

## Opinion

# Refractory Headaches

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## Introduction

Headaches are among the most ancient disorders that are still commonly present. We can find headache description dated 6000 years ago [1]. Thus, clearly there have been extensive research and our headache knowledge is constantly growing. Based on our new understanding of headache pathophysiology new treatment modalities are being developed. First placebo controlled trial of ergotamine was conducted in 1928 and it became one of the first specialized and highly effective abortive (rescue) medications used for acute migraine management [2]. We are still frequently using ergotamine containing medications in a large population of migraineurs and cluster headaches sufferers with great success. In early 1970s search for a new abortive medications began and in 1991 sumatriptan was officially introduced [3]. Number of triptans has grown since and they remain the most commonly used migraine-specific abortive medications. In addition to triptans and ergotamine containing medication less specific migraine (as well other headache types) treatment options exist including non-steroidal anti-inflammatory drugs, muscle relaxants, opioids etc. For patients with chronic migraines variety of prophylactic medications is available and include tricyclic antidepressants, anticonvulsants, beta-blockers, calcium channel blockers, botulinum toxin type A etc. We broadly utilize non-pharmacological methods that include low tyramine diet, maintaining regular sleep pattern and regular meals, biofeedback and physical therapy. Yet, every day in clinical practice we see patients who despite all the clinical advances are still not able to find an effective remedy for their painful and highly disabling condition. I am not talking about patients with chronic headaches only (although undoubtedly this groups of patients represent the majority) but also about sufferers with episodic headaches such as episodic migraines, cluster headaches, SUNCT syndrome etc., that are not controlled with “traditional” approaches. These patients are frequently referred to as “difficult patients” and they represent patients with so called refractory headaches.

It is clear that we need to find and develop different therapeutic approach that will help manage this challenging group of patients. It is also imperative that we have unified and clear diagnostic criteria and definition of refractory headaches which would help early recognition and perhaps early and timely referral of these patients to specialists who could provide these challenging patients with appropriate level of care and who would address their refractory headache problem using more advanced and sophisticated treatment modalities including interventional approaches.

## Diagnostic Criteria

At this point there are no officially recognized and universally accepted criteria for refractory headaches. Several diagnostic criteria were proposed over the years and although they may not be complete they certainly represent a step in a right direction and ground for future research. It is well accepted at this point that to qualify for refractory headache it should be disabling and resistant to medical treatment. In one of the diagnostic criteria proposed in 2008 by Schulman refractory migraine should be resistant to not only prophylactic agents but also to abortive medications [4,5]. While discussing prophylactic treatment failures it is also important that we use common and universally accepted standards. In our office we ask all new patients to complete questionnaire where we ask them to check previously tried medications (both prophylactic and abortive). It is not unusual to face the situation when most of the medications that are considered to be standard care in headache management had been tried yet none of them provided any substantial pain relief. These patients are frequently being referred to our Clinic and at first glance they do represent therapeutic challenge and may “qualify” for refractory headache diagnosis simply based on the fact that some of these patients had tried more than 20 different prophylactic medications. In cases like this I tend to ask these patients about medication doses and duration of therapeutic trial. And although there are patients who had tried therapeutic doses of certain drugs for several months or even years, many of them would provide information that would reveal either subtherapeutic doses and/or short treatment trial (1-2 weeks). I do believe that in most cases it is physician’s failure to explain the patient treatment goals and set realistic expectations. It is understandable that patients who have been struggling from chronic, daily, incapacitating headaches for many years would expect and wish to finally experience pain relief if not immediately but at least within few days after treatment initiation. Once their expectations fail, they frequently discontinue treatment. Thus, it is important to recognize that in order to “fail” prophylactic treatment one must be able to take prophylactic medicine at a therapeutic dose and at least for 2 months. As far as abortive medications trials – we recommend our patients to try any given abortive agent for treatment of 3-4 migraines episodes. We spent a lot of time educating our patients about migraine presentations, associated symptoms and advise patients to early recognize migraines headaches and implement treatment at migraine onset rather than when pain becomes incapacitating. We do recommend to start migraine abortive treatment with triptans or ergotamine containing medications (if clinically appropriate) rather than with “non-specific” pain medications (nonsteroidal anti-inflammatory agents, opioids etc.). Only after this type of trial do we suspect a drug failure.

At this point it is recommended that at least 2 prophylactic medications groups (beta-blockers, calcium channel blockers, anticonvulsants, antidepressants, botulinum toxin type A etc.) should fail to consider diagnosis of refractory headache.

Another important point in most proposed criteria is that patients with refractory headaches do not require meeting diagnostic criteria for chronic headaches, but may suffer from truly intractable and refractory episodic form of headache.

In more recently proposed diagnostic criteria of refractory headache Silberstein et al suggests to divide patients in to classes based on the failure of one or more prophylactic or abortive medications [6]. Thus, patient who failed single prophylactic medication should be categorized as class I or mild, and patients who failed at least 3 prophylactic agents and inpatient treatment should be considered as class IV or very severe. It was also proposed to use similar principles in relation to failure of abortive medications. For example, patients who had failed simple analgesics (NSAIDs etc.) should be considered as class I or mild, while patients who failed more specific medications such as triptans and ergotamine containing medications should be subcategorized as class II or moderate. Those patients who had failed specific anti-migraine medication and in addition did not respond to opioids or corticosteroids should be classified as class III or severe. Option of dividing patients in to classes helps determining which treatment modalities could be utilized. For example it was suggested to consider interventional approach for patients with class III (severe) or class IV (very severe) of refractory headaches.

## Refractory Headache Pathogenesis

There is still no clear understanding of refractory headaches mechanisms. Several theories have been proposed over the years. Some studies indicate certain anatomical peculiarities such as increased iron content in periaqueductal gray matter among patients with migraines, which may affect its descending modulation of pain [7,8].

In clinical practice, it appears that medication overuse headache has been among most common contributing factors to refractory headaches [9,10]. It has been well established that presence of medication overuse negatively affects effectiveness of prophylactic medications. And although some studies demonstrated positive outcomes of medication overuse headache treatment with topiramate (without discontinuation of an overused drug) [11] it is a standard recommendation to discontinue medications that are causing "rebound" headaches.

We also have looked in to psychological aspect of refractory headaches and it appears that patient with refractory migraines and medications overuse headaches have higher rates of depression and anxiety, ineffective pain coping strategies and frequently learned pain behavior [12,13].

Despite all the advances in our understanding of migraine biology and pathogenesis none of the currently available theories propose clear answer to mechanisms of refractory headaches.

As definition of these headaches clearly states – management of refractory headaches is still very challenging. We frequently use combination of two or even three different prophylactic medications, and trying to find at least two abortive medications that patients may rely on. Yet, frequently that is not enough. At our Clinic we developed multidisciplinary inpatient program where we use intensive parenteral treatment combined with non-pharmacological modalities such as biofeedback, physical therapy, acupuncture, psychological evaluation

aimed to identify stressors and develop new coping strategies. We also educate patients on importance of following low tyramine diet and maintaining regular sleep and exercise program. In appropriate candidates we utilize interventional treatment modalities that include occipital and supraorbital nerve blocks, trigger point injections, sphenopalatine ganglion blocks, facet medial branch nerve blocks and radiofrequency ablations. Some patients may also benefit from more sophisticated interventions such as occipital and/or supraorbital stimulations, sphenopalatine ganglion stimulation etc [14,15]. Although most of these interventional treatment modalities have been used in clinical practice for years and with great success there are still not enough clinical trials that would bring these interventions to a level of standard of care.

It is clear that more research is needed to gain better understanding of refractory headaches and help develop new treatment approaches.

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