Propranolol	Beta blocker	31 (80%)	Dizziness, hypotension
	Flunarizine	Calcium channel blocker	20 (51%)	Drowsiness, weight gain, tremors
	Divalproex sodium	Anti epileptic	15 (39)	Loss of appetite, weight gain, hair loss

Acute attacks	Naproxen	NSAID	39 (100%)	Indigestion, dryness of mouth
	Ergotamine and caffeine combination	Ergot alkaloid and caffeine	20 (51)	Sedation, constipation, hypotension
	Sumatriptan	Triptan : $5HT_1$Receptor agonist	10 (26%)	Neck pain, dizziness, jaw pain
Anxiety and depression	Clonazepam	Benzodiazipine	27 (69%)	Sedation, memory impairment
	Amitriptyline	Anti depressant	25 (64%)	Sleepiness , constipation, dryness of mouth,limb oedema,, difficulty in urination
	Escitalopram	Anti depressant	15(39)	Nausea, diarrhoea, fatigue
	Chlordiazepoxide	antidepressant	15(39)	Sleepiness , constipation, dryness of mouth,limb
Vomiting	Prochlorperazine	Dopamine antagonist	20 (51)	Orthostatic hypotension
Giddiness	Betahistine	Anivertigo	20 (51)	Headache, nausea, allergy
Gastritis	Pantoprazole	Proton pump inhibitor	15 (39)	Headache, flatulence, diarrhoea

Table 3: Most common adverse effects of drugs observed in patients with migraine.

Adverse effects	Number of patients (%)	Responsible drug/s
Dryness of mouth	10 (26)	Amitriptyline
Limb oedema	5(13)	Amitriptyline
Weight gain	5(13)	Divalproex sodium
Daytime sleepiness	15(39)	Clonazepam , chlordiazepoxide
Dyspepsia	5(13)	Naproxen
Difficulty in breathing	1(3)	Propranolol

DISCUSSION

Migraine is mostly common in women as compared to men when comparing gender wise. Patients with migraine have to endure frequent attacks of severe headaches that require acute, abortive treatment.

In the present study the demographic features and triggers including stress, hunger, menstruation and other related factors correlate well with similar studies conducted by Bartleson, *et al.*, (2010).[6] A study conducted by Lipton *et al.*, (2003) also showed that patients with migraine will have other problems that exacerbate their tendency to headaches: these include depression, anxiety.[7] The patients in the study were also prescribed drugs for depression and anxiety on a prophylactic basis.

Most drugs effective in the treatment of acute attack of migraine are the members of one of three major pharmacologic classes: anti-inflammatory agents, 5-HT1B/1D receptor agonists, and dopamine receptor antagonists.[8] Both the severity and duration of a migraine attack can be reduced significantly by anti-inflammatory agents. NSAIDs are most effective when taken early in the migraine attack.[9] The actions of triptans like sumatriptan are mediated by 5-HT(1B/1D) receptors and include vasoconstriction of painfully dilated cerebral blood vessels, inhibition of the release of vasoactive neuropeptides by trigeminal nerves, and inhibition of nociceptive neurotransmission.[10]

Drug absorption is impaired during migrainous attacks because of reduced gastrointestianl motility. Therefore, when oral NSAIDs and/or triptan agents fail, the addition of a dopamine antagonist such as prochloperazine, 10 mg, should be considered to enhance gastric absorption. In addition, dopamine antagonists decrease nausea/vomiting and restore normal gastric motility.[11]

The drugs that have been approved for the management of chronic migraine include the following groups[12-13]:

- Calcium channel blocking agents
- Antihypertensive agents
- Antidepressants
- Antiepileptic drugs

Beta-adrenergic receptor blockers are the most widely used agents for migraine prophylaxis. Propranolol is one of the most common beta blocker used in the treatment. The staring dose of is 20 mg/day.[14] A few different classes of antidepressant agents may be used for migraine prophylaxis, namely tertiary amines or tricyclic antidepressants (amitriptyline), selective serotonin reuptake inhibitors (SSRIs, e.g. escitalopram), as well as dual reuptake serotonin and noradrenaline inhibitors (SNRIs). These medications relieve migraine by affecting levels of various brain chemicals (including serotonin). The most common side effects of antidepressants are decreased libido, weight gain, constipation, dryness of mouth, Dry mouth, weight gain, postural hypotension, drowsiness.[15] The anti-seizure drugs relieve migraine pain by calming the overactive brain nerves. Several of these agents have shown increasing potential in migraine prevention. Treatment options include valproate, gabapentin, topiramate and lamotrigine.[15] In patients with episodic migraine,

divalproex 250-750 mg/day is recommended. Divalproex and sodium valproate are comparable in efficacy to propranolol, flunarizine and topiramate.[16] Flunarizine in doses of 5-10 mg per day has been found to be comparable to propranolol, topiramate, and valproic acid for migraine prophylaxis.[17]

The mechanism of action of this calcium channel antagonist in migraine prophylaxis is uncertain. It prevents contraction of vascular smooth muscles and inhibition of Ca++ dependent enzymes involved in prostaglandin formation. A case report by Brette R. *et al.*, (2015) has made dietary and lifestyle changes as a recommendation for treatment of migraine.[18]

Use of poly pharmacy is very common in the treatment of patients with chronic migraine. The treatment, especially the prophylactic phase, should be continued for 3 months to 12 months depending upon the response to the drugs. Previous studies have been conducted on one particular parameter or maximum two parameters but we planned a short term study on migraine which includes many parameters such as gender based distribution, triggers of headache, nature of headache, common age and pharmacological treatment especially the use of multiple co administered drugs.

Future prospects

A new approach for the treatment of acute migraine target calcitonin gene-related peptide (CGRP). The newer drug telcagepant has undergone trials as an acute treatment. However, the development of the drug was stopped by the company owing to its adverse hepatic actions.[19]

Established treatments for other neurologic conditions like as memantine, which is used for Alzheimer's disease, are being tried for the prevention of refractory migraine. Choice of drugs should be made on the basis of efficacy of drug, adverse events, patient preference, headache profile, and the presence or absence of coexisting disorders.[20]

CONCLUSION

Multiple drugs are used in the management of acute episodes as well as prevention of future attacks of headache in patients with migraine. Polypharmacy has an established role in decreasing the frequency of recurrent attacks and also altering the natural history of the disease. Newer pharmacological agents are being developed and aggressive research is

warranted for the further understanding of the cause and progression of migraine. Till then poly pharmacy appears to be one of the most effective methods of treatment.

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