Chapter 7

Headache of Analgesic Abuse as a Cause of New Pain Pathways Development

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Additional information is available at the end of the chapter

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Abstract

Medication-overuse headache (MOH) is a worldwide health problem with a prevalence of 1–2%. It is a severe form of headache where the patients often have a long history of unsuccessful headache treatments. MOH is characterized by chronic headache and the overuse of different headache medications. Through the years, withdrawal of the over-used medication has been recognized as the treatment of choice. However, currently, there is no clear consensus regarding the optimal strategy for the management of MOH. Treatment approaches are based on expert opinion rather than scientific evidence. This chapter focuses on an overall discussion of medication abuse as a novel pain pathway in headaches.

Keywords: headache treatment, migraine, medication-overuse headache, pain pathways, chronic headache

1. Introduction

Headache is one of the first causes for pain consultation in primary care settings and one of the major complaints of pain made at the neurology clinic [1]. Overall it is estimated that 4% of the general population suffer from migraine, representing at least 280,000,000 people requiring treatment only for just one cause of cephalea [2]. If the number of all other headache causes is added to the total number of migraine patients, the number of people requiring treatment for headaches represents almost one-sixth of the global population.

Due to the high number of patients as well as the varied causes of headaches, cephalea treatments are varied ranging from mild, over-the-counter painkillers such as paracetamol [3], to high complex molecules, intended to act as neuromodulators and prevent pain crisis, such

as topiramate [4], and sometimes further requiring nonopioid and opioid analgesics such as ketoprofen [5] and codeine [6]. With so many people suffering from headaches and having such a varied set of available drugs for treatment, it is no surprise that the problem of overuse and abuse of such treatments exists, leading to the appearance of secondary adverse effects such as the development of new pain pathways, among a certain group of patients. To understand the complexity of a problem like this, it is necessary to gain a deep knowledge of headache physiopathology, pharmacological options, and treatment guidelines, in order to identify the reasons leading to cephalea treatment overuse, and the arising of such a tricky problem such as the development of new pain pathways.

2. Classification of headaches

Although the concept of cephalea has mostly remained the same since it was first used to describe this type of disorder, its classification has been evolving continuously in line with modern physiopathological and pharmacologic concepts. The term cephalea or cephalalgia denotes pain located anywhere in the head and neck, regardless of the etiology; however, such a vast subject requires a very detailed classification scheme to determine which would be the best treatment for each type. Headaches are divided into two major groups: primary headaches and secondary headaches. Primary headaches are those appearing spontaneously with no association to any other disease or medical condition, while secondary headaches are those appearing in close temporal relation to another condition known to produce cephalea [7]. The main difference between both groups is whether or not an association is found with another cause, thus primary headaches have an intrinsic physiopathology while secondary cephalea is the consequence of another disease, trauma, or medical condition.

Primary cephalalgia is divided into four major categories:

(1) Migraine

(2) Tension-type headache

(3) Trigeminal autonomic cephalalgias

(4) Other primary headache disorders [8]

While secondary cephalea has eight:

(1) Headache attributed to trauma or injury to the head and/or neck

(2) Headache attributed to cranial or cervical vascular disorder

(3) Headache attributed to nonvascular intracranial disorder

(4) Headache attributed to a substance or its withdrawal

(5) Headache attributed to infection

(6) Headache attributed to disorder of homoeostasis

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(7) Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structure

(8) Headache attributed to psychiatric disorder [9]

From the above-mentioned cephalea types, migraine and tension-type headaches represent up to 80% of all cases [10]; however, it is important to recognize all other types of cephalea so as to avoid misdiagnosis and treatment errors since these could be the first steps toward the overuse and abuse of headache treatment drugs.

3. Headache physiopathology

A detailed description of the physiopathology of each type of headache goes far from the reach of this chapter, thus the discussion will be focused on the most common subtypes; migraine and tension-type headache as well as on a common feature for each cephalea type: the pain pathway.

3.1. Physiopathology of migraine

Despite being the most common cause of headache, the underlying pathogenesis of migraine is not known and every day, new data is being made available which aid in the clarification of the possible processes behind such a major public health problem.

Once considered a cephalalgia of vascular origin involving intracranial blood vessel dilatation, recent data reveals that the physiopathology of migraine is much more complex; abnormal modulation of brain nociceptive systems [12], brain excitability, recurrent activation, and sensitization of the trigeminovascular pathway [13] all work together not only to produce but also to prolong the migraine.

The integration of the above-mentioned factors is shown in **Figure 1**, where the interaction and upregulation of each element over the other is made clear.

Moreover, **Figure 1** demonstrates why there are so many available migraine treatments, as each one has to work on a very narrow cluster of the whole pathogenic chain and why the effect of a particular therapy may diminish over time due to the upregulation and potentiation between different pathological events associated with migraine.

The good news behind such a complex physiopathology is the high number of therapeutic targets available to work with, rendering the therapeutic options almost infinite. Although the ideal treatment would be one that could act over all the mechanisms, or at least the most important one, unfortunately, such a treatment is far from being available, and current knowledge points to what seems to be the convergence point of all migraine pathogenic mechanisms: serotonin [14]. Abnormally low levels of this important neurotransmitter seem to be the cause of at least two of the pathological aspects: blood vessel dilation and brain hyperexcitability; hence, it is not surprising to find that there is a remarkable therapeutic effect by serotonin agonists on migraine.

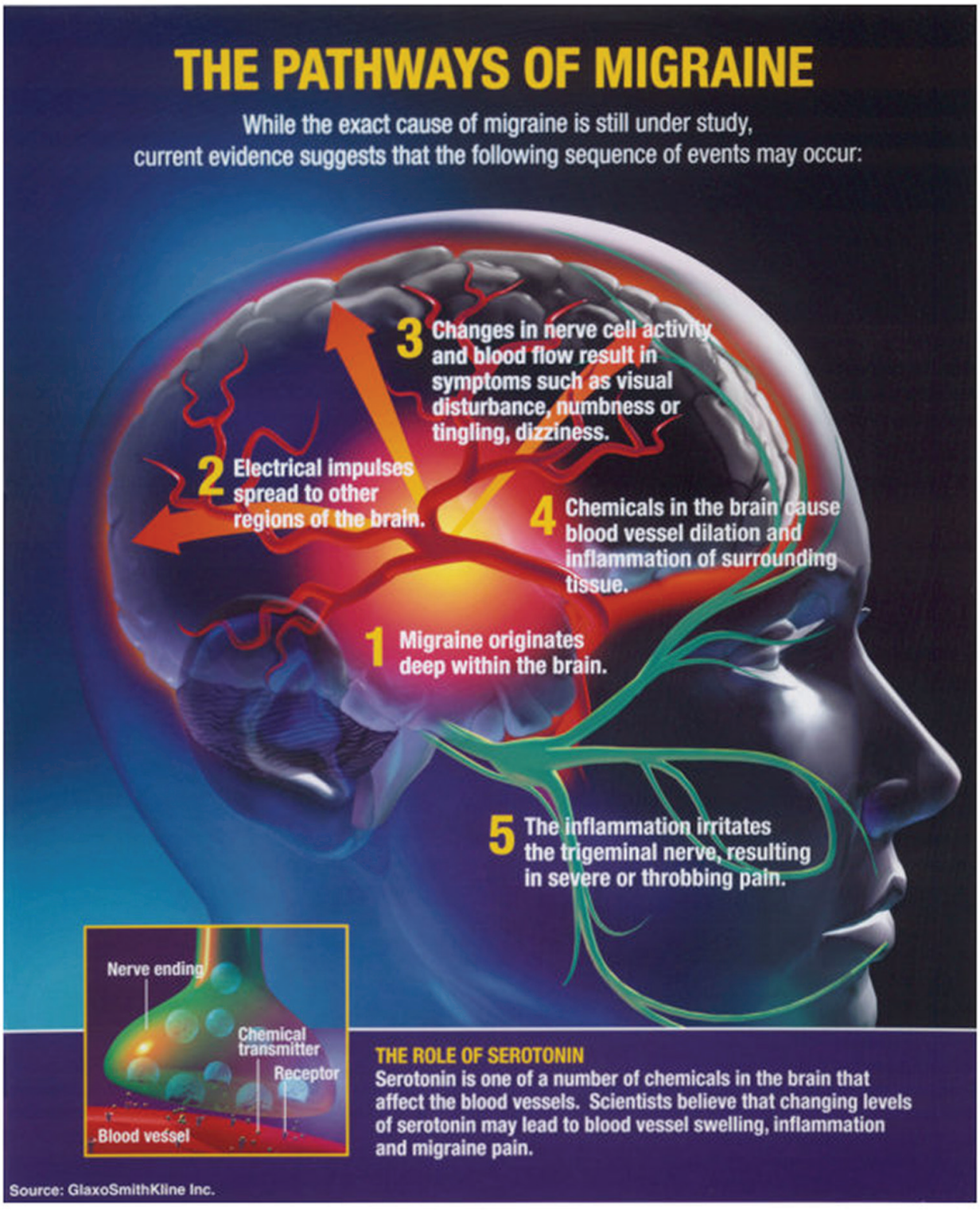

Figure 1. The pathways of migraine [11].

3.2. Physiopathology of tension-type headaches

Even though migraine represents a major public health concern and is the leading cause of headache, tension-type headache should not be underestimated since it represents

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the second most common cause of cephalalgia with a prevalence of 46.9% in the general population [15], and provides the potential for a great field of study as tension-type headaches may be present in an acute scenario (known as episodic tension-type headache) or chronically, being called in such cases chronic tension-type headache. The most interesting fact regarding this dual presentation profile is that in some people tension-type headache remains acute and sporadic while some others progress toward a chronic condition. At the initial stage, both episodic and chronic tension-type headaches share a common pathophysiological pattern associated with scalp and head muscles chronically contracting as well as certain neck movements [16], these are usually identified as the triggers and are the targets for therapy in the past; however, recent investigations have shown that chronic muscle contraction alone is not enough to cause a pain crisis, but it also includes the presence of central nervous system factors such as a hypersensitivity to pain stimuli which causes a tension-type headache to evolve from just a simple contraction [17] to a chronic disorder affecting quality of life [18].

It is possible that at the very beginning all tension-type headaches begin this way but when there is increased excitability of the central nervous system generated by repetitive and sustained pericranial myofascial input [19] permanency occurs and upregulation creates a cycle of chronic tension-type headache, with lower stimuli requirements needed to trigger the next pain crisis. At the molecular level, chronic tension-type headache has been associated with low serotonin levels [20] acting as an upregulator in the case of migraine, on the other hand, there is the recent description of nitric oxide playing a role in both migraine and tension-type headaches, acting as a cranial and extracranial blood vessel dilator as well as a central nervous system sensitizer, these findings have led to a hypothesis about a common pain pathway shared by all primary chronic cephalalgias or at least between the two major groups, migraine and chronic tension-type headache [21].

4. Headache pain pathway

It is a well-known fact that cerebral tissue has no pain receptors, making it impossible to generate painful stimuli directly from the brain; most head and neck tissues such as bone, muscle, skin, and even blood vessels share a common innervation pattern where nociceptive C and A-delta fibers from the first root of the trigeminal nerve are involved as seen in **Figure 2**.

The aforementioned common innervation pattern may cause headache to arise from almost any head structure from muscles to meningeal membranes progressing to a chronic condition based on preexisting genetic, biochemical, and behavioral characteristics of each individual. Once the pain has become chronic, at least two molecular events have been identified as responsible (totally or partially) for pain upregulation: low serotonin levels and high nitric oxide, both of them upregulating pain pathways in at least two major headache groups: migraine and chronic tension-type cephalalgia [23]. Based on the above, positive strides can be made toward the development of new drugs intended not only to treat pain but also to prevent it [24] since the existence of both a common neurologic pain pathway as well as shared molecular features among major primary headache groups provides that possibility; moreover, it

could be possible to treat different primary headache types with a single drug working on key, shared points of the pain pathway [25]; however, more extensive research as well as a deeper understanding of different pain pathway integration is needed to achieve such goals; primary headache treatments still focus on two main targets: pain control and crisis prevention.

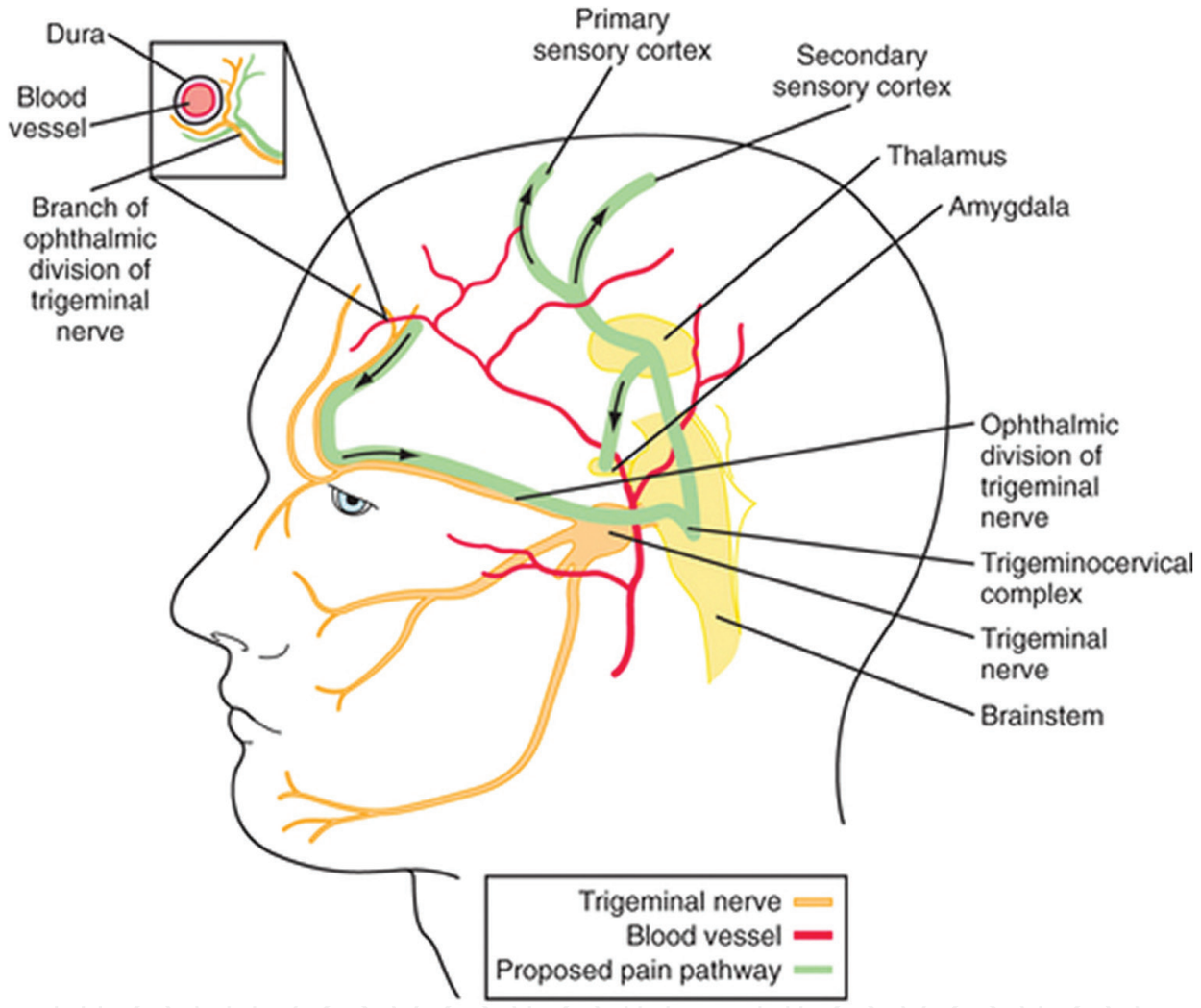

Figure 2. Blood vessel innervation pattern and migraine associate pain pathways [22].

5. Pharmacological options for headache treatment

It is a well-known fact that prevention of a medical condition is usually the best approach because it tends to be easier, cheaper, and cost effective; hence the aim of primary headache treatment should be focused on such a target. However, at this moment, prevention strategies for primary headache are not 100% reliable and the failure rates are high [26] leading to the use of palliative measures in order to relieve patients' suffering derived mainly from migraine and tension-type headache.

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In this regard, current pharmacological approaches include two major groups of action: pain relief and brain modulation, each one aimed to act on a particular stage. Although pain relief should be the last resort and be used only when modulation and prevention have failed, this is the main therapeutic approach in real life, treating the problem once it has fully showed up; the reason behind such behavior could be related to the ancient approach toward headache based on pain relief, used for decades when primary headache was not known as it is today and no other therapeutic option was available; and although there may be numerous and powerful effective pain killers and analgesics available, this option should be restricted only to cases where prevention has failed; always giving priority to novel, preventive therapies offering patients a better quality of life [27]. With the everyday increase in knowledge on primary headache pathophysiology, neurochemistry, and pain pathways, modern, current treatments of primary headaches intended to act as brain modulators have gained popularity because they are more expensive than conventional pain killers, such drugs are able to give patients a better quality of life, decreasing the negative impact of headache on both personal and work commitments [28]. Novel migraine and tension-type headache treatments exert their action in several ways but with a common goal: reduction of pain crisis by downregulating sensitized brain pathways, which usually act as a trigger or maintain the headache pain crisis, leading to an overall reduction of acute primary headache and thus a drop in the requirements for over-the-counter (OTC) painkillers and prescription analgesic use.

According to the U.S. Headache Consortium the scope of modern migraine treatment must be to:

- *Reduce attack frequency and severity*
- *Reduce disability*
- *Improve quality of life*
- *Prevent headache*
- *Avoid headache medication escalation*
- *Educate and enable patients to manage their disease* [29]

It is clear that the use of OTC painkillers and analgesics are a last resort and is considered to be a damage control strategy, leading the way not only to better control of the migraine but also to a reduction in headache medication overuse [30].

Hence, the aforementioned medications may be extrapolated for use with tension-type and cluster headaches due to them having similar pathological pathways and neurotransmitters shared by the three major causes of primary headache.

The modern approach toward current headache management is shown in **Figure 3**.

After careful analysis of **Figure 3**, one can deduce that primary headaches still remain a diagnostic and therapeutic challenge, where a misdiagnosis or improper drug selection could lead

to treatment failure, with unexpected consequences not only by reducing the patient's quality of life but also due to the possible development of complications, thus it is mandatory to have a clear idea of available treatments and their mechanisms of action in order to properly select one or another option when necessary.

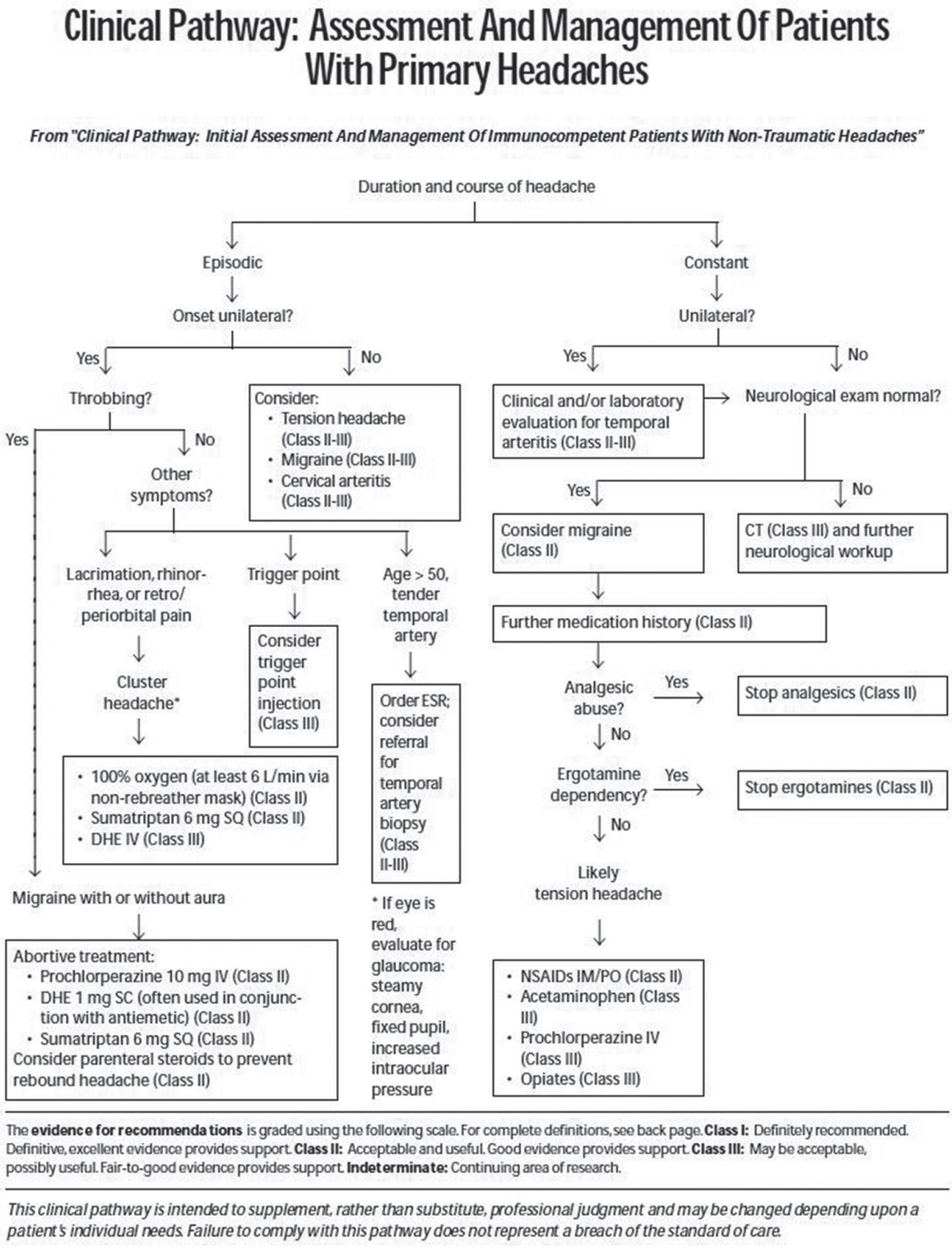

Figure 3. Assessment and management of patients with primary headaches [31].

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5.1. Comparison of the mechanism of action of different primary headache treatments

Due to the complex underlying pathologic mechanisms regarding primary headaches, common pain pathways, as well as the different drugs types and mechanisms of action, it is best to evaluate the most effective treatment for a particular patient by using a comparison chart because even though general guidelines may be helpful, primary headache treatment still needs to be individualized and adapted to the particular requirements of each patient. Modern therapeutic options for primary headaches as well as their primary and complementary mechanisms of action and indications are summarized in **Table 1**.

Preventive and abortive treatments

Drug*	Drug class	Mechanism of action	Indication
Amitriptyline [32] (Nortriptyline)	**Tricyclic antidepressants**	**Primary:** Serotonin reuptake inhibitor **Secondary:** Still not properly known	**Migraine** (prevention) **Tension-type headache** (prevention) [33]
Sumatriptan [34] (Rizatriptan, Naratriptan, Eletriptan, Donitriptan, Almotriptan, Frovatriptan, Avitriptan, Zolmitriptan)	**Triptans**	**Primary:** Selective Intracranial Blood Vessels constrictor acting as 5-HT1B and 5-HT1D serotonin receptors agonists **Secondary:** Blockage of sensitized neural pathways [35]	**Migraine** (Pain crisis abortive medication) **Cluster headache** (Pain crisis abortive medication)
Ergotamine (Dihydroergotamine)	**Ergopeptine**	**Primary:** Constriction of intracranial extra cerebral blood vessels working as 5-HT1B receptor agonist and 5-HT1D serotonin receptor blocker **Secondary: I**nhibition of trigeminal neurotransmission	**Migraine** (Long lasting pain crisis) [36]
Propranolol [37] (Nadolol, Timolol, Metoprolol, Atenolol)	**Beta blockers**	**Primary:** Inhibition of intracranial extra cerebral blood vessels dilation through Beta adrenergic receptors blockage	**Migraine** (prevention) **Cluster Headache** (prevention)
Valproic Acid - valproate -	**Antiepileptic drug** *not chemically related to other anticonvulsivant*	**Primary:** Under investigation, it's presumed that valproate may decrease nerve impulse transmission in previous sensitized pain pathways [38]	**Migraine** (Pain crisis abortive medication) [39] **Cluster Headache** (Preventive) [40]
Topiramate	**Anticonvulsant**	**Primary: M**odification of several receptor-gated and voltage-sensitive ion channels, including voltage-activated Na^+ and Ca^{2+} channels and non-NMDA receptors [41] **Secondary:** Modulation of gamma-aminobutyric acid- (GABA-) and/or glutamate-mediated neurotransmission [42]	**Migraine** (prevention) [43] **Cluster headache** (Adjunctive treatment) [44] **Tension-type headache** (Prevention) [45]

Preventive and abortive treatments			
Drug*	**Drug class**	**Mechanism of action**	**Indication**
Rescue treatments (pain control)			
Acetylsalicylic acid - Aspirin-**	**NSAIDs**	**Primary:** COX-1 and COX-2 inhibition	**Tension-type headache** (Rescue) [46]
Paracetamol**	**Mild analgesic**	**Primary:** - Suppression of signal towards the dorsal horn from the peripheral nerves by blocking TRPA1-receptors (peripheral pain pathway blockage) [47] - Inhibition of the reuptake of the endogenous cannabinoid/ vanilloid anandamide by neurons down regulating TRPV1 nociceptor stimulation (central pain pathway blockage) [48]	**Tension-type Headache** (Rescue) **Migraine** (Rescue) [49]+
Ibuprofen** (Ketoprofen)	**NSAIDs**	**Primary:** COX-2 inhibition [50]	**Tension-type headache** (Rescue) [51] **Migraine** (Rescue) [52]
Butorphanol	**Opiates**	**Primary:** Binding to central opioids receptors, down regulating central pain stimuli transmission [53]	**Migraine** (Rescue)++

*The model drug is shown as the main drug even when there are other molecules sharing the same mechanism of action (shown below the main category group in brackets).

**Even when each one has good therapeutic effect using alone, recent investigations suggest that combination of fixed doses of paracetamol, NSAIDs, and caffeine is more effective that any single drug alone [54].

+Some studies show that the addition of metoclopramide to paracetamol potentiates its effects on migraine patients [49].

++Despite the well-known analgesic effect of opiates, there is no strong clinical trials supporting their use in migraine, thus its use must be considered when all other available therapies have failed [55].

Table 1. Comparison of different primary headache available treatments.

Different options are available to stop migraine attacks: acute, symptomatic treatment. According to recent clinical evidence, the common approach to treating a migraine attack is based on early intervention when the pain is still mild, which can result in shortening the time to achieve a pain-free response. A proper clinical approach, individual considerations for each patient and a quick view of the guidelines may help to provide the best treatment for specific case [56].

5.2. Acute, sporadic headache treatment

Many people in the general population have experienced at least one headache crisis which is usually of no major concern since it may be treated with OTC painkillers with no further complications or sequelae. In fact, sporadic headaches need no medical attention and most cases are resolved by the patients themselves [57].

The most popular treatments for this type of acute, primary headache include paracetamol, when pain intensity is mild to moderate, and aspirin or any other NSAIDs such as ibuprofen, for high intensity headaches; it usually requires no more than a single dose to control the crisis [58]. From this perspective, acute sporadic headache treatment represents no problem at all

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since the risk of complications derived from treatment use and abuse are low or even null; however, many tension-type headaches begin as sporadic ones and with time they progress to a classic chronic cephalalgia. On the other hand, many undiagnosed migraine patients with low intensity crisis make it through the year with a very low frequency of intense attacks (less than one a month) and may handle their headache as a sporadic one with relative success in its initial stages [59] but sooner or later, a chronic pattern will develop, requiring medical assistance, with treatment optimization and monitoring in order to avoid headache treatment abuse-related problems. Since paracetamol, aspirin, ibuprofen, and various other OTC drugs are effective, safe treatments for acute headache crisis [60], there are no major concerns regarding the risks and so the use of such medication must not be discouraged because it is not a threat for patients; however, the underdiagnosis of migraine as well as tension-type headaches must be addressed. Many undiagnosed patients are left to deal with, on their own, against complex headaches which do require professional counseling in order to obtain proper relief and avoid headache overuse treatment-related problems, which are much more difficult to manage.

5.3. Chronic headache treatment

It is clear that a common, acute headache crisis presents no danger neither for the patient nor public health; however, when headache crises become more frequent requiring regular self-medication, often with poor outcomes and when such crises are accompanied by other symptoms such as auras or nausea, it becomes compulsory on the part of the physician to evaluate the patient for more complex etiologies, more than just a sporadic headache, in this case, a thorough medical consultation is mandatory in order to properly assess the patient, providing a diagnosis and a treatment intended not only to relieve pain but also to prevent recurrences. As stated previously, a high percentage of migraine sufferers have had no formal diagnosis of the disease [61], while some others progress from acute crisis of the tension-type headache to a chronic pattern when sensitization pathways become activated [62]; in both cases, symptoms may develop so subtly that patients are not fully aware of the disease state and may remain on the same self-medicating strategy for years despite the poor outcome. Even worse, this increases the chances of developing complications associated with improper management of chronic cephalea and treatment abuse. In this regard, the best strategy to conquer this problem is education. Beyond pharmacological treatment, it is important to inform the general public about primary headaches and how such entities may be easily confused with a banal headache and explain why their insidious evolution may render them undiagnosed for a long period of time; it is mandatory to educate patients about their diseases, giving emphasis to how important preventive medications are as primary therapy intended to reduce the likelihood of pain crises and increase their quality of life, leaving analgesics and OTC painkillers as a last resort when prevention has failed [63].

Implementation of education programs about headaches from school and on to the general public can be a key strategy to address the problem of underdiagnosis, misdiagnosis, and improper management of headaches [64]. The aim of such programs must be to encourage people to seek medical advice when certain headache patterns show up and this will help direct them to specialized physicians who will provide the appropriate care and counseling [65, 66]. Unfortunately, due to an increase in the access to over-the-counter treatments, low income, lack of medical secure coverage, and unawareness about migraine, tension-type headaches, and other primary cephalalgias, the trend is moving toward self-medication instead of professional counseling [67] which

has led to the improper use or even abuse of headache medications; however, once a headache patient has reached regular medical care, efforts must be made in order to enhance doctor-patient communication and provide as much information as possible to the patient [68] since having an in-depth knowledge of these diseases will lead to better management [69]; once patients are aware of a medical condition such as primary headaches, they act as multipliers among their families, relatives, friends, and coworkers [70], making it easier to catch public interest on a public health problem like migraine and other primary headaches. It remains clear that education and information play a key role in addressing chronic primary headache; however, once a patient has grasped these important concepts and the physician has given a diagnosis, it is necessary to utilize the right tools in order to correctly estimate the impact of headache on their quality of life [71] and to choose the right treatment for each individual case; otherwise, using standardized protocols even in the medical community may present the danger of improper treatment and abuse of certain medications [72]. To accomplish such a delicate task, health care providers rely on many tools such as MIDAS (Migraine Disability Assessment Score) intended to objectively evaluate headache frequency, pain intensity, and associated symptoms so as to measure not only the impact of headache on quality of life but also to assess treatment outcomes leading to a personal, tailored treatment regimen for each patient [73]. Once the diagnosis has been achieved and the impact on both quality of life and productivity is assessed [74], the precise treatment can then be chosen for each patient. It is important to note that the main goal of chronic primary headache treatment is to lower as much as possible the number of pain crises (preventive treatment), the secondary objective is to end a possible a crisis once it has evolved and has been triggered (abortive treatment), and finally, rescue patients once a crisis has stopped (rescue treatment). Long-term treatment options for each step of therapy have widened, providing physicians with a variety of drugs acting on different key points in the pathological chain as seen in **Table 1**. Everyday there is the development of a more complex therapeutic arsenal against migraine as well as other primary headaches. Gaining the proper knowledge of all available treatment options may be a challenge to even the most expert specialists; thus, this report has rendered the task easier by providing an organized list of all available therapeutic options summarized in **Tables 2** and **3**.

First-line preventive medications for migraine			
Drug name	**FDA-approved**	**Formulation**	**Dosage**
Onabotulinum toxin A	Yes	Injection	Dose: Varies (FDA official dose is 155 units via 31 injections every 3 months)
Anticonvulsants			
Topiramate	Yes	Oral	Total dose varies from 25 or 50 mg/day up to 400 mg/day
Valproic or divalproex sodium	Yes	Oral	Usual dose: 500–1000 mg/day in divided doses
B-blockers			
Propranolol	Yes	Oral	60–120 mg/day
Metoprolol	No	Oral	25–100 mg/day
Atenolol	No	Oral	25–50 mg/day
Nebivolol	No	Oral	2.5–10 mg/day

First-line preventive medications for migraine			
Drug name	**FDA-approved**	**Formulation**	**Dosage**
Tricyclic antidepressants			
Amitriptyline Nortriptyline	No	Oral	Stating dose: 10 mg at bedtime, titrate up to 25–50 mg at night. Maximum dose: 150 mg/day
Doxepin	No	Oral	Starting dose: 10 mg at bedtime, titrate up to 25–50 mg/day. Maximum dose: 150 mg/day
Protriptyline	No	Oral	5–20 mg/day
NSAIDs*			
Naproxen	No	Oral	500–550 mg/day; maximum dose 1000–1100 mg/day
Calcium channel blocker			
Verapamil	No	Oral	120 mg/day slow-release tablet, titrate to 240 mg/day

Table reproduced and adapted from the original source [75].
*Other NSAIDs are useful as well.

Table 2. First-line migraine preventive medications.

Second-line migraine preventive therapy*			
Drug name	**FDA-approved**	**Formulation**	**Dosage**
Antiseizure medications			
Gabapentin	No	Oral	Usual dose: 600–2400 mg/day Some patients do well on low doses (100–300 mg/day)
Pregabalin	No	Oral	25 mg bid to 150 tid
Muscle relaxants			
Cyclobenzaprine	No	Oral	5–10 mg/day
Tizanidine	No	Oral	Usual dose: 2–4 mg every night; patients start with ¼ to ½ tablet. May be increased to 12 mg/day
Antidepressants			
Desvenlafaxine	No	Oral	50–100 mg/day
Duloxetine	No	Oral	30–60 mg/day
Venlafaxine	No	Oral	75–225 mg/day
Natural agent			
Purified butterbur	No	Oral	100–150 mg/day

Table reproduced and adapted from the original source [76].
*Polypharmacy also is commonly used as second-line treatment of migraine (i.e., amitriptyline with propranolol or amitriptyline with valproic acid).

Table 3. Second line migraine preventive medications.

With the above information in mind it makes it easier to decide what the best options are for each patient; however, migraine treatment as well as the treatment for chronic tension-type and other primary cephaleas must be chosen considering each particular patient condition, available treatments at their location, exposure to triggers, and so on [77]. Usually this type of initial approach is enough to achieve adequate control of symptoms but if unsuccessful, it becomes mandatory to prioritize which attributes from each drug are better for a particular patient in order to choose the best mix of pharmacologic therapy [78]. In this regard, when precise medical treatment has been chosen, it is very important to measure its impact [79], not doing so could run the risk of the patient receiving a useless treatment over a long period of time leading to further problems regarding that particular treatment as well as future therapies. In this sense, it is also important to address the patient's expectations of the treatment in order to be able to provide not only a good outcome but also to gauge what the patient is expecting from treatment regarding tolerability, effectiveness, side effects, and other aspects of therapy; otherwise, there is a high risk of noncompliance which may lead patients toward self-medication and all the implied risk attributed to it. In addition, it is necessary to be aware of the adverse effects because even though the therapeutic action is good enough to improve the quality of life, the development of adverse side effects may lead to therapy discontinuation. A summary of the main adverse side effects associated with the main treatment categories are summarized in **Tables 4–6**.

Medications for abortive therapy	
Drug name	**Possible side effects**
Ergot Dihydroergotamine mesylate	Nausea, numbness of fingers and toes
Triptans Sumatriptan succinate* Zolmitriptan* Rizatriptan* Naratriptan+ Almotriptan malate*× Frovatriptan succinate+ Eletriptan hydrobromide*	**Side effects for all the triptans are similar** **This class of drugs is well tolerated but the more common side effects may include:** Nausea, headache, sleepiness, dry mouth, dizziness, fatigue, hot/cold sensations, chest pain, and flushing Other potential side effects that rarely occur include: Head, jaw, chest and arm discomfort/tightening/tingling; throat discomfort, muscle cramps, and flushing

*Short-acting.

+Long-acting.

×FDA approved for teens ages 12–18.

Table reproduced and adapted from the original source [80].

Table 4. Side effects of main first-line migraine abortive drugs.

It remains clear that proper treatment selection, impact evaluation, and limiting the side effects are all challenging tasks requiring highly specialized medical staff with adequate experience; otherwise, the outcome may not be satisfactory leading to possible therapy discontinuation,

self-medication, and the use of alternative treatments whose effectiveness and safety may not be well known. Unfortunately, there are still many cases worldwide of misdiagnosis, erroneous management, and self-medication due to lack of specialized medical assistance. All these factors are a "recipe for disaster" since many headache rescue treatments are available over the counter and thousands, perhaps millions of people try to fight alone against migraine, tension-type headache, and other primary cephaleas, lacking proper advice, leading to one of the worst complications of primary cephalalgias: drug overuse and abuse.

Medications for preventive therapy		
Drug name	**Possible major side effects**	**Instructions when used for headaches**
Nonsteroidal anti-inflammatories Naproxen sodium	GI** upset, GI bleeding, nausea, vomiting, rash and change in liver function, rebound headache	Is take twice a day, every day, for headache prevention
Tricyclic antidepressants Imipramine HCl Amitriptyline HCl	Dizziness, drowsiness, dry mouth, weakness, weight gain Fatigue, dry mouth, weight gain and constipation	Frequently started at low dosages and slowly increased Frequently started at low dosages and slowly increased to a therapeutic level; taken by night, EKG*** optional
Antihistamines Cyproheptadine HCl	May induce sleep or may shorten migraine attack, weight gain, drowsiness	Usually started at low dosages and slowly increased; often taken at bedtime
Selective serotonin receptor inhibitors (SSRIs)* Fluoxetine HCl	Nausea, dry mouth, increased appetite, agitation	Usually started at low dosages and slowly increased; usually taken at morning
Beta blockers Atenolol Propranolol	Fatigue, depression, weight gain, memory disturbance, faintness and diarrhea, decreased performance in athletes	Depending on the form, may be taken one to three times a day
Calcium channel blockers Verapamil Diltiazem HCl	Constipation and dizziness; hair loss	Frequently started at low dosages and slowly increased. Taken twice a day; usually the first dose is taken in the morning
Anticonvulsants Valproic acid	Nausea, drowsiness, weight gain, tremors and rare liver failure; may cause birth defects	Frequently started at low dosages and slowly increased. Periodic blood tests required
Topiramate	Rare: Glaucoma, kidney stone at high doses (>150 mg), weight loss, word finding difficulties	Frequently started at low dosages and slowly increased; may be taken 2 to 3 times/daily
Gabapentin	Generally well tolerated	Usually started at low dosages and slowly increased; may be taken 2–3 times/daily

Table reproduced and adapted from the original source [80].

*Other SSRIs include citalopram, escitalopram, fluvoxamine, paroxetine, sertraline.

**GI, gastrointestinal.

***EKG, electrocardiogram.

Table 5. Side effects of main first-line migraine preventive drugs.

Over-the-counter medications for symptomatic relief		
Drug name	**Symptoms relieved**	**Precautions and possible side effects**
Nonsteroidal anti-inflammatories		
Aspirin	Relief of fever and pain	Do not use in children under 14 years of age due to the potential for Reye's Syndrome Side effects may include: heartburn, gastrointestinal (GI) bleeding, bronchospasm or constriction that causes narrowing of the airways, anaphylaxis and peptic ulcer
Acetaminophen	Relief of fever and pain	Few side effects, if taken as directed, although they may include: changes in blood counts and liver functions
Ibuprofen	Relief of fever, pain and inflammation	Side effects may include gastrointestinal upset, GI bleeding, nausea, vomiting, rash and changes in liver function
Naproxen Sodium	Headache pain relief	Side effects may include GI upset, GI bleeding, nausea, vomiting, rash and changes in liver function

Table reproduced and adapted from the original source [80].

Table 6. Side effects of main migraine rescue drugs.

6. Primary cephalea treatment overuse and abuse statistics worldwide

Once a patient receives the diagnosis of migraine or any other primary headache, treatments usually become supervised by a medical team and patients are directed on what to do and what not to do regarding pharmacological therapy and although this group of patients carries a certain risk for medication abuse or overuse, usually there are no major concerns unless the patient abandons regular control and supervised treatment. Unfortunately, up to 50% of migraine patients remain undiagnosed [81] and even worst, up to 82% of patients with a diagnosis of nonmigraine headache actually meet the major migraine criteria [82] leading to improper handling and medication.

Regarding chronic tension-type headaches, up to 40% of patients have not received a formal diagnosis and are not aware of what disease they are suffering from [83]; they often think they have a benign condition causing the self-medication of migraine rescue drugs (OTC painkillers and analgesics) to become a trend, leading to the worsening of their underlying disorder.

On the other hand, a group of patients with a formal diagnosis of a primary headache disorder abandon follow-up due to lack of insurance, discouraging results or moving away to an area with no specialists with experience on headache treatment, keeping their treatment as something they do on their own, usually increasing dosing and dose intervals, leading to preventive and abortive medication overuse [84]. Aside from the above mentioned, there is another group of existing patients suffering from *chronic daily headache* affecting up to 5% of

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the general population [85], self-medicating with over-the-counter painkillers and analgesics to deal with pain crisis, increasing the risk of evolution toward chronic headache [86] due to central nervous system sensitization [87].

Even when not included in the International Headache Society Classification of Headache, chronic daily headache is a common disorder defined by some authors as "*a disorder where patients suffer very frequent headaches (15 or more days/month), including those headaches*", *furthermore, "Chronic Daily Headache (CDH) may be divided into two main groups; Primary CDH is not related to any structural or systemic illness. Population based studies suggest that Chronic Tension Type Headache is the leading cause of primary CDH, on the other hand, Secondary CDH occurs 15 or more times a month or has some identifiable underlying cause* [88]" (secondary CDH is summarized in **Table 7**).

Chronic daily headache
Primary chronic daily headache
Headache duration >4 hours
Chronic migraine (previously transformed migraine)
Chronic tension-type headache
New daily persistent headache
Hemicrania continua
Headache duration <4 hours
Cluster headache
Paroxysmal hemicranias
Hypnic headache
Idiopathic stabbing headache
Secondary chronic daily headache
Posttraumatic headache
Cervical spine disorders
Headache associated with vascular disorders (arteriovenous malformation, arteritis including giant cell arteritis, dissection, and subdural hematoma)
Headache associated with nonvascular intracranial disorders [intracranial hypertension, infection (EBV, HIV), neoplasm]
Other (temporomandibular joint disorder, sinus infection)

Abbreviations: EBV, Epstein-Barr virus; HIV, human immunodeficiency virus.
Table reproduced and adapted from the original source [89].

Table 7. Chronic daily headache causes.

Among all these patients "*thirty-five percent overused simple analgesics, 22% ergotics, 12.5% opioids, and 2.7% triptans; the remaining 27.8% have overused different combinations*" [28]. The major concern about these statistics is that although treatments may be helpful in the initial

stages, their chronic, unsupervised use and abuse tends to lead toward pain chronification; increasing the number of pain crises, intensity of pain, and resistance to regular analgesic dosing. Moreover, relapsing after medication withdrawal is still a major issue regarding both preventive and rescue primary headache treatments [90]. How many patients progress toward chronification will vary depending on the abused medication, according to Bigal "*available data suggest that opioids induce migraine chronification (progression), and the effect is dose dependent (critical dose around 8 days of exposure per month) and more pronounced in men. Barbiturates also induce migraine progression, and the effect is dose dependent (critical dose around 5 days of exposure per month) and more pronounced in women. Triptans induce migraine progression only in those with high migraine frequency at baseline (10–14 days per month), but not overall. NSAIDs protect against migraine progression unless individuals have 10 or more headache days per month (when they become inducers, rather than protective). Finally, caffeine-containing over-the-counter products increase risk of progression*" [91], thus each available drug used must be monitored individually in order to avoid overuse and abuse-related complications. Why and how primary headaches progress to chronification because of treatment abuse is still partially unknown and a field of very active research.

7. Underlying pathways for headache chronification following treatment abuse

It is a well-known fact that chronic exposure to pain treatment [92] as well suffering from chronic pain, especially chronic headache, increase the risk of chronic pain development due to "*reduced endogenous inhibition of pain, implying that an individual's processing of pain-related information changes with the onset of the syndrome*" [93]; however, the underlying mechanisms behind it still remain partially unknown.

Among the painful syndromes, chronic headache is one of those most commonly associated with long lasting analgesic consumption, termed medication overuse headache (MOH) when it occurs, a pathological entity "defined by the International Headache Society as a headache induced by the overuse of analgesics, triptans, or other acute headache compounds whose detailed pathophysiology is still unknown" [94]. Current knowledge indicates that it can take up to 25 years for a chronic pain condition to develop after the use of chronic analgesics MOH [95] with strong evidence to support that chronic use of analgesics is a good predictor of an increased occurrence of both migraine and nonmigrainous headaches within the next 11 years, with a combined risk ratio of 19.6%, which is extremely high when compared to only 3.1% for patients who do not overuse analgesic treatments [96]. But analgesics are not the only medications involved in MOH, ergots and triptans also play a key role in MOH, with a shorter interval between initial treatment and development of induced chronic headache. "*The delay between first intake and these attacks is the shortest for triptans (1–2 years), longer for ergots (3–5 years)*" [97] and the longest for analgesics as it was previously mentioned. In this regard, the risk of induced chronic headache is lower for triptans (i.e., sumatriptan) than for ergotamine [98], which is good news for patients since triptans are the drug of choice before ergotamine. The problem when trying to establish a prevention/treatment strategy for drug-induced headache

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as well as MOH arises from the fact that different drugs are involved in their development; hence, there is no single way to explain the related mechanisms or physiopathology. Even more complex is the attempt to establish the diagnosis of MOH or drug-induced headache since most of the time the clinical profile of the primary entity is the same as the induced one, making it very difficult to establish a difference among them and even worse, to determine when the primary headache has ended and MOH appeared. A single approach to establish such differences is symptom improvement with treatment withdrawal [99]; the headache was drug induced and not of a primary origin and once the trigger (the drug) has ceased, symptoms should improve.

Figure 4 shows a schema of what happens during drug-induced headache and how the diagnosis may be addressed regardless of the underlying molecular mechanisms.

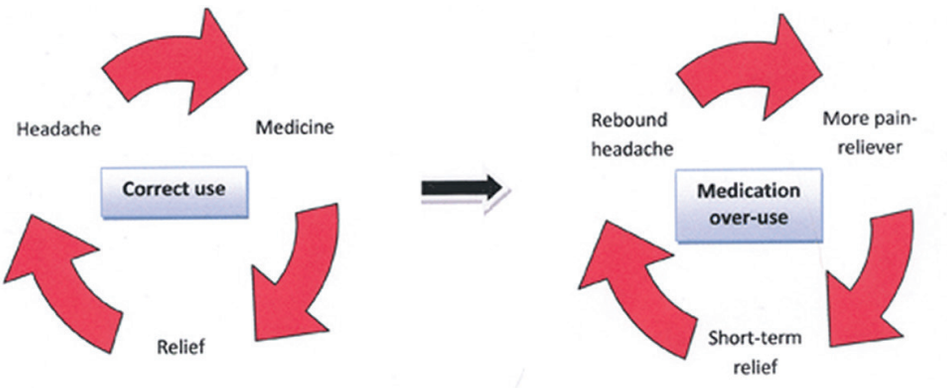

Figure 4. Drug-induced headache vicious circle [100].

Of note, opioids have been found to be one of the most problematic drugs found to induce chronic headache, regardless of the purpose of their use whether it be chronic headache or any other chronic pain condition such as back pain, oncologic pain, and so on. The underlying mechanism seems to be "*the activation of toll-like receptor-4 on glial cells, resulting in a pro- inflammatory state that manifests clinically as increased pain*" [101], such activation may explain not only the development of MOH but also of the transformation to migraine [102].

Another hypothesis sustained by preclinical research is the presence of neuroadaptive changes related to chronic use of opiates; such changes "*include increased expression of calcitonin gene-related peptide (CGRP) in trigeminal primary afferent neurons. Centrally, they include increased excitatory neurotransmission at the level of the dorsal horn and nucleus caudalis. Critically, these neuroadaptive changes persist for long periods of time and the evoked release of CGRP is enhanced following morphine pretreatment* [103]*; all these changes lead to Induced Hyperalgesia* [101, 104] *and thus Headache Chronification*."

But opiates are not the only molecules associated with MOH, there is also strong evidence suggesting that combined analgesics as well as joined ergotamine-caffeine preparations may induce a metabolic decrease in several brain areas, especially the orbitofrontal

cortex leading to a decrease in intrinsic pain downregulation circuits and the development of chronic headaches such as MOH and modified migraine (MM) [105]. Such metabolic changes may be associated with the sensitization of the trigeminal and somatic nociceptive systems; another possible path leading to MOH was demonstrated by Ayzenberg et al. on triptan-induced MOH [106].

Furthermore, the mechanisms stated earlier may be connected to others both centrally and peripherally by a complex net of interactions currently unknown but feasible such as "*upregulation of calcitonin gene–related peptide, substance P, and nitric oxide synthase in trigeminal ganglia; expansion of receptive field and decreased nociceptive threshold of central trigeminal neurons; decrease in diffuse noxious inhibitory control; and increased susceptibility to develop cortical spreading depression (CSD). These changes indicate an increase in excitability of cortical and trigeminal neurons. The neuronal hyperexcitability may be the result of derangement of a central, possibly serotonin (5-HT)-dependent, modulating control system. Experiments with animals with low 5-HT showed that the processes of CSD and trigeminal nociception are enhanced in this condition*" [107] as it has been demonstrated by Bongsebandhu et al. in animal models.

The available information clearly supports the theory that analgesics and painkillers play an active role in the chronification of headache, which is a real concern for the medical community considering the high number of available over-the-counter analgesics. Furthermore, primary therapies such as triptans are also involved in MOH development after chronic use and there is even weaker evidence to explain the underlying pathways that cause this occurrence. At the moment the most probable mechanism of triptan-induced MOH is "*induction of neural adaptations that result in a state of latent sensitization, which might increase sensitivity to migraine triggers"* [108], in addition, *"triptan administration promotes increased expression of neuronal nitric oxide synthase in dural afferents, which is critical for enhanced sensitivity to environmental stress, which is a biological basis for increased frequency of headache following*" [109].

Certainly, current knowledge regarding MOH and other types of headache chronification caused by the use of therapy is still lacking although the results from many research reports are available. However, until a deeper scientific understanding is available regarding this relatively new entity, it becomes necessary to improve the diagnostic criteria and methods, enhance treatment protocols, and provide proper monitoring not only to chronic primary headache patients but also to each one suffering from a chronic pain condition.

Until a more precise and wider scope of information is available, prevention remains the best, most cost-effective option used to prevent headache treatment abuse-related complications. When the disorder of MOH and drug-induced headache presents, the main treatment must be treatment withdrawal and even then the discussion on what is the best withdrawal method (stationary vs. ambulatory) still remains inconclusive [110]; as a preventive strategy, drug combinations must be avoided as much as possible and high-risk patients who develop MOH must be regularly evaluated to ensure that no late complications are showing up during long-term treatment.

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