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EDITORIAL

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Chronic daily headache: how to manage it?

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Abstract The role of daily analgesic use (also called abuse) in chronic daily headache (CDH) for the maintenance of chronic headache is discussed. The comprehension of the underlying mechanisms of actions is lacking mainly because of the absence of animal models. The abuse should be considered as a compulsive behavior rather than linked to the type of analgesic used and related both to "how" the drug is taken and to "what" drug is used. Moreover, there is no evidence of addictive personality in these patients, and also predictive factors for the long-term outcomes are inconsistent. In the literature specific indications are lacking for the treatment to be performed in these patients. In conclusion, the main problem for these patients is to manage their headaches, and the aim of the therapy should be to enable patients to feel in control of their migraine rather than feel that migraine or analgesic drugs control them.

Key words Chronic headache • Analgesics • Treatment • Abuse

Introduction

Headache occurs at some time in almost everyone during one's lifetime; in the great majority of cases these headaches are a nuisance, whereas in rare cases they are disabling. From then on these headaches have been classified in a number of definitions such as: highly frequent migraine, daily headaches, chronic headaches, chronic cluster headache, hemicrania continua and so on.

When headaches increasingly worsen the quality of life, then analgesic use becomes near daily, pain is continuous and the patients are classified, according to their actual condition, as suffering from chronic daily headache (CDH). In this stage of disease, the clinical picture induces a clear and shared diagnosis that, by contrast, is not universally accepted nor clearly stated by the classification of the International Headache Society (IHS) [1]. Moreover, in the course of worsening of the disease, it is unclear and difficult to define when the headache or migraine turns into CDH.

In these patients, quality of life is significantly reduced, as indicated by many items of the Short Form (SF)-36 scale. The items more affected, in comparison with the normal population, are: role-physical, bodily pain, mental health and role-emotional. The comparison with migraine patients shows differences in both the physical and mental scores.

Nevertheless, in the IHS classification the issue of CDH was not fully addressed, and settlement of this controversial matter is needed. In fact, it is obvious that in the absence of a common definition of CDH it is impossible to develop guidelines for the treatment and evaluation of outcomes [2].

This paper outlines some problems regarding CDH, suggests a critical point of view on drug use, or abuse, and stimulates a discussion in light of the conflicting literature reports.

Nosographic aspects of CDH

Chronic headaches are an important problem for many headache centers around the world. At the same time, terms used to indicate frequent headaches (over 15 episodes per month) are many (Table 1) and probably do not imply iden-

Table 1 Terms used to indicate highly frequent headaches

Terminology	Reference
Chronic daily headache	Silberstein et al. [3, 4]
Chronic migraine	Manzoni et al. [5]
Chronic tension-type headache	Silberstein et al. [3]
Chronicized migraine	Sicuteri et al. [6]
Hemicrania continua	Silberstein et al. [3]
Migraine with interparoxysmal headache	Manzoni et al. [5]
Mixed headache (migraine plus tension-type headache)	–
New daily persistent headache	Silberstein et al. [3]
Transformational migraine[a]	–
Persistent daily headache	Mathew [7]
Evolutive migraine	Mathew [8]
Transformed migraine	Mathew [8]

[a] Used by psychologists

tical clinical situations. Looking at these terms, it becomes clear that there are two items involved in this nosographic attempt: the first one is the presence of headaches classified only by clinical patterns (chronic daily, tension chronic, etc), while the second item involves a concept of transformation, evolution from migraine to a new ill status.

The natural history of these patients indicates that the majority of them move from a history of migraine into a near daily headache with clinical features closer to tension-type headache than to migraine attacks [5].

Recently, Pascual et al. [9] reported that about 40% of patients attending a specialized headache clinic met the CDH criteria, and most of these patients (80%) overused symptomatic medications. These data should be considered specific for headache clinics, and cannot be extrapolated to the general population, where the prevalence of chronic headache, with or without analgesic overuse, is around 1%–3% [10–13].

The real incidence of this problem is undefined. In a study oriented to recognize headaches associated with overuse of analgesic drugs in a population of headache patients treated in a Norwegian neurological center, Bekkelund and Salvesen found that 28% of 945 patients reported headache 3 days or more per week and used analgesic drugs on a daily basis [14]. In this series a specific diagnosis of headache was given by neurologists in 51% of the patients, but only two patients suffered from a possible drug-associated headache.

Pathophysiology of CDH

Chronic headache has been defined as a highly frequent headache. However, chronic tension headache is just - and is always - an extension of the acute variety [15]. Probably these two varieties differ essentially.

In clinical experience, CDH also clearly differs from paroxysmal headaches, which are unresponsive or poorly sensitive to the majority of analgesic drugs. In fact, patients report that they take drugs in an attempt to prevent the oncoming or feared headache, but this prevention is often useless; therefore, they continue with a poor quality of life. Moreover, these patients are resistant to prophylactic therapies and suspension of analgesic drugs dramatically (but temporarily) improves the situation. These features suggest different pathophysiological mechanisms of this chronic pain versus the acute pain of headaches and migraine.

Increased tenderness of myofascial tissues is a normal finding in CDH patients, and painful impulses from these tissues play a relevant role in the pathophysiology of tension-type headache [16]. The central sensitization and the increased excitability of neurons induced by prolonged nociceptive stimuli seem to be crucial factors in the pathophysiology of chronic pain [17]. This type of sensitization is associated with activation of neural nitric oxide synthase (nNOS) [18], and the prolonged elevation of NO at the spinal level contributes to the maintenance of central sensitization in primates [19].

In humans, the score of muscle hardness in patients with tension-type headache was significantly reduced by treatment with a NOS inhibitor (L-*N*-methyl arginine hydrochloride), while tenderness was not affected [20]. The discrepancies in these results may reflect the fact that in this study tenderness also decreased after treatment and not after placebo. It should be noted, however, that these parameters are rather stable features in these patients, and possibly an acute experiment could not elicit clinically measurable responses. These results support central sensitization as a crucial mechanism in the chronicization of head pain, and the reduction of nNOS could represent a means of future treatment of CDH as well as of other chronic pain [21].

The chronic use of analgesic compounds may contribute to the development of chronic headache. CDH associated with daily drug use may be due to a rebound effect, wherein medication withdrawal triggers the next headache, which requires other analgesic drugs, leading to a vicious cycle of drug-headache-drug. In this situation, drugs that maintain sustained levels might prevent the development of drug-induced headache [22].

In patients overusing drugs, the discontinuation of analgesic drugs could increase the activity of on-cells in the pain modulation system of the brainstem and could enhance the response to any painful or non-painful stimuli, with a mech-

anism similar to narcotic withdrawal [23]. Continued high fluctuations of analgesics could result in resetting the pain control mechanisms in susceptible individuals, perhaps enhancing central sensitization through NMDA receptors or blocking antinociceptive changes. Compensatory adaptive changes may not be enough to compensate the drug tolerance, and when the drug levels are low the response is renewed. Drug overuse may, in part, prevent the occurrence of antinociceptive adaptive changes [23].

Unfortunately, the use of long-acting medications, such as analgesics in long acting devices and with long half-lives, is not widespread among headache sufferers. By contrast, the use of ergot derivatives (drugs with long half-lives) has decreased in the last few years and has been replaced by the use of triptans (drugs with short half-lives).

There is evidence, obtained in animals, supporting the role of serotonin in nociception, and the antinociceptive activity of some non-steroidal anti-inflammatory drugs (NSAIDs) has been proved to be mediated by the serotonergic system [24]. The same drugs are also used widely in the treatment of headaches and migraine attacks. Evidence of an influence of these drugs on opioid systems has also been reported. These data suggest possible links between the serotonergic system and the endogenous opioid systems, well known to be the main systems involved in the final modulation of pain control and of the reward mechanism. In this way, the same neurotransmitters play a role in modulating nociception and reward mechanisms, and this suggests that drugs acting on these pathways could induce or favor the reward behavior.

The main problem regarding the role of daily analgesic use (or so-called abuse) in the maintenance of chronic headache depends on the lack of animal models for evaluating, in an experimental setting, the relationship between drug use and headache.

There is a lack of prospective and well-controlled clinical trials. Objective and ethical reasons do not allow the design of placebo-controlled trials to measure the habit potency of antimigraine drugs in headache sufferers. Moreover, there appears to be some confusion among the terms "medication misuse headache", "overuse headache" and "abuse headache". Therefore, abuse must be considered to be a compulsive behavior not necessarily linked to the type of analgesic used but related more to "how" the drug is taken than to "what" drug is used. Finally, there is no evidence of addictive personality in these patients [25], and a correlation between sensation-seeking behaviors and intensity dependence of auditory potentials is lacking in patients with chronic headache [26].

To treat or not to treat

It is generally accepted that it is difficult to treat patients suffering from CDH, and more so when they overuse antimigraine drugs, even though the poor quality of life implies that an effective management in trying to help these patients is important. The rationale for all treatments is the positive evaluation of the cost-benefit or risk-benefit ratio. Therefore, starting a treatment implies knowledge of the expected results.

A series of studies was performed to evaluate the efficacy of different therapeutic strategies in treating CDH with a large variability of population samples and outcomes. The unique point recognized by all authors was withdrawal from analgesics as the preliminary condition necessary to improve the clinical condition. This condition is also listed in IHS criteria for the diagnosis of drug-related headache (point 8 of the classification).

To determine a therapeutic strategy, it is relevant to know the prognostic factors (if any) for long-term outcome. The type of starting headache was referred to as a significant parameter in conditioning the evolution of the headache history, whereas the data in the literature are conflicting (Table 2).

Table 2 Factors that were significantly different for the long-term outcome of CDH treatment

	Patients, n	Initial headache type	Headache duration	Type of abused drug	Overuse duration	Type of withdrawal	Prophylatic treatment	Gender
Tfelt-Hansen, Aebelholt Krabbe [27]	40	–	–	–	$p<0.05$	–	NS	-
Diener et al. [31]	103	Migraine ($p<0.05$)	–	Ergot vs. other ($p<0.03$)	$p<0.05$	–	–	–
Schnider et al. [28]	38	Migraine ($p<0.01$)	–	–	$p<0.05$	–	–	NS
Suhr et al. [31]	101	TTH vs. others	–	Monotherapy vs. polytherapy	NS	–	–	F vs. M
Pini et al. [29]	102	-	$p<0.01$	NS	$p<0.03$	NS	NS	NS
Lu et al. [40]	106	NS	$p<0.05$	–	$p<0.05$	-	-	NS

TTH, tension-type headache; *NS*, not significant

The duration of chronic drug overuse was found by some authors to be a significant parameter [27–29]; for example, the type of analgesic abused was relevant in maintaining CDH and drug abuse [29–31]. On the other hand, others did not find any significant prognostic factor for long-term outcome in CDH patients [32, 33].

The literature is lacking in indications for the type of treatment to perform in these patients. Treatment should be divided into two distinct steps: the first one, the suspension of the analgesic drugs, and the second one, the prophylactic treatment to prevent relapse in chronic headache and drug overuse.

The suspension of overused headache medications results in withdrawal headaches, often associated with nausea and vomiting. The duration of these withdrawal headaches changes, depending upon the drugs overused, being longer for analgesics than for triptans [34]. Moreover, these latter patients use fewer rescue medications than do ergot and analgesic overusers.

Hering and Steiner [35] solved the problem with an abrupt withdrawal of analgesics in 46 outpatients. They were supported with an adequate explanation of the disorder, regular follow-up, amitriptyline (10 mg at night), and naproxen (500 mg) for the relief of headache symptoms. The study reported an 80% reduction of the headache index at a six-month follow-up.

Silberstein proposed that outpatients gradually taper the overused medications at a rate of 10% per week, often replacing them with NSAIDs [23].

A German Migraine Society's consensus paper recommended outpatient withdrawal for highly motivated patients who do not take barbiturate-containing analgesics, suggesting hospitalization only for these latter patients [36].

Zed et al. [37] examined numerous therapies for the acute management of CDH, although no rigorously conducted clinical trials were identified. Therapies evaluated included the abrupt withdrawal of analgesics, initiation of dihydroergotamine, NSAIDs, methylergonovine, dihydroergotamine, sumatriptan, amitriptyline, dexamethasone, piracetam, prothipendyl, and valproate.

In conclusion, almost all drugs available for the treatment of headache were used, but the literature concerning the treatment of patients with CDH is scant and of poor quality, making it difficult for clinicians to choose an appropriate therapy. It appears that complete withdrawal of the overused medications is required for favorable long-term results [37].

I did not find any differences in reducing the headache severity and analgesic consumption among different treatments both in the withdrawal phase and in the choice of prophylactic therapy. There were no differences in the suspension of analgesics between inpatients and outpatients, with the exception of patients using barbiturates, nor were long-term outcomes affected by the type of prophylactic therapy followed [29].

In the following phase, pharmacological treatment should be integrated with psychological, behavioral and physical interventions, even if there is no scientific evidence for a specific efficacy of this treatment that, anyway, seems to be reasonable.

The initial success rate in the treatment of CDH is quite variable, ranging between 47% according to Walker et al. [38] and 97% according to Katsarava et al. [34].

The long-term outcome of these patients is uncertain. In our first study [39], we reported that there were no significant differences among several withdrawal treatments with respect to the final outcome. The follow-up study confirmed these data, and the history of these patients did not give information about the efficacy of treatment. All therapeutic attempts elicited a similar success rate; moreover, the relapse in chronic headache and drug overuse showed a high rate 4 years later. Causes and reasons underlying this relapse are numerous, and we do agree that one of them is noncompliance to the pharmacological and behavioral treatments. But the question is only displaced: why did these patients not comply with the treatments?

Nevertheless, after 4 years the relapse rate into drug overuse in our patients ranged around 60%, whereas Lu et al. [40] found a 44% relapse rate into drug overuse after two years. It may not be so surprising considering that the relapse rate reported by Bigal et al. [41] was 30% and that by Katsarava et al. [34] was about 35% after only a one-year follow-up, with an initial success rate of 97% in the Katsarava series vs. an initial success rate of 60% in our patients [39]. These data suggest that the increasing frequency in relapse into drug overuse is related to the prolongation of the follow-up period.

A problem within the problem regards chronic daily headache in children and adolescents. In these patients, the positive family history predisposes children to develop headache, like other environmental, biological and psychological processes. Data are lacking about which therapies are better for children, and the management is derived from CDH experience in adults [42]. This way of action was encouraged by Hering-Hanit et al. [43], who showed a successful withdrawal from analgesic abuse in a group of youngsters with chronic daily headache. In a series of 26 children over a three-year follow-up, these authors achieved the complete withdrawal from analgesics in 20 cases, and only one child maintained the chronic headache and daily drug use.

Conclusions

At the moment, there is a sole answer to the question: to treat or not to treat? In fact, the overall consensus in these patients is "stop the daily analgesic use" before starting any

other therapeutic venture. Therefore, the answer could be: first of all, stop analgesic medications.

The efficacy of subsequent treatments has not been well evaluated. There is agreement on a variety of treatments, even pharmacological and behavioral, but there is no consensus on precise indications or guidelines. Anyway, to start with some treatment after the withdrawal phase is generally accepted. In the literature there is poor evidence on the efficacy of treatments, and scheduled strategies seem to be founded more on the good will of patients than on the pharmacological properties of drugs used.

It is clear that patients relapsing into chronic use are subjects with a worse quality of life, but these patients need care and help by doctors more than others. Moreover, these patients are stronger drug "abusers", often taking mixtures (especially in Europe), with the majority showing psychological disturbances [44]. Patients who overuse medication may feel ashamed and unable to provide an accurate history of drug abuse. The condition of medication rebound should be explained as a part of the natural history of migraine.

The use of antimigraine drugs needs to be scheduled and monitored by patients themselves, to educate them to be aware to control their own headaches, and feel this ill as a part of their own lives, more than as an external accident against which there are no defences and the use of a drug is the only response. In this way, patients feel as guilty as addicts, and this anxiety increases the fear of the pain enhancing the central sensitization, and facilitating the relapse in CDH and drug overuse. In fact, some reports suggested a compulsive mode of assumption of antimigraine analgesics by chronic sufferers, i.e. time-scheduled assumption, preventive assumption of analgesic because of a forecast of headache linked to a particular life event (trip, job, dinner meeting, etc.). This fact could suggest the role of the drug significance in abuse or addictive behavior present in chronic headache patients.

The main problem for these patients is to manage their headaches, and I agree with Dowson [11] who concluded that both prophylactic and acute treatments were needed, but the aim of therapy should be to enable patients to feel in control of their migraine rather than feel that migraine controls them. This conclusion leads to considering analgesic drugs as a resource for both patients and doctors, which should be managed to improve the quality of life and not only considered as a risk for potentially addictive drugs. Finally, we should not forget to strengthen the idea that the task of our activity is to improve the quality of life of our patients.

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