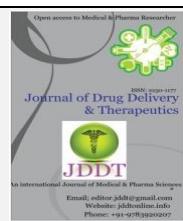


Available online on 15.07.2019 at <http://jddtonline.info>

# Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

© 2011-18, publisher and licensee JDDT, This is an Open Access article which permits unrestricted non-commercial use, provided the original work is properly cited



Open Access

Review Article

## Burden of Migraine

Saptarshi Panigrahi <sup>1\*</sup>, Riyanka Sengupta <sup>2</sup>

1. Department of Pharmacology, Key Laboratory of Neuropsychiatric Diseases, China Pharmaceutical University, Nanjing, China-210009

2. B.C.D.A College of Pharmacy &amp; Technology, Kolkata - 700127

### ABSTRACT

Migraine is a chronic neurological disorder with several trigger factors including dietary, hormonal and environmental factors. Migraine is a primary headache disorder characterized by recurrent headaches that are moderate to severe. Typically, the headaches affect one-half of the head, are pulsating in nature, and last from two to 72 hours. Nitrates, such as cardiac therapeutics and food additives, are common headache triggers, with nitric oxide playing an important role. Trigger factors are frequent in migraine patients, it avoidance may decrease headache frequency and also improve patients quality of life. Facultative anaerobic bacteria in the oral cavity may contribute migraine-triggering levels of nitric oxide through the salivary nitrate-nitrite-nitric oxide pathway.

**Keywords:** Migraine, Magnetic resonance imaging, Computerized tomography, Sumatriptan

**Article Info:** Received 09 May 2019; Review Completed 21 June 2019; Accepted 26 June 2019; Available online 15 July 2019



### Cite this article as:

Panigrahi S, Sengupta P, Burden of Migraine, Journal of Drug Delivery and Therapeutics. 2019; 9(4):648-650  
<http://dx.doi.org/10.22270/jddt.v9i4.3146>

### \*Address for Correspondence:

Saptarshi Panigrahi, Department of Pharmacology, Key Laboratory of Neuropsychiatric Diseases, China Pharmaceutical University, Nanjing, China-210009

### INTRODUCTION

Migraine is a massively common and impairing primary headache disorder, which was ranked the third highest cause of disability among the population under 50 years of age by the Global Burden of Disease studies. It is conceptualized as a multiphasic neurobiological disorder, which is characterized by various accompanying symptoms besides pain, such as phonophobia, photophobia, nausea, vomiting or cutaneous allodynia. Although these symptoms often occur simultaneously with headache, several behavioural, affective and cognitive symptoms exist, which follow a specific sequence over time and start days before<sup>7</sup> or after the migraine attack. Changes in appetite or in mood, yawning or fatigue typically precede the attacks, while, for example fatigue, tiredness, euphoria or dysphoria frequently follow the headache. Several findings of advanced neuroimaging supported this assumption, identifying brain structural and functional alterations in migraineurs compared to healthy controls, not just during migraine attacks, but in interictal stages too. Interracial imaging showed for example reductions in frontal and parietal lobe density along with an executive function deficit in set-shifting task; and an enhanced reactivity of the visual cortex after visual stimulation. These alterations are often positively correlated with disease duration and headache frequency. More than half of migraines in women occur right before, during, or after a women has her period. This often is called Menstrual migraine. But just a small fraction of women who have migraine headaches at other times of the month as well. Just

before the cycle begins, level of the female hormones, (estrogen and progesterone) go down sharply. This drop in hormones may trigger a migraine because estrogen controls chemicals in the brain that affect a women's pain sensation.

### NITRATE ASSOCIATIONS WITH HEADACHES AND MIGRAINES

Nitrate-containing compounds have been identified as normal headache triggers. Food preservatives are frequently identified triggers for those who suffer from migraines (1). There are two differing mechanisms behind these two headache types. Immediate headaches appear to be connected to nitric oxide (NO)-mediated vasodilatation; in contrast, delayed migraines, similarly to migraines caused by foods, stress, and other factors, appear to be activated by the release of calcitonin gene-related peptide (CGRP), glutamate, cyclic GMP (cGMP), or S-nitrosylation-mediated changes in ion channel function (2). Nitrate-induced headaches manifest in one of two ways: "immediate" headaches with mild to medium severity growing within an hour of medication ingestion and "delayed" headaches happening 3 to 6 h after nitrate intake that are much more acute, with migraine-like symptoms (3,4). Also, cardiac medications containing nitrates may cause severe headaches, which occur in over 80% of patients taking them. Indeed, just about 10% of patients cannot tolerate nitrate therapies due to intolerable headaches (5). Dextromigraines appear to be dose dependent and are more likely to occur in individuals with a

family history of migraines (6). Notably, S-nitrosylation is dependent on the presence of NO.

**Nitrate-reducing bacteria in the oral and fecal samples of the AGP** Because only bacteria, and not human cells, can reduce nitrate to nitrite (7). this may represent a symbiotic relationship by which our oral microbes maintain cardiovascular health using molecules present in our food. It has also been reported that in murine macrophages *in vitro*, the bacterial nitric oxide reductase NorB increases the decomposition rate of *S*-nitrosothiol (SNO) (8). This represents a potential connection between nitric oxide reductases and nitrate-induced migraines. Therefore, we determined the presence and abundance of nitrate, nitrite, and nitric oxide reductase genes in predicted metagenomes from stool and oral samples in the American Gut Project (AGP) cohort and correlated these genes with self-reported migraine status.

## CAUSE

The underlying causes of migraines are unknown. However, they are believed to be related to a mix of environmental and genetic factors. They run in families in about two-thirds of cases (5) and rarely occur due to a single gene defect. While migraines were once believed to be more common in those of high intelligence, this does not appear to be true. A number of psychological conditions are associated, including depression, anxiety, and bipolar disorder, as are many biological events or triggers.

## SIGNS AND SYMPTOMS

Migraines typically present with self-limited, recurrent severe headache associated with autonomic symptoms. About 15–30% of people with migraines experience migraines with an aura and those who have migraines with aura also frequently have migraines without aura. The severity of the pain, duration of the headache, and frequency of attacks are variable. A migraine lasting longer than 72 hours is termed status migrainosus. There are four possible phases to a migraine, although not all the phases are necessarily experienced:

- The prodrome, which occurs hours or days before the headache
- The aura, which immediately precedes the headache
- The pain phase, also known as headache phase
- The postdrome, the effects experienced following the end of a migraine attack

Migraines are associated with major depression, bipolar disorder, anxiety disorders, and obsessive compulsive disorder. These psychiatric disorders are approximately 2–5 times more common in people without aura, and 3–10 times more common in people with aura.

### Prodrome phase

Prodromal or premonitory symptoms occur in about 60% of those with migraines, with an onset that can range from two hours to two days before the start of pain or the aura. These symptoms may include a wide variety of phenomena, including altered mood, irritability, depression or euphoria, fatigue, craving for certain food(s), stiff muscles (especially in the neck), constipation or diarrhea, and sensitivity to smells or noise. This may occur in those with either migraine with aura or migraine without aura.

### Aura phase

An aura is a transient focal neurological phenomenon that occurs before or during the headache. Auras appear

gradually over a number of minutes and generally last less than 60 minutes. Symptoms can be visual, sensory or motor in nature and many people experience more than one. Visual effects occur most frequently; they occur in up to 99% of cases and in more than 50% of cases are not accompanied by sensory or motor effects.

### Pain phase

Classically the headache is unilateral, throbbing, and moderate to severe in intensity. It usually comes on gradually and is aggravated by physical activity. In more than 40% of cases, however, the pain may be bilateral and neck pain is commonly associated with it. Bilateral pain is particularly common in those who have migraines without an aura. Less commonly pain may occur primarily in the back or top of the head. The pain usually lasts 4 to 72 hours in adults,

### Postdrome

The migraine postdrome could be defined as that constellation of symptoms occurring once the acute headache has settled. Many report a sore feeling in the area where the migraine was, and some report impaired thinking for a few days after the headache has passed. The person may feel tired or "hung over" 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." For some individuals this can vary each time.

## DIAGNOSIS

If you have migraines or a family history of migraines, a doctor trained in treating headaches (neurologist) will likely diagnose migraines based on your medical history, symptoms, and a physical and neurological examination.

- **Blood tests** - Your doctor may order these to test for blood vessel problems, infections in your spinal cord or brain, and toxins in your system.
- **Magnetic resonance imaging (MRI)**: An MRI uses a powerful magnetic field and radio waves to produce detailed images of the brain and blood vessels. MRI scans help doctors diagnose tumors, strokes, bleeding in the brain, infections, and other brain and nervous system (neurological) conditions.
- **Computerized tomography (CT) scan**: A CT scan uses a series of X-rays to create detailed cross-sectional images of the brain. This helps doctors diagnose tumors, infections, brain damage, bleeding in the brain and other possible medical problems that may be causing headaches.
- **Spinal tap (lumbar puncture)**: Your doctor may recommend a spinal tap (lumbar puncture) if he or she suspects infections, bleeding in the brain or another underlying condition.

In this procedure, a thin needle is inserted between two vertebrae in the lower back to remove a sample of cerebrospinal fluid for analysis in a lab.

## TREATMENT

### Self-care

- ❖ Common triggers include alcohol, caffeine or poor sleep.

- ❖ Pursuing an enjoyable activity or frustration to reduce stress and improve mental health.
- ❖ Good sleep practices include having a regular bedtime schedule and avoiding naps, mobile and TV before bedtime.
- ❖ Adjusting diet to reduce triggers causing disease dietary deficiencies.

Many medications have been designed to treat migraines. Some drugs often used to treat other conditions also may help relieve or prevent migraines.

- ❖ Over the years there have been positive developments in acute medication for migraine. These treatments can't stop you from getting migraine but they can reduce your pain and other symptoms.
- ❖ Drugs called triptans have been designed especially for migraine attacks. Their main effect is to reduce pain information coming to the brain.

**1. Anti-emetics (Anti-sickness):** Metoclopramide, Domperidone, Prochlorperazine, [Anti-emetics relieve the nausea associated with migraine attacks]

**2. Serotonin (5-HT<sub>1</sub>) agonists or 'Triptans' :** Sumatriptan, Almotriptan, Eletriptan, Frovatriptan, Naratriptan, Rizatriptan, Zolmitriptan, [Selective 5-HT<sub>1</sub> agonists relieve pain by narrowing blood vessels in the head and blocking the transmission of pain in sensory nerves supplying the skin and structures of the face]

**3. Tricyclic antidepressants (TCAs):** Amitriptyline, Nortriptiline

These drugs were previously used for depression, however, they are also effective at preventing migraine. They can be helpful in people with migraine who also have difficulty sleeping.

Tricyclic antidepressants are thought to:

- Block the re-uptake of 5-HT and norepinephrine
- May block 5-HT<sub>2</sub> receptors.

**4. Analgesics:** Aspirin, Aceclofenac, Diclofenac, Tolfenamic acid, Naproxen, Paracetamol

## CONCLUSIONS

Many people continue to have migraine attacks in older age. Special attention should be paid to the diagnosis of new migraine-like symptoms, especially visual migraine symptoms without headache. Any other co-existing health conditions have an important role not only in diagnosis but also in treatment choices. Acute and preventative medication should be chosen carefully. Effective treatment is available and, as for all age groups, careful management improves the quality of life.

## ACKNOWLEDGEMENTS:

This work was supported by grants from the National Natural Science Foundation of China (81573413 and 81773714 to Hao Hong) and the Fundamental Research Funds for the Central Universities (2632017PT01). SP is a recipient of China Govt. Scholarship-Chinese University Program (China Scholarship Council) for foreign students at China Pharmaceutical University.

**Conflict of Interest:** The authors declare no conflict of interest.

## References

1. Mlsna, Lucas J. 2009. Foods and supplements in the management of migraine headaches. 57 (8): 1236-9.
2. Siminovitch L, McCulloch EA, Till JE, 2006. Side effects of using nitrates to treat angina. Expert Opin Drug Saf 5:667-674.
3. Bellantonio P, Micieli G, Buzzi MG, Marcheselli S, Castellano AE, Rossi F, Nappi G. 1997. Haemodynamic correlates of early and delayed responses to sublingual administration of isosorbide dinitrate in migraine patients: a transcranial Doppler study. Cephalgia 17:183-187.
4. Juhász G, Zsombók T, Gonda X, Bagdy G. 2004. Nitroglycerin-induced headaches. OrvHetil 145:2323-2328. (In Hungarian.)
5. Bagdy G, Riba P, Kecskeméti V, Chase D, Juhász G. 2010. Headache-type adverse effects of NO donors: vasodilation and beyond. Br J Pharmacol 160:20-35.
6. Lundberg JO, Weitzberg E, Cole JA, Benjamin N. 2004. Nitrate, bacteria and human health. Nat Rev Microbiol 2:593- 602.
7. Laver JR, Stevanin TM, Messenger SL, Lunn AD, Lee ME, Moir JW, Poole RK, Read RC. 2010. Bacterial nitric oxide detoxification prevents host cell S-nitrosothiol formation: a novel mechanism of bacterial pathogenesis. FASEB J 24:286 - 295.
8. Mandal S, Van Treuren W, White RA, Eggesbo M, Knight R, Peddada SD. 2015. Analysis of composition of microbiomes: a novel method for studying microbial composition. MicrobEcol Health Dis 26:27663.
9. Langille MG, Zaneveld J, Caporaso JG, McDonald D, Knights D, Reyes JA, Clemente JC, Burkepile DE, Vega Thurber RL, Knight R, Beiko RG, Huttenhower C. 2013. Predictive functional profiling of microbial communities using 16S rRNA marker gene sequences. Nat Biotechnol 31:814 - 821.
10. Baskin, SM; Lipchik, GL; Smitherman, TA (October 2006). "Mood and anxiety disorders in chronic headache". Headache. 46 Suppl 3: S76-87.
11. Ousings G, Hijazze S, Van de Laar FA, Fahey T (Jul-Aug 2011). "Diagnostic accuracy of the ID Migraine: a systematic review and meta-analysis". Headache. 51 (7): 1140-8.
12. Russell, G; Abu-Arafeh, I; Symon, DN (2002). "Abdominal migraine: evidence for existence and treatment options". Paediatric Drugs. 4 (1)
13. Magis, D; Jensen, R; Schoenen, J (June 2012). "Neurostimulation therapies for primary headache disorders: present and future". Current Opinion in Neurology. 25 (3): 269-76.
14. Silberstein, S.D. (26 September 2000). "Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology". Neurology. 55 (6): 754-762
15. Shevel, E (March 2011). "The extracranial vascular theory of migraine - a great story confirmed by the facts". Headache. 51 (3): 409-17.
16. Hyde ER, Luk B, Cron S, Kusic L, McCue T, Bauch T, Kaplan H, Tribble G, Petrosino JF, Bryan NS. 2014. Characterization of the rat oral microbiome and the effects of dietary nitrate. Free Radic Biol Med 77: 249 -257.
17. Eren AM, Maignien L, Sul WJ, Murphy LG, Grim SL, Morrison HG, Sogin ML. 2013. Oligotyping: differentiating between closely related microbial taxa using 16S rRNA gene data. Methods Ecol Evol 4:1111-1119.
18. Doel JJ, Benjamin N, Hector MP, Rogers M, Allaker RP. 2005. Evaluation of bacterial nitrate reduction in the human oral cavity. Eur J Oral Sci 113:14 -19.
19. Hoang A, Wisler K, Rico A. 2016. Bacteremia and mycotic aneurysm due to *Rothia mucilaginosa*. ClinMicrobiol Case Rep 2:026.
20. Latyshev Y, Mathew A, Jacobson JM, Sturm E. 2013. Purulent pericarditis caused by *Haemophilusparainfluenzae*. Tex Heart Inst J 40: 608 - 611.
21. Hershey, AD (February 2010). "Current approaches to the diagnosis and management of pediatric migraine". Lancet Neurology. 9 (2): 190-204.