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## Frequent analgesics consumption in migraineurs: comparison between chronic and episodic migraineurs

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**Abstract** To assess the frequent consumption of symptomatic medications in migraineurs, we consecutively recruited 536 migraineurs from a headache clinic. Among them, 194 (36.2%) had chronic migraine and 342 had episodic migraine. When grouped according to duration of headache, the proportion of patients with chronic migraine increased from 25.5% to 50.9% as headache history increased from <1 to >20 years. The percentage of patients with frequent analgesics consumption also increased with the duration of headache, in patients with both chronic migraine (from 25.0% to 85.7%) and episodic migraine (from

20.0% to 59.3%). Nonetheless, patients with chronic migraine had a higher prevalence of frequent consumption of abortive medications than patients with episodic migraine regardless of duration of headache history, and the common odds ratio across strata of headache duration was 2.8 (95% confidence interval, 1.9–4.1). However, we found that a long headache history is an important risk factor for frequent consumption of symptomatic medications in migraineurs in patients with both episodic migraine and chronic migraine.

**Key words** Chronic daily headache • Chronic migraine • Drug overuse

### Introduction

Chronic daily headache (CDH) accounts for 40% or more of patients visiting headache clinics, and chronic migraine is the most common form of CDH [1–5]. Many patients with CDH (50%–82%) use excessive amounts of analgesics or other medications to abort the frequent attacks of headache [1, 6–9]. Frequent consumption of daily symptomatic medication is more common in patients with chronic migraine than in those with other forms of CDH [8]. While overusing these medications, patients are usually refractory to prophylactic treatment.

Discontinuation of overused medications usually results in the development of withdrawal symptoms and a short period of exacerbated headache followed by improvement of headache [8, 10]. Iatrogenic deterioration of migraine through analgesics or ergot abuse is generally believed to be one of the major causes of transformation from episodic migraine to chronic migraine. However, medication overuse was also interpreted as the deterioration of headache or neuroticism [6]. While some studies suggested that drug overuse was the cause rather than the result of frequent headache [1, 4, 7, 11], other studies found that chronic overuse of analgesics did not increase the frequency of headache [12, 13].

It is difficult at present to determine whether the overuse of symptomatic medications facilitates the onset of CDH or the overuse is just an incidental characteristic accompanying its development. Nevertheless, drug overuse remains a troublesome problem in chronic headache patients. In our daily practice here in Taiwan, chronic headache with analgesics overuse is also a major problem. However, no local clinical study has been performed to evaluate this issue. To clarify the role of frequent consumption of symptomatic medications in migraineurs, we examined the prevalence of chronic daily headache in our headache clinic and compared the clinical profiles of chronic migraine patients with those of episodic migraine patients.

## Patients and methods

We recruited consecutive patients with the chief complaint of migraine headache through the headache clinic at Sin-Lau Christian Hospital in Tainan, Taiwan, from January 1995 to December 1997. The diagnosis of migraine followed the operational diagnostic criteria proposed by the International Headache Society (IHS) published in 1988 [14]. We included all patients who fulfilled IHS criteria for either migraine without aura (IHS code, 1.1) or migraine with aura (IHS code, 1.2). Patients with chronic tension-type headache, new daily persistent headache, or hemicrania continua were excluded. Chronic migraine was diagnosed when the headache fulfilled the following criteria: daily or near-daily attacks lasting more than 4 hours if not treated, occurring more than 15 days per month for more than one month, and fulfilling the proposed headache classification for chronic daily headache described by Silberstein and Lipton [5].

The information in this study was collected by review of medical records without invasive procedure. No personal data were presented individually. Informed consent was not required according to the guidelines set by the National Science Council of Taiwan, R.O.C., the governmental agency in charge of issues regarding research ethics.

We collected information on characteristics of headache using a semistructured questionnaire at the first visit of each patient, which incorporated all items required for diagnosing headache according to IHS criteria. The questionnaire was initially completed by a well-trained assistant through interviewing the patient and then validated

by the first author. Patients were asked to report all kinds of headache that bothered them. For each type of headache, we recorded: the nature, duration, location, frequency, and intensity of headache (mild, moderate, severe or intractable); the aggravating factors, including the influence of routine physical activities; the relieving factors; and the associated symptoms, including nausea, vomiting, photophobia, and phonophobia. Sleep habits and medication consumption were also recorded. All patients underwent detailed neurological and physical examinations, and electroencephalographic and neuroimaging studies were conducted on those with suspected organic disorders. We defined "frequent consumption" as taking abortive medications more than 3 treatment days per month for headache. In addition, we followed the original description in each cited paper when we used their comments [15, 16].

To evaluate the association between chronic migraine and headache history, we categorized the patients into six groups according to the duration of headache: >1 year, 1–5 years, 6–10 years, 11–15 years, 16–20 years, and <20 years. To evaluate the association between frequent analgesic consumption and duration of headache, we compared the prevalence of frequent analgesics consumption among the chronic migraine patients by these six groups. The prevalence of frequent analgesics consumption among patients with episodic migraine was also calculated for comparison. Differences in the prevalence were evaluated by chi-square test, and differences in the odds ratios were evaluated by the Breslow-Day test for homogeneity of the odds ratios. All statistical tests were performed using the SAS package at a two-tailed significant level of 0.05.

## Results

Of the 1965 patients who visited the headache clinic during the 3-year study period, 1088 (55.4%) had migraine. Of these, 536 patients (65 with aura and 471 without aura) met the selection criteria and were included in this analysis. The female-to-male ratio was 5:3, and the mean age was 40.6 years (SD=13.9; range, 5–81 years). The mean duration of headache was 10.3 years (SD=8.6 years).

There were 194 patients with chronic migraine (36.2%), and most of these (69.1%) used analgesics frequently (Table 1). The prevalence of frequent analgesics consumption was 43.3% among the 342 patients with episodic migraine, sig-

**Table 1** Characteristics of 536 patients with migraine, by migraine type

	Chronic migraine (n=194)	Episodic migraine (n=342)	<i>p</i> <sup>a</sup>
Men, n (%)	28 (14.4)	57 (16.7)	NS
Frequent analgesics use, n (%)	134 (69.1)	148 (43.3)	<0.001
Family history, n (%)	23 (11.9)	30 (8.8)	NS
Disturbed sleep, n (%)	148 (76.3)	261 (76.3)	NS

<sup>a</sup>*p* value for chi-square test  
NS, not significant

nificantly lower than that for chronic migraine ( $p<0.001$ ). The distributions of male gender, patients with family history of chronic headache, and patients with sleep disturbed by headache were similar between the two groups.

Most migraineurs (about 80%) came to our clinic because of the poor response to the usual abortive medications, while others (about 20%) came because of partial effectiveness or short response. We did not collect the response rate and the drugs used in each attack although clinically, in each attack, most patients took 1–2 drugs except in the few cases with intractable situation. They commonly took simple analgesic or combination drugs for common cold to abort their headaches; the medications most frequently used were: acetaminophen (88.5%), anhydrous caffeine (80.8%), methylephedrine (42.3%), chlorpheniramine maleate (40.8%), guaifenesin (23.1%), ethenzamide (23.1%), aspirin (15.4%), phenylpropranolamine (11.5%), and Chinese medications (7.7%). These drugs were either

prescribed by local medical doctors or bought directly by the patients from a local pharmacy.

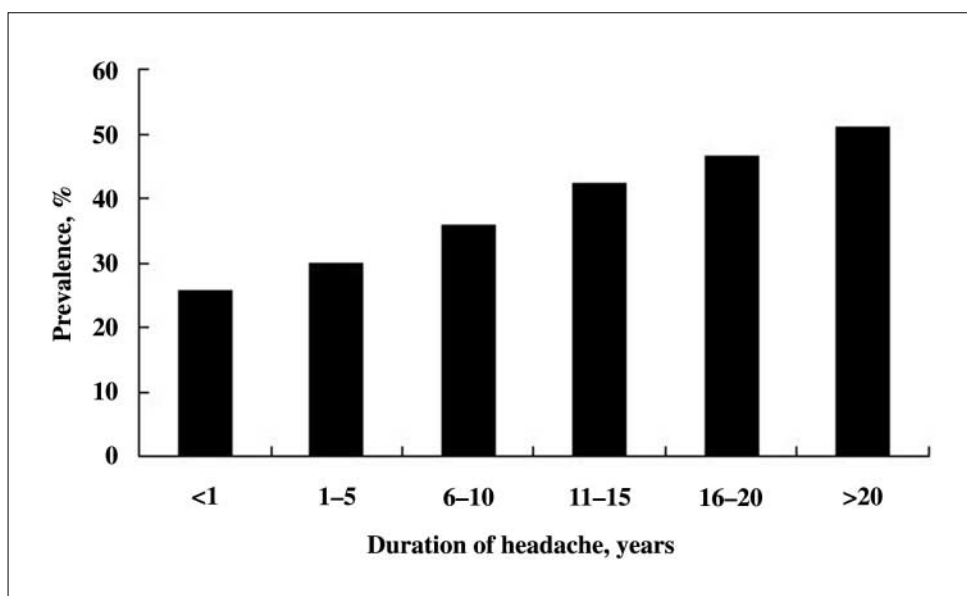
The prevalence of chronic migraine among these headache patients increased from 25.5% to 50.9% as the duration of headache increased (Table 2, Fig. 1). For both chronic migraine and episodic migraine, the proportion of patients with frequent analgesics consumption also increased (from 25.0% to 85.7% in chronic migraine patients and from 20.0% to 59.3% in episodic migraine patients) as the duration of headache history increased ( $p<0.001$ ; Fig. 2). The prevalence of frequent analgesics consumption was higher in patients with chronic migraine than those with episodic migraine in all strata classified by duration of headache history, and the differences in odds ratio among the strata were not statistically significant (Breslow-Day test,  $p=0.744$ ). The Mantel-Haenszel common odds ratio (OR) across the strata was 2.8 with a 95% confidence interval from 1.9 to 4.1.

**Table 2** Prevalence of chronic migraine and frequent analgesics consumption among 536 patients with migraine, by history of headache

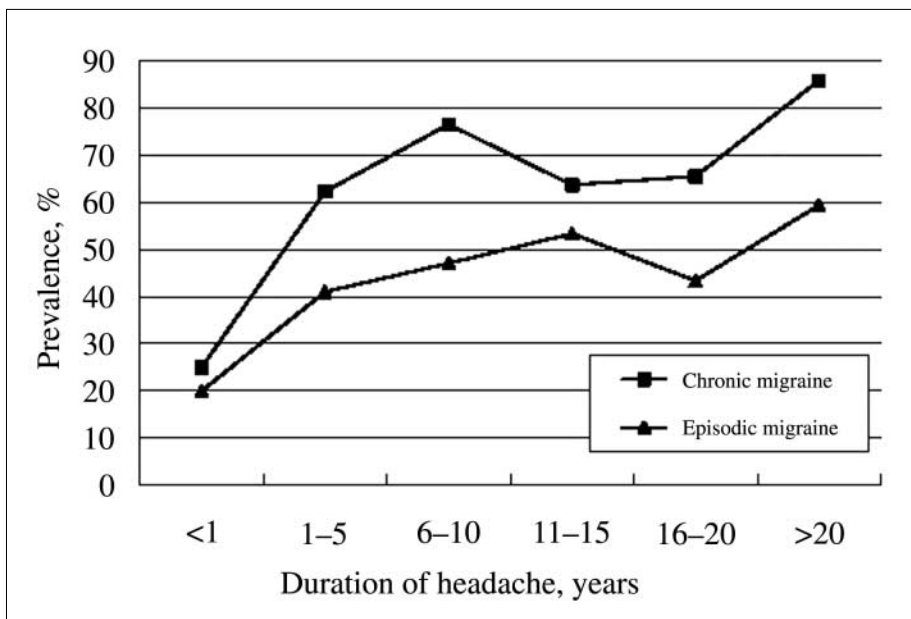
Headache duration, years	Patients, n (%)		
	Total	Chronic migraine <sup>a</sup>	Frequent analgesics consumption <sup>b</sup>
<1	47	12 (25.5)	10 (21.3)
1–5	150	45 (30.0)	71 (47.3)
6–10	202	72 (35.6)	116 (57.4)
11–15	26	11 (42.3)	15 (57.7)
16–20	56	26 (46.4)	30 (53.6)
>20	55	28 (50.9)	40 (72.7)

<sup>a</sup> $p=0.024$  on chi-square test

<sup>b</sup> $p<0.001$  on chi-square test



**Fig. 1** Prevalence of chronic migraine among 536 patients with migraine (with or without aura)



**Fig. 2** Prevalence of frequent analgesics consumption among 536 patients with migraine (with or without aura)

## Discussion

Migraine is no longer considered to be a purely episodic disorder. In patients with a long history of migraine, headache may initially show an increasing frequency of attacks and finally become a daily event, a condition called “chronic daily headache.” Year by year, the proportion of patients with chronic migraine should therefore increase; this was found among our patients. Factors affecting the course of migraine have not been clearly identified. In a paper on “status migrainosus,” Couch and Diamond reported that the most common precipitating events were psychiatric factors, medication abuse and withdrawal, diet, and changes in estrogen levels [17]. Mathew et al. [4] were probably the first researchers to study through a systematic approach the problem of transformation of migraine. They found that some factors such as abnormal personality profile, excessive stress, hypertension, and abuse of analgesics or ergotamine were associated with the transformation of migraine [4].

The present study confirms the strong association of frequent analgesic consumption with chronic migraine. We did not find any difference in gender ratio, family history, or sleep disturbance between patients with chronic migraine and those with episodic migraine.

Prophylactic therapy should be considered when the frequency of headache attacks is greater than two or three per month and when headaches cannot be treated satisfactorily with optimized abortive treatment [15, 18]. Nearly all patients used abortive drugs before they came to our headache clinic. Only some patients took an incomplete

course of prophylactic treatment due to other comorbidity disorders. While the importance of medication overuse in chronic migraine is emphasized, there is no agreement in the literature and various terms and definitions have been used. Some believe that overuse occurs when patients take abortive medication more than 2–3 treatment days per week for any drug. Silberstein et al. [19] differentiated between the drugs classes, and stated that overuse can be characterized by as little as 3 doses of simple analgesics or non-steroidal anti-inflammatory drugs (NSAIDs) more than 5 days/week, combination analgesics or triptans more than 3 days/week, ergotamine tartrate more than 2 days/week, or opioids more than 2 times/week. By the new IHS definition, medication-overuse headache refers to those headaches presenting over 15 days/month, which develop or markedly worsen after at least 3 months’ regular drug overuse. The amount of overuse depends on the type of drug: ergotamine, triptans, opioids, and combination analgesics  $\geq 10$  days/month; and simple analgesics  $\geq 15$  days/month. Although the term “frequent” is generic, we used “frequent consumption” in order not to be confused with “abuse” and “overuse” that are used in the literatures. We defined “frequent consumption” as taking abortive medications more than 3 treatment days per month for headache. In addition, we followed the original description in each cited paper when we used their comments.

Most patients with CDH used excessive amounts of analgesics, sedative-caffeine-analgesic combinations, or ergotamine on a nearly daily basis. Analgesics may suppress the activity of central serotonergic pathways involved in pain regulation [20, 21]. Overuse of sympto-

matic medications was considered to be a major factor that influences and perpetuates migraine into CDH. Withdrawal of daily symptomatic medications and initiation of prophylactic antimigraine therapy reduces the attacks of headache. Although the association between chronic headache and regular intake of analgesics is a common clinical observation, it is not necessarily a causal relationship. Nevertheless, frequent analgesics consumption and medication overuse are still different between episodic migraine and chronic migraine. As revealed by our study, frequent analgesics consumption is much higher among chronic migraine patients (69.1%) than episodic migraine patients (43.3%).

Excessive use of medications can be interpreted as the effects of chronic pain or neuroticism. Analgesics abuse was reported by 74% of subjects with chronic migraine transformed from episodic attacks, but it seemed to be a consequence of the deterioration of illness [6]. There was no significant difference in symptomatic drugs consumption between the control group and chronic migraine group before chronicity [6]. Among the migraineurs in our study, the patient groups with longer headache durations had higher percentages of frequent medication consumption. Long headache history is a risk factor for frequent or habitual medication consumption in patients with both episodic migraine and chronic migraine.

Drug overuse in chronic headache cannot be explained merely by frequent attacks of headache. A study examined 235 migraineurs with and without a history of drug abuse who were taken off their usual medications and, in most cases, placed on interval therapy such as beta-blockers or antiserotonin agents, with or without antidepressants [11]. The results were encouraging initially, but the relapse rate was over 50%. The researcher concluded that "excessive intake of these drugs is much more a cause than a consequence of frequent and chronic migraine," which was sup-

ported by the observation of the relapses of migraineurs who had been placed on analgesics for other disorders [11]. In our study, the prevalence of frequent analgesics consumption was significantly higher in those with chronic migraine than in those with episodic migraine (overall OR = 2.8). This result provides further evidence for a constant relationship between frequent analgesics consumption and CDH.

It should also be noted that the prevalence of frequent analgesics consumption also increased in those without chronic migraine. In other words, there were patients who had frequent analgesics consumption for a long time without the transformation of migraine. Many reports revealed that 10%–30% of patients with CDH remained intractable even under intensive detoxification and prophylactic treatment [16, 22, 23]. The relationship between frequent analgesics consumption and migraine transformation is by no means a simple one. The roles of behavior, genetic predisposition, and the activity of nociceptive regulation system, especially the serotonergic pathways in this complex need to be clarified in further studies.

In conclusion, frequent analgesics consumption is not only a common problem in chronic migraineurs, but also often seen in those with episodic migraine. There are increasing trends of both frequent analgesic consumption and CDH ratio in migraineurs as disease progressed into the chronic stage. However, there is a steady ratio of the prevalence of frequent analgesics consumption in patients with chronic migraine to that in those with episodic migraine by the years of headache history. Although the clinical significance about this high ratio in chronic migraine remains a problem of debate, it is clear that long headache history is also an important risk for frequent analgesic consumption in migraineurs. We hope that this result helps clarify the role of analgesics consumption in chronic migraine.

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