# Neurological Sciences

**Official Journal of the Italian Neurological Society**
**Founded by Renato Boeri (1979–1993) continued by Giuliano Avanzini (until 2011)**



**Continuation of**
**The Italian Journal**
**of Neurological Sciences**

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# Neurological Sciences

## Official Journal of the Italian Neurological Society

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Neurological Sciences is intended to provide a medium for the communication of results and ideas in the field of neuroscience. The journal welcomes contributions in both the basic and clinical aspects of the neurosciences. The official language of the journal is English. Reports are published in the form of original articles, short communications, editorials, reviews and case reports. Original articles present the results of experimental or clinical studies in the neurosciences, while short communications are succinct reports permitting the rapid publication of novel results. Original contributions may be submitted for the special sections History of Neurology, Health Care and Neurological Digressions - a forum for cultural topics related to the neurosciences. The journal also publishes correspondence book reviews, meeting reports and announcements.

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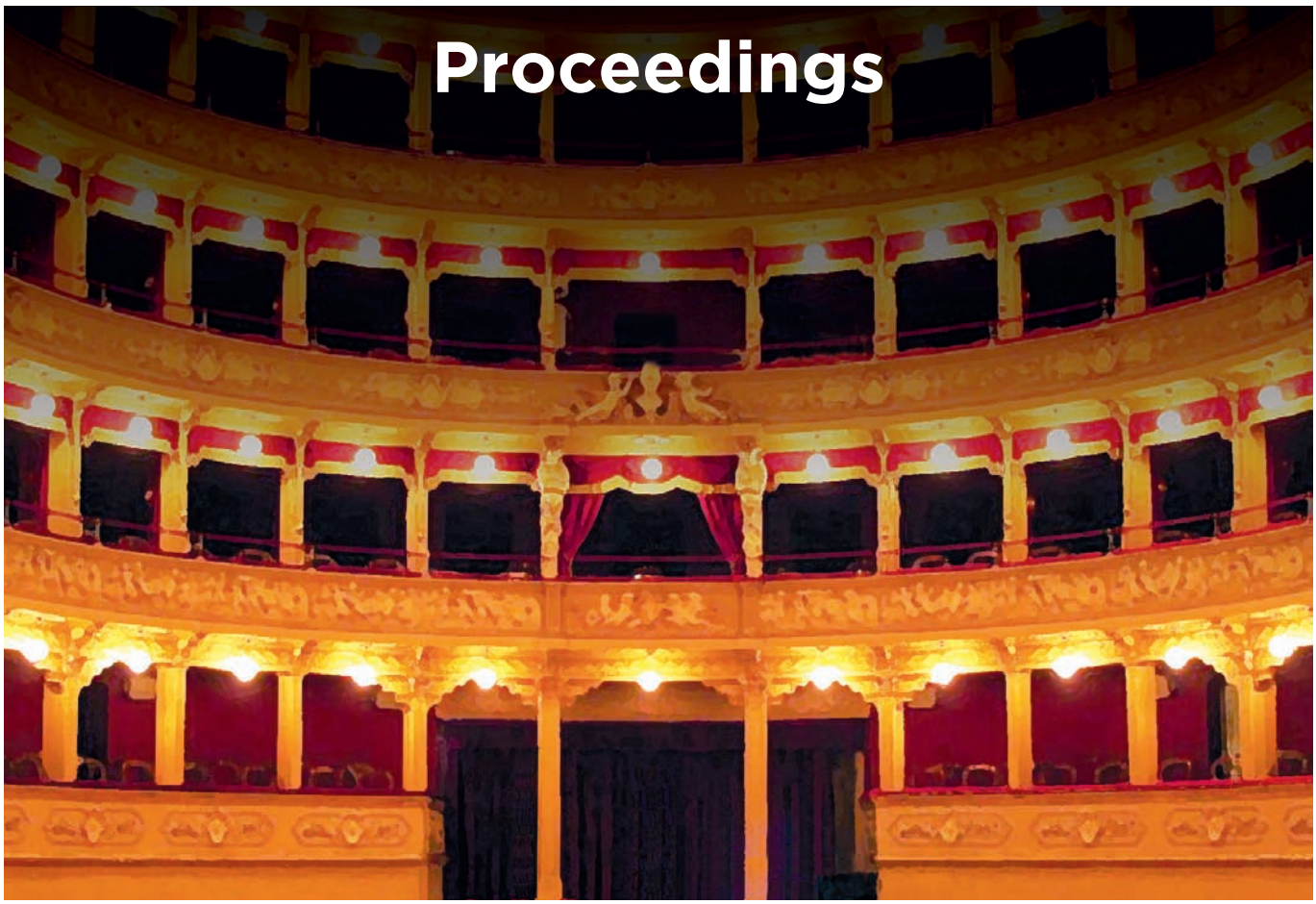
# HEADACHE AND SOCIAL CONTEXT

Asti, Italy
29-31 May 2014

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6th National ANIRCEF Congress

# HEADACHE AND SOCIAL CONTEXT

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The ANIRCEF Congress, which takes place this year in Asti, Piemonte, will examine social aspects of headache. The Congress will be concerned with the impact of headache on the worlds of work, school, diet and media, particularly since headache is the second most important condition in terms of incidence worldwide. The Congress will seek to evaluate the extent to which headache is responsible for absences, reduced productivity and inefficient working in various workplace contexts.

ANIRCEF has carried out a study on headache incidence using a brief questionnaire. The study was performed in collaboration with pharmacists of Piemonte who administered the questionnaire to persons as they were buying medications. From the data obtained it would seem that the incidence of migraine is greatly underestimated; that it is also underdiagnosed, and often inadequately treated. The full results will be presented at the Congress.

Ample space at will also be given to the issue of headache and diet. Much has been written and spoken about the links between diet and headache, but unfortunately the available information is often confused and contradictory. There will be sections on nutraceuticals and their potential for treating headache, as well local treatments for headache of both the traditional and 'alternative' types.

Another intriguing topic being examined by this year is the relation of multimediality and the world of communication to headache, in which will be examined how the communication of headache is influenced by different scientific rationales. The aim is to find the right balance between scientific accuracy and the need to communicate.

The Congress will involve a wide range of heath professionals as speakers and participants including specialist neurologists, neurosurgeons, family doctors and pharmacists, who will contribute varied and important elements to the continuing medical education accreditation provided by the Congress.

**Marco Aguggia**

ANIRCEF president and president of VI National ANIRCEF Congress

The Editor in Chief authorizes the publication of the Proceedings of the 6th ANIRCEF National Congress - HEADACHE AND SOCIAL CONTEXT. The authors and the Guest Editor are fully responsible for the scientific contents of the papers.

**Conflict of Interest Statement**

Marco Aguggia declares that he has no conflict of interest related to the publication of this Supplement.

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# Prevention, education and information: the role of the community pharmacist in the management of headaches

**M. Giaccone · F. Baratta · G. Allais · P. Brusa**



**Abstract** Headaches are among the most common disorders of the nervous system. On a global level, it is estimated that the prevalence of headache disorder in adults is 47 %. A proper treatment of headaches requires training of health care personnel, careful diagnosis and recognition of the condition, appropriate treatment with cost-effective drugs, simple changements in lifestyle and patient education. Unfortunately, a large number of people suffering from headache disorders are not diagnosed and treated. The unsatisfied needs in migraine can be faced by involving the pharmacist in the management of the pathology. To really understand which are the activities and the potential of community pharmacies in the management of patients with headache or migraine we took into account studies conducted around the world during the last 5 years. Based on the data collected it is clear that the role of the community pharmacist may be crucial in managing patients with headache or migraine but only if he receives an adequate and continuous education both on the management of therapies and maintains a stable relationship with the medical doctor and/or patient. In Piedmont a specific study to identify migraine sufferers has involved the community pharmacies in the administration of a questionnaire, specially crafted by the Italian Headache Foundation (FICEF non-profit association).

**Keywords** Community pharmacy · Counseling · Headache · Migraine · Patient health education

**Abbreviations**
WHO World Health Organization
OTC Over the counter

## Introduction

The World Health Organization (WHO), in the "Atlas of headache disorders and resources in the world 2011", summarizes the current situation concerning problems related to headaches. According to the WHO, headaches are very common disorders of the nervous system. Headache is painful and invalidating, featuring a small number of primary headaches, in particular migraine, tension-type headache and cluster headache. Headaches can also be triggered by other conditions, such as medication overuse headache. Worldwide, the prevalence in the adult population of current headache disorders (symptomatic at least once in the past year) is 47 %. In the world more than half of adults aged 18–65 years have suffered from headache during the last year and among these people more than 10 % has reported migraine. Globally, headache affects the population for more than 15 days per month from 1.7 to 4 % of cases. Although there are regional variations, the headaches are a global problem that affects people of all ages, races, economic availability and geographical areas. Headache is not only painful, but also creates disability. Headaches are a public health problem due to the large amount of disability and

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economic costs to society (mainly lost work hours and decreased productivity). Moreover, many of those disturbed by headaches do not benefit effective treatments. For example, in the USA and the UK, only 50 % of the subjects detected with migraine had consulted a doctor for reasons related to headache in the previous year and only two-thirds were properly diagnosed. Most of the patients used only over-the-counter (OTC) medications. A proper treatment of headaches requires the training of health workers, careful diagnosis and recognition of symptoms, appropriate treatment using cost-effective medicines, simple changes in lifestyle and patient education. The drugs most commonly used to treat headaches are: painkillers, anti-emetics and prophylactic drugs. However, many people with headaches are not diagnosed and treated [1].

The unsatisfied needs of migraine can be dealt by involving the pharmacist in the management of migraine. In the context of the community pharmacy the work of the pharmacist is not limited to dispensing medicine but also entering into direct relationship with citizens through initiatives in health education, primary and secondary prevention campaigns. Therefore, a trained pharmacist can be actively involved in preventive screening and monitoring of therapeutic adherence.

In this context, the pharmacist can improve incomplete diagnosis referring headache patients with suspected migraine to health care worker. The pharmacist can identify and refer patients who require preventive therapy, can also educate and advise patients receiving preventive therapies on their correct and safe use [2].

Community pharmacies are also potential locations where the risks associated with self-medication could be prevented. The lack of counseling is linked to easy access to OTC medicines that can make patients believe that OTC medicines are always safe. However, studies show that self-medication has potential for abuse and may lead to improper use of drugs, which increases the rate of drug-related problems and may compromise the patient's safety. The community pharmacists have an overall view both of prescriptions and OTC medications that patients are assuming. They have an high level of knowledge and are easily accessible to patients. This situation places them in a privileged position to support self-medication [3].

## The worldwide community pharmacist role in the management of headaches

Given the important role that the community pharmacist may have in the management of patients with headache or migraine, in recent years several studies have dealt with this issue.

In order to really understand which are the activities and the potentiality of community pharmacies in this context, we considered the studies carried out worldwide over the past 5 years.

The keywords used for the bibliographic research have been "community pharmacy" and "headache". The period covered by data has been 2008–2013.

The highlights of the studies that we have considered are reported in chronological order.

### 2008: UK, Germany, Australia

In a study conducted in UK, Germany and Australia, a migraine questionnaire (MQ) was designed to assist pharmacists to detect consumers with migraine suitable for a non-prescription treating with triptans. During the course of the study, 1,353 recruited subjects filled out two independent evaluations with two designated health care providers, a pharmacist and a doctor. The aim was to evaluate the accuracy of the pharmacist evaluation of eligibility for treatment with a triptan with respect to the primary care clinical evaluation. Based on the findings the pharmacists less frequently concluded that a subject was suitable for a triptan (48.8 %) than the physicians (76.8 %). Discrepancy between pharmacists and physicians has been mainly related to the diagnosis of headache. In addition, the pharmacists, using MQ, were more prudent than the physicians in the assessment of cardiovascular contraindications and cardiac risk. In conclusion, the MQ has proven to be an effective instrument to sustain the pharmacist indication of non-prescription triptans [4].

The goal was to evaluate the impact of pharmaceutical care (defined as intensified organized counseling between the patient and the pharmacist) for patients with headache and migraine; a number of 112 pharmacies were randomly allocated to the intervention group or to the control group. The pharmacists in the intervention group participated in a 2-day education program carried out by experts. The intervention group took 201 patients who received pharmaceutical care, while the control group consisted of 209 patients who received standard advice. Based on the findings pharmaceutical care, sometimes not extensive, seems to improve patient's quality of life, even if it has not changed substantially the number and severity of the headache. So a continuous training for pharmacists may improve and/or strengthen the outcomes for patients with headache [5].

### 2009: Malta

In a study conducted in Malta, the purpose was to develop two protocols configured to help pharmacists' care for consumers who seek treatment for headaches and back

pain, and then use the protocols to evaluate the management of pharmacists of these conditions. Ten community pharmacies were involved. Consumers who went to the pharmacy with a prescription, to purchase a specific product or for advice on how to approach the symptoms were enrolled in the study. In this study, patients who required counseling for the management of their symptoms have achieved the highest degree of interaction with the pharmacist. The results suggest a lack of counsel given to consumers who are in the pharmacy to ask for a specific product [6].

2012: Slovenia, Belgium

In the Slovenian study the targets were to evaluate the consulting related to paracetamol through the method of simulated patients and to evaluate the approach of the patient (symptom-based vs. direct requests of products) as a key factor of counseling. The simulated patient methodology was applied in 17 community pharmacies. This study shows that pharmacy staff gave professional counseling (the information most commonly provided were dosage and side effects), particularly in the case of requests based on the symptoms. Patients who have denounced their symptoms have been provided with more detailed advice in terms of demand and supply of information than patients who have requested a specific product. There were no particular differences in the consulting quality between the masters of pharmacy and pharmacy technicians (the small sample size could have elicited this discrepancy) [3].

The observational study based on community pharmacy carried out in Belgium, aimed to evaluate the characteristics of the headache and of the use of drugs by people with regular headaches (headaches that occur minimum once a month) presenting for self-medication. Pharmacy customers who bought an OTC for headache were asked to fill out some questionnaires. The study allowed the identification of underdiagnosis of migraine, low use of prophylaxis for migraine and of triptan and moreover the high prevalence of medication overuse between subjects in search of self-medication for the headache. Based on the findings of this study, recommendations for a better management of headache complaints by community pharmacy must be formulated because the pharmacists are in a front line to improve the recognition of migraine in primary care; they can then play a significant role in the prevention and early detection of excesses in medicine use and the subsequent headache. Furthermore, migraine patients with frequent invalidating attacks that are not living sufficient relief from pain with their current therapy should be referred to a physician to receive other therapeutic options [7].

2013: Thailand, Brazil

Recently in 2013, two studies involved two different developing countries: Thailand and Brazil.

The study conducted in Thailand was designed to evaluate the practice and the knowledge of pharmacy staff in managing the mild to moderate migraines and to compare pharmacists and non-pharmacists in relation to practice and knowledge. The sample included 142 community pharmacies selected randomly. Simulated patients visited the pharmacy to request for the treatment of mild to moderate migraines. The main results of this study were that the majority of pharmacists had insufficient practice and insufficient knowledge regarding the management of mild to moderate migraines. The most part of pharmacists and non-pharmacist staff provides inappropriate question asking, dispensing drugs and giving recommendations for mild to moderate migraine. Many pharmacists unreasonably dispensed prophylactic drugs for the management of migraine, especially in moderate disorder. Typically in developing countries, community pharmacists diagnose disease, dispense medicines and provide recommendations to patients. In the study, pharmacists demonstrated a more suitable knowledge in making a diagnostic history compared to non-pharmacists. However, their level of knowledge was not enough for diagnosis. Their knowledge on counseling for migraine was also minimal. In conclusion, educational interventions need to be developed (both at the level of the schools of pharmacy and after graduation) to improve the knowledge and practice of the pharmacy staff in the management of migraine [8].

The purpose of the study conducted in Brazil was to assess the skills of counseling of community pharmacists in terms of managing headaches using the approach of the simulated patient. The study involved 24 pharmacists. The simulated patient lamented that he experienced headaches approximately twice a week, for which he hired paracetamol. However, the patient felt the need of a more effective treatment and therefore went to the pharmacy. The simulated patient had a passive role, only responding to questions when asked and not providing information spontaneously. The majority of the pharmacists in the study provided information voluntarily and the 50 % of pharmacists asked about signs and symptoms of the patient. The majority of the pharmacists recommended a painkiller. The most discussed topics in the simulated visits were contraindications (70.8 %), information (41.6 %) and timing of administration of drugs (33.3 %). None of the pharmacists recommend non-pharmacological treatment options. This study showed that the counseling skills of pharmacists and the information provided by pharmacists to the simulated patient were not sufficient for the satisfactory management of headache; this fact may be related to the graduation of

pharmacists in Brazil. Of the 64 disciplines offered by the course of pharmacy, only 6 were part of the core in social pharmacy [9].

## Discussion

The analyzed studies have shown that:

- generally people suffering from headache do not treat themselves in an appropriate manner favoring acute treatment and ignoring the existence of preventive treatments;
- a trained pharmacist is able to recommend the most appropriate OTC therapy to a subject affected by headache;
- a trained pharmacist is able to identify people suffering from migraine and addressing them to the physician for a diagnosis;
- a trained pharmacist can play an important role in identifying and addressing a suitable subject for pharmacological prevention of migraine to the physician;
- a trained pharmacist can provide important information regarding the management of subjects' therapies in acute or preventive treatment.

Unfortunately, the studies also have shown that:

- in case of a prescription or request for a specific product the pharmacist does not usually provide explanations to the patient;
- pharmacists usually do not recommend non-drug alternatives;
- in developing countries the knowledge of pharmacists have not adequately proved and, moreover, the technicians act as if they are pharmacists. This problem stems from the lack of university education and continues for the lack of post-graduate training.

On the basis of the foregoing it is clear that the role of the community pharmacist can be crucial in the management of patients with headache or migraine but only if he receives an adequate and continuous training on both the management of therapies and the relationship with physician and/or patient.

In consideration of the potential and the capacity of the community pharmacist in the management of headaches, in Piedmont (Italy) it has been conducted a study that involves the administration of a questionnaire to patients that go to the pharmacy for the management of migraine with an OTC. The questionnaire was specially crafted by the Italian Headache Foundation (FICEF). Through the questionnaire pharmacists will be able to identify and address to a physician those who suffer from migraine and tend to self-medication, too frequently incurring the risk of therapy abuse and related adverse drug reactions.

**Conflict of interest** All the authors certify that there is no actual or potential conflict of interest in relation to this article.

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# Migraine attacks in the pharmacy: a survey in Piedmont, Italy

**P. Brusa · G. Allais · G. Bussone · S. Rolando · M. Giaccone · M. Aguggia · C. Benedetto**



**Abstract** Headache patients often consult a pharmacist in an attempt to obtain momentary pain relief without having been given any previous expert advice. A specific questionnaire was distributed to the pharmacies in order to assess the patterns of use and dispensing of analgesic medications to the headache patient who turns to the pharmacist for relief of a painful attack. This study aimed at identifying migraine patients who self-medicated, with further end points including whether these patients shared any particular clinical characteristics, the most common type of analgesic medications used, and what, if anything, was recommended by the pharmacist; lastly, which health care professional, if any, routinely managed the patient's headaches. A total of 9,100 questionnaires were distributed to the pharmacies and the complete 3,065 were included in the database. The ID Migraine Screener Test was used to classify subjects into 4 groups: "Definite migraine" (3/3 positive answers: $n = 1{,}042$; 34 %), "Probable migraine" (2/3: $n = 969$; 31.6 %), "Unlikely migraine" (1/3: $n = 630$; 20.5 %), and "Other headaches" (0/3: $n = 424$; 13.8 %). Only Definite and Probable migraines ($n = 2{,}011$) are considered in this paper. Amongst the drugs usually taken by the patients, NSAIDs were more common in the Probable migraine group (60.7 %) than in the Definite migraine (44.7 %) group ($p < 0.001$). On the contrary, triptans were more commonly used by the Definite migraine group (42.9 %) than the Probable migraine (23.7 %) group ($p < 0.001$), and combination drugs were preferentially ($p < 0.001$) chosen by the Definite (13.8 %) rather than the Probable migraine group (8.7 %). A total of 29.2 % of respondents reported that for the management of their headaches, they did not avail themselves of any type of professional healthcare, such as their general practitioner, a headache specialist, or a Headache Center.

**Keywords** Community pharmacy · Headache · ID Migraine Screener Test · Migraine · Questionnaire

**Abbreviations**
NSAIDs Nonsteroidal anti-inflammatory drugs

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## Introduction

It is common for patients with headache, in particular those suffering from migraine, to alleviate pain with analgesic medications, which in some cases may lead to a misuse, if not an abuse, of analgesics [1, 2]. These patients often consult a pharmacist in an attempt to obtain momentary pain relief without having been given any previous specific expert advice. The Italian Headache Foundation (FICEF Onlus), in collaboration with the Order of Pharmacists of

Turin, Regional Deputy, and the Department of Scienza e Tecnologia del Farmaco, University of Turin, promoted and disseminated the project "Questionnaire on the use of analgesic medications given to the migraine patient by the pharmacist".

A specific questionnaire was distributed to the pharmacies in the Piedmont area in an attempt to assess the patterns of use and dispensing of analgesic medications, to the headache patient who turns to the pharmacist for relief of a painful attack. This study aimed at identifying patients suffering from migraine who self-medicated, with further end points including whether these patients shared any particular clinical characteristics, the most common type of analgesic medications used, and what, if anything, was recommended by the pharmacist; lastly, which healthcare professional, if any, routinely managed the patient's headaches.

## Patients and methods

A specific questionnaire was distributed to the pharmacies in the Piedmont area, between December 2012 and March 2013; the areas investigated included the provinces of Turin, Asti, Alessandria, Cuneo, and Novara. Inclusion criteria were as follows: reporting the presence of a headache attack and asking the pharmacist for help to relieve the pain. The questionnaire covered the following points: gender; age; the three questions in the ID Migraine Screener Test [3, 4]: (nausea or vomiting [Yes, No], photosensitivity [Yes, No], and limited daily activities during headache [Yes, No]); the frequency of attacks in the previous 3 months; any drugs usually taken to relieve an acute attack: nonsteroidal anti-inflammatory drugs (NSAIDs), ergot derivatives, triptans, combination drugs, and any other analgesics; class of medicines eventually recommended by the pharmacist on consultation; which healthcare professional, if any, is responsible for the management of this patient's headache: none, their general practitioner, a headache specialist, a Headache Center.

## Statistical analysis

Data analysis was performed by calculating descriptive statistics presented as count and percentages. In order to verify the existence of significant associations between the different groups of respondents, identified by the ID Migraine Screener Test, a chi-square test was performed for two rows by two columns contingency tables. For tables of larger dimensions, a Freeman–Halton extension of Fisher's exact test was applied, and when a significant relationship occurred, comparisons between column proportions were performed by $z$ test with adjusted $p$-values Bonferroni method. All analyses were carried out using the Software IBM-SPSS Statistics Analysis System package (version 21).

## Results

A total of 9,100 questionnaires were distributed to the pharmacies in the Piedmont area and solicited a good percentage of response (36.1 %). Meaning that a total of 3,285 questionnaires had been filled in and collected, 220/3,285 were incomplete and were, therefore, excluded, the remaining complete 3,065 were included in the database. The subdivision of these questionnaires according to province showed that Turin had submitted 2,024 questionnaires (66.0 %), Asti 131 (4.3 %), Alessandria 281 (9.2 %), Cuneo 569 (18.6 %), and Novara 60 (2.0 %). A gender subdivision revealed that 2,154/3,065 (70.3 %) respondents were females and 911/3,065 (29.7 %) males. The average age of respondents was $44.1 \pm 13.5$.

Amongst the migraine symptoms considered in the ID Migraine Screener Test, nausea or vomiting were reported by 1,626 patients (53.1 %), photosensitivity by 2,014 (65.7 %), and limited daily activities by 2,054 (67.0 %). When the answers to the questions in the ID Migraine Screener Test were subdivided according to gender, nausea or vomiting were reported by 60.2 % of women and 36.2 % of men, photosensitivity by 69.2 % of women and 57.5 % of men, and limited daily activities by 71.3 % of women and 57.0 % of men. The ID Migraine Screener Test was used to classify subjects into four groups: "Definite migraine" (3/3 positive answers), "Probable migraine" (2/3), "Unlikely migraine" (1/3), and "Other headaches" (0/3): 424 of patients had Other headaches (13.8 %), 630 Unlikely migraine (20.5 %), 969 Probable migraine (31.6 %), and 1,042 Definite migraine (34.0 %).

The distribution of the types of headache, according to the ID Migraine Screener Test for males and females, is shown in Table 1. The percentage of males, for any type of headache identified using the ID Migraine Screener Test, never exceeded 30 %. Furthermore, although there were more or less 10 % more females than males for both Other headaches and Unlikely migraine, data on Probable migraine showed that 72.4 % were females against 27.6 % of males and that for Definite migraine, 81.6 % were females against 21.1 % of males. From these data, it can be concluded that, in agreement with the literature, females are more subject to headache (Freeman–Halton extension of Fisher's exact test: $p < 0.001$) and that the most evident difference was observed in the Probable and Definite migraine groups ($p < 0.05$ with the $p$-values Bonferroni adjustment procedure).

**Table 1** Distribution of the types of headache, according to the ID Migraine Screener Test, for males and females

| | Other headaches | Unlikely migraine | Probable migraine | Definite migraine | Total |
|---|---|---|---|---|---|
| Gender | | | | | |
| Male | | | | | |
| Count | 189 | 263 | 267 | 192 | 911 |
| % Within gender | 20.7 | 28.9 | 29.3 | 21.1 | 100.0 |
| % Within ID migraine | 44.6 | 41.7 | 27.6 | 18.4 | 29.7 |
| Female | | | | | |
| Count | 235 | 367 | 702 | 850 | 2,154 |
| % Within gender | 10.9 | 17.0 | 32.6 | 39.5 | 100.0 |
| % Within ID migraine | 55.4 | 58.3 | 72.4 | 81.6 | 70.3 |
| Total | | | | | |
| Count | 424 | 630 | 969 | 1,042 | 3,065 |
| % Within gender | 13.8 | 20.6 | 31.6 | 34.0 | 100.0 |
| % Within ID migraine | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |

This paper takes into consideration only data on those patients who reported an ID Migraine Screener Test score compatible with Probable migraine (2/3) or Definite migraine (3/3), i.e. a total of 2,011 respondents. The mean number of headache attacks in the 3 months prior to the survey administration was $13.5 \pm 18.5$, ranging from a minimum of 0 in 6 individuals to a maximum of 90 attacks in 45 cases. A total of 1,552/2,011 respondents were females with a mean number of attacks in the 3 months prior to the pharmacy consultancy of $14.4 \pm 19.3$, 0 in 5 cases and 90 in 39; there were 459 males with a mean number of attacks prior to the pharmacy consultancy of $10.6 \pm 14.9$, 0 in 1 case and 90 attacks in 6. There were 969 respondents for Probable migraine (2/3) with a mean number of attacks of $12.1 \pm 17.3$, 4 cases with 0 attacks and 18 with 90 attacks; whilst for Definite migraine (3/3), there were 1,042 respondents, with a mean number of attacks of $14.8 \pm 19.5$, 2 cases with 0 attacks and 27 cases with 90.

The pain medications usually taken for acute attacks were NSAIDs in 1,054 (52.4 %), Ergot derivatives in 184 (9.1 %), triptans in 677 (33.7 %), combination drugs in 228 (11.3 %), other analgesics in 326 (16.2 %). The distribution of answers for each medicine was in Probable migraine sufferers: NSAIDs in 588 (60.7 %), Ergot derivatives in 79 (8.2 %), triptans in 230 (23.7 %), combination drugs in 84 (8.7 %), other analgesics in 175 (18.1 %). In patients with Definite migraine were NSAIDs in 466 (44.7 %), Ergot derivatives in 105 (10.1 %), triptans in 447 (42.9 %), combination drugs 144 (13.8 %), other analgesics in 151 (14.5 %). NSAIDs were more commonly used in the Probable migraine group (60.7 %) than in the Definite migraine (44.7 %) group (chi-square test: $p < 0.001$); likewise, there were more other analgesics used ($p < 0.034$) in the Probable migraine group (18.1 %) than in the Definite migraine group (14.5 %). On the contrary, triptans were more commonly used by the Definite migraine group (42.9 %) than the Probable migraine (23.7 %) group ($p < 0.001$) and combination drugs were preferentially ($p < 0.001$) chosen by the Definite migraine group (13.8 %) rather than the Probable migraine group (8.7 %). When the percentage of patients who used Ergot derivatives were taken into consideration, there was no statistically significant difference between the two groups ($p = 0.142$).

In any case, NSAIDs were chosen by 52.4 % of respondents, in both groups, followed by triptans (33.7 %). Each respondent had the possibility to provide more than one answer to the question on pain medications taken regularly for an acute attack; the distribution of the number of pain medications taken was 0 in 0.3 %, 1 in 79.1 %, 2 in 18.4 %, 3 in 1.8 %, and 4 in 0.2 %.

Table 2 shows the frequency of multiple responses given as to the types of pain medications taken regularly for an acute attack.

A review of the frequency distribution of the pain medications taken for an acute attack in the respondents classified as Probable migraine (Table 2) showed that 19.8 % of patients took more than one type of medication for the treatment for migraine attacks; the most frequent choices were NSAIDs in 50.9 % followed by triptans in 19.9 %. The frequency distribution of the medications chosen during an acute attack by the Definite migraine group (Table 2) showed that 26.2 % of the respondents used several types of pain medication during an attack, the most common were NSAIDs (in a lower percentage (35.5 %) than the Probable migraine group) and triptans (where the percentage rose to 34.0 % compared to 23.8 % in the Probable migraine group).

Table 3 shows the classes of pain medication recommended by the pharmacists. When the frequencies for the

**Table 2** Frequency of multiple responses as to the types of analgesic medications taken regularly for an acute attack subdivided for all migraines (i.e. probable migraine + definite migraine), probable migraine and definite migraine

| Medicines used for acute attacks | All migraines | | | Probable migraine | | | Definite migraine | | |
|---|---|---|---|---|---|---|---|---|---|
| | Answers | | % of cases | Answers | | % of cases | Answers | | % of cases |
| | *n* | % | | *n* | % | | *n* | % | |
| NSAIDs | 1,054 | 42.7 | 52.6 | 588 | 50.9 | 60.9 | 466 | 35.5 | 44.8 |
| Ergot derivatives | 184 | 7.5 | 9.2 | 79 | 6.8 | 8.2 | 105 | 8.0 | 10.1 |
| Triptans | 677 | 27.4 | 33.8 | 230 | 19.9 | 23.8 | 447 | 34.0 | 43.0 |
| Combination drugs | 228 | 9.2 | 11.4 | 84 | 7.3 | 8.7 | 144 | 11.0 | 13.8 |
| Other analgesics | 326 | 13.2 | 16.3 | 175 | 15.1 | 18.1 | 151 | 11.5 | 14.5 |
| Total | 2,469 | 100.0 | 123.1 | 1,156 | 100.0 | 119.8 | 1,313 | 100 | 126.2 |

**Table 3** The classes of pain medications recommended by the pharmacists subdivided for all migraines (i.e. probable migraine + definite migraine), probable migraine and definite migraine

| Class of pain medications recommended by the pharmacist | All migraines | | Probable migraine | | Definite migraine | |
|---|---|---|---|---|---|---|
| | Answers | | Answers | | Answers | |
| | *n* | % | *n* | % | *n* | % |
| None | 647 | 32.2 | 250 | 25.8 | 397 | 38.1 |
| NSAIDs | 943 | 46.9 | 520 | 53.7 | 423 | 40.6 |
| Ergot derivatives | 21 | 1.0 | 10 | 1.0 | 11 | 1.1 |
| Triptans[a] | 94 | 4.7 | 32 | 3.3 | 62 | 6.0 |
| Combination drugs | 80 | 4.0 | 35 | 3.6 | 45 | 4.3 |
| Other analgesics | 182 | 9.1 | 102 | 10.5 | 80 | 7.7 |
| Dietary supplements | 10 | 0.5 | 4 | 0.4 | 6 | 0.6 |
| Herbal products | 5 | 0.2 | 3 | 0.3 | 2 | 0.2 |
| Homeopathic remedies | 29 | 1.4 | 13 | 1.3 | 16 | 1.5 |
| Total | 2,011 | 100 | 969 | 100 | 1,042 | 100 |

[a] under prescription

Probable migraine group were taken into consideration, it was observed that NSAIDs were recommended in 53.7 % of the cases against only 3.3 % of triptans (under prescription) and that the pharmacist refrained from recommending anything in 25.8 % of the consultations. Similarly, evaluating the frequency distribution of the advice given by the pharmacists, it was observed that NSAIDs were recommended only 40.6 % of the time; there was a slight increase in the number of times triptans (under prescription) were recommended (6.0 %) as well as a rise in how many respondents were not given any medical advice at all by the pharmacists (38.1 %). When offered, the advice given by the pharmacists showed a statistically significant difference (chi-square test: $p < 0.001$) depending on the type of migraine (Probable or Definite).

There were no statistically significant differences between the Probable migraine and Definite migraine groups when the distribution of the classes of pain medications was subdivided by gender.

Table 4 shows the answers to the last question in the questionnaire, i.e. "who is responsible for the management of your headache problem?" A total of 29.2 % of respondents reported that they did not avail themselves of any type of professional health care, such as their general practitioner, a headache specialist, or a Headache Centre, whilst 7.0 % reported that they took advantage of more than one professional health care advisor/centre and the most frequent choice fell to their general practitioner (39.4 % of cases). The percentage of individuals who did not seek advice at all rose to 39.1 % in the Probable migraine group, whilst 5.0 % of respondents consulted more than one person; the most frequent choice was their general practitioner (39.1 %), whilst headache specialists and Headache Centres had a similar frequency percentage of around 13 % (Table 4).

There was a steep drop to 20 % in the percentage of individuals who did not seek advice in the Definite migraine group (Table 4), whilst 8.9 % turned to more than one health care professional. However, the most frequent choice was still their general practitioner (39.7 %) followed by a Headache Centre (27.4 %). Therefore, it may be concluded that the behaviour of individuals in the Probable migraine group differed from that of those in Definite migraine group (chi-square test: $p < 0.001$): 39.1 % of those in the Probable migraine group and 20 % of the Definite migraine group did not consult anybody; 21.8 % of the Definite migraine group consulted a specialist against 13.1 % of those in the Probable migraine group; 27.4 % of the Definite migraine group were under the care of a Headache Center against 13.6 % of individuals in the Probable migraine group. Both of these categories consulted their general practitioner ($p = 0.78$): 39.7 % in the Definite migraine group and 39.1 % in the Probable migraine group.

## Discussion

The pharmacist is a common reference figure for those who suffer from headaches and often need urgent remedies to

**Table 4** Frequency of answers to the question "who is responsible for the management of your headache problem"? subdivided for all migraines (i.e. probable migraine + definite migraine), probable migraine and definite migraine

| Who is responsible for the management of your headache problem? | All migraines | | | Probable migraine | | | Definite migraine | | |
|---|---|---|---|---|---|---|---|---|---|
| | Answers | | % of cases | Answers | | % of cases | Answers | | % of cases |
| | *n* | % | | *n* | % | | *n* | % | |
| None | 587 | 27.3 | 29.2 | 379 | 37.3 | 39.1 | 208 | 18.3 | 20.0 |
| General practitioner | 793 | 36.8 | 39.4 | 379 | 37.3 | 39.1 | 414 | 36.5 | 39.7 |
| Headache specialist | 354 | 16.4 | 17.6 | 127 | 12.5 | 13.1 | 227 | 20.0 | 21.8 |
| Headache Center | 418 | 19.4 | 20.8 | 132 | 13.0 | 13.6 | 286 | 25.2 | 27.4 |
| Total | 2,152 | 100.0 | 107.0 | 1,017 | 100.0 | 105.0 | 1,135 | 100.0 | 108.9 |

alleviate an acute attack. Our survey demonstrated that women predominate in those who seek advice for headache in the pharmacy (70.3 % of our sample population). This percentage rises steeply when other headaches (55.4 %) are compared to Definite migraine (81.6 %), in parallel the well-known datum of an higher percentage of females in migraine population. Nevertheless, it is worth of note that usually women, in any case, go to the pharmacy more often than men do [5].

In our study group, the headache sufferers that consulted the pharmacist reported having a mean of 13.5 attacks over the 3-month period that proceeded our survey. This frequency of attacks, in itself, defines a population that necessitates migraine prophylaxis, in as much as they have more than 3 crises per month and, consequently, need more than only acute pain treatment.

The most commonly used pain medications for an attack of migraine were NSAIDs, even if the percentage of triptans used was higher in the Definite migraine group than in the Probable migraine group. However, the most striking datum to come to light in this study was the fact that as many as 30.0 % of the individuals that met the ID migraine criteria for migraine sufferers reported that they were not under the care of any kind of professional healthcare worker or center, but that they took a "do-it-yourself" attitude.

The Probable migraine group had a higher percentage of self-prescription (39.1 %) than did the Definite migraine group (20.0 %). About 40 % of migraine attacks were treated by local general practitioners, whilst 13.1 % of the Probable migraine group turned to a headache specialist as did 21.8 % of the Definite migraine group. Unfortunately, only 20.8 % of migraine sufferers consulted a Headache Center, i.e. 13.6 % of the Probable migraine group and 27.4 % of the Definite migraine group.

Although this is a preliminary survey and covers only one of the Italian regions, it makes quite an adequate account of a problem that seems to be widespread in numerous countries throughout the world. We are of the opinion that the volume of adequate and correct information given to the headache sufferers, physicians, and pharmacists alike must be enhanced so as to counter the trend of do-it-yourself medication [6] and to stave off the possibility of creating a vicious circle that might well lead to an abuse of non-specific painkillers and make headache pain chronic.

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# Symptomatic treatment of migraine: from scientific evidence to patient management

**Gian Camillo Manzoni · P. Torelli**



**Abstract** All migraine patients need symptomatic treatment to stop individual attacks or, at least, significantly relieve pain. When attacks are very frequent (more than 3 days of headache per month on average), they will also need preventive treatment. The first physician the patient must address to for preventive treatment is the general practitioner (GP). If the medication prescribed by the GP is not effective or there is overuse of symptomatic drugs, the patient will have to be referred to a neurologist or a headache clinic. The drugs to be used as symptomatic treatment are triptans and non-steroidal anti-inflammatory drugs. Combination therapy with antiemetics is also important. While specialists will base their therapeutic decisions on guidelines in the literature and on their personal experience, GPs do not yet have any easy-to-use tools to support them. To fill this gap, an algorithm is proposed here that can be easily used by GPs to make decisions during their patients' migraine attacks.

**Keywords** Migraine · Therapy · Symptomatic treatment

## Introduction

An epidemiological survey conducted in the US in the late 1990s on a sample representative of the general population showed that only about 6 % of the subjects with migraine received a correct diagnosis and were adequately treated and followed up [1].

Nearly half the people with migraine never sought treatment; about half of those who sought treatment did not receive a correct diagnosis; only half of those who sought treatment and received a correct diagnosis were adequately treated; and only half of those who were adequately treated accepted to show up regularly for the planned follow-up visits.

The last two obstacles to a correct management of migraine patients are primarily a consequence of the many flaws that still exist in the therapeutic approach.

Recently, 21 patients and 15 healthcare providers were interviewed for a qualitative analysis of what theoretically represents optimal behaviors in the symptomatic treatment of migraine and what still hinders their implementation. The analysis showed two major problems for patients [2]. The first problem is an objective difficulty in recognizing in the early phases of an attack if it is migraine or another kind of headache, such as tension-type headache, which not rarely alternates with migraine in the same patient. Recognizing what kind of headache the patient is suffering from is important, because symptomatic medication varies depending on headache type and is more effective if it is taken earlier. The second problem is a series of role conflicts, including role responsibilities (e.g. employee, parent, spouse, or caretaker) that interfere with performing behaviors required to optimally use acute headache medication. Migraine patients may be so enthralled in what they are doing that they cannot or will not take time to treat an attack right away and tend to make excessive use of symptomatic drugs.

If we want to address the question of symptomatic migraine treatment in a systematic way, we need to consider the three actors involved: the patient, the physician,

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and the medication. Then, we must try to determine what kind of patient can be treated with a certain therapy, what kind of physician is responsible for recommending treatment, and what kind of medication can be used.

## What kind of patient?

All migraine patients during an attack must immediately take a drug to stop it or at least relieve pain. In general, therapeutic behavior strongly depends on the frequency of attacks [3].

With an average frequency of attacks of up to 3 days of migraine per month, there is no need for preventive treatment. Patients can receive only symptomatic treatment, provided the drugs used significantly relieve pain within an hour and completely eliminate it within 2 h with no side effects.

With an average frequency of attacks of 4–10 days of migraine per month, patients will have to receive preventive treatment and will be allowed to continue taking their usual symptomatic drugs if these are effective and well tolerated.

With an average frequency of attacks of more than 10 days of migraine per month, in addition to receiving preventive treatment patients should change their usual symptomatic drugs, even if they are effective, because it is legitimate to suspect that their frequent use may have actually worsened migraine [4].

## What kind of physician?

For a correct management of migraine patients, it is imperative to clearly establish who should do what within the complex framework of healthcare services.

In view of the remarkable prevalence of headache disorders and the need to ensure adequate care to all people in a cost-effective way, the European Headache Federation working jointly with a WHO campaign called "Lifting the Burden" has suggested a three-tier organization of healthcare services [5]. Epidemiological data indicate that most headache patients can be effectively treated by their GPs (first tier) and only a small proportion needs treatment from medical specialists, such as a neurologist (second tier) or a headache clinic (third tier).

GPs, then, are primarily responsible, at least initially, for administering symptomatic migraine treatment to patients (Fig. 1).

## What kind of medication?

Today we can satisfactorily answer this question, thanks to the different guidelines in the literature, some of which are very recent and up to date [6–8].

The best assets a physician has once the migraine attack has started are triptans and NSAIDs.

In the past there was a hot debate on how to administer these two classes of drugs. Today, the prevailing tendency is to follow a so-called "layered approach" as opposed to a "stepped approach". Thus, instead of using an NSAID first and then switching to a triptan should there be no response to the NSAID, a tailored therapy is preferred, which can be varied depending on the kind of patient and the clinical features of migraine.

It has been demonstrated that symptomatic medication is more effective when it is taken earlier. When deciding on the best route of administration, it should be borne in mind that over 70 % of patients experience nausea and/or vomiting during a migraine attack [9]. As a general rule, however, triptans can be administered orally, even on an empty

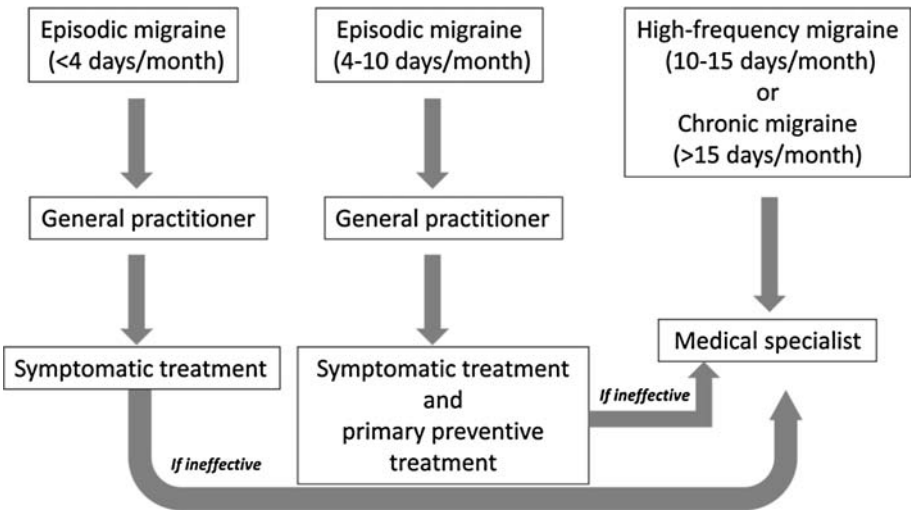
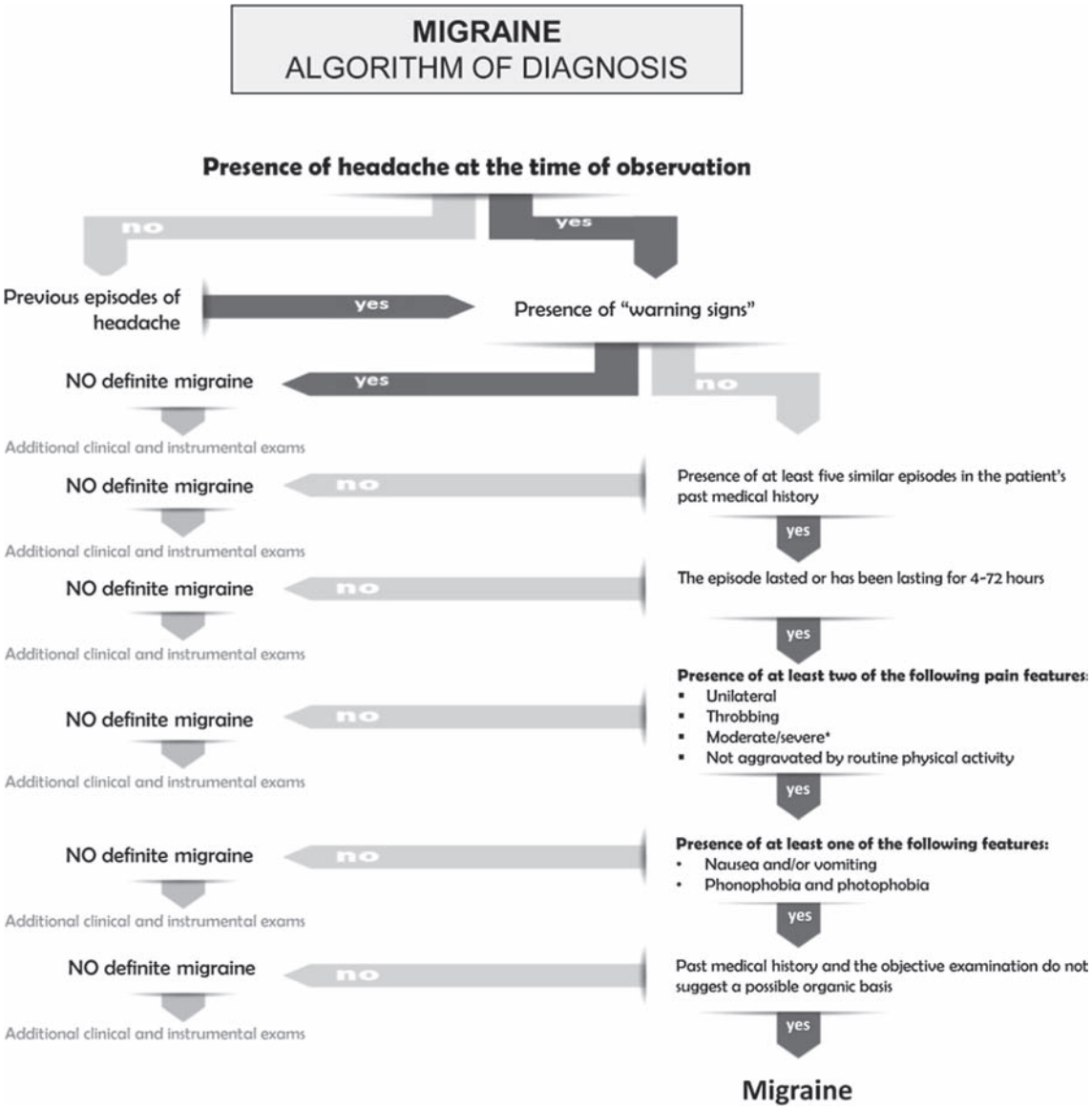



**Fig. 1** Individual roles of general practitioners and medical specialists in the management of migraine patients

stomach, while non-steroidal anti-inflammatory drugs (NSAIDs) should be administered rectally or parenterally.

A more complex question is whether to prefer single therapy or combined therapy. Here, too, great importance should be attached to the presence of nausea and/or vomiting since the early phases of the attack. In that case, an antiemetic drug can be associated to the triptan or the NSAID. Today, widely used combinations are lysine acetylsalicylate with metoclopramide and especially indomethacin with prochlorperazine and caffeine. The latter, in the form of coated




**Warning signs**

- Age at onset >50 years
- Intense pain with sudden onset
- Vomiting at headache onset
- Fainting at headache onset
- Signs of focal neurological damage and/or confusion
- Fever
- Nuchal rigidity
- Headache onset during physical/sexual activity

**Fig. 2** Algorithm for the diagnosis of migraine attacks

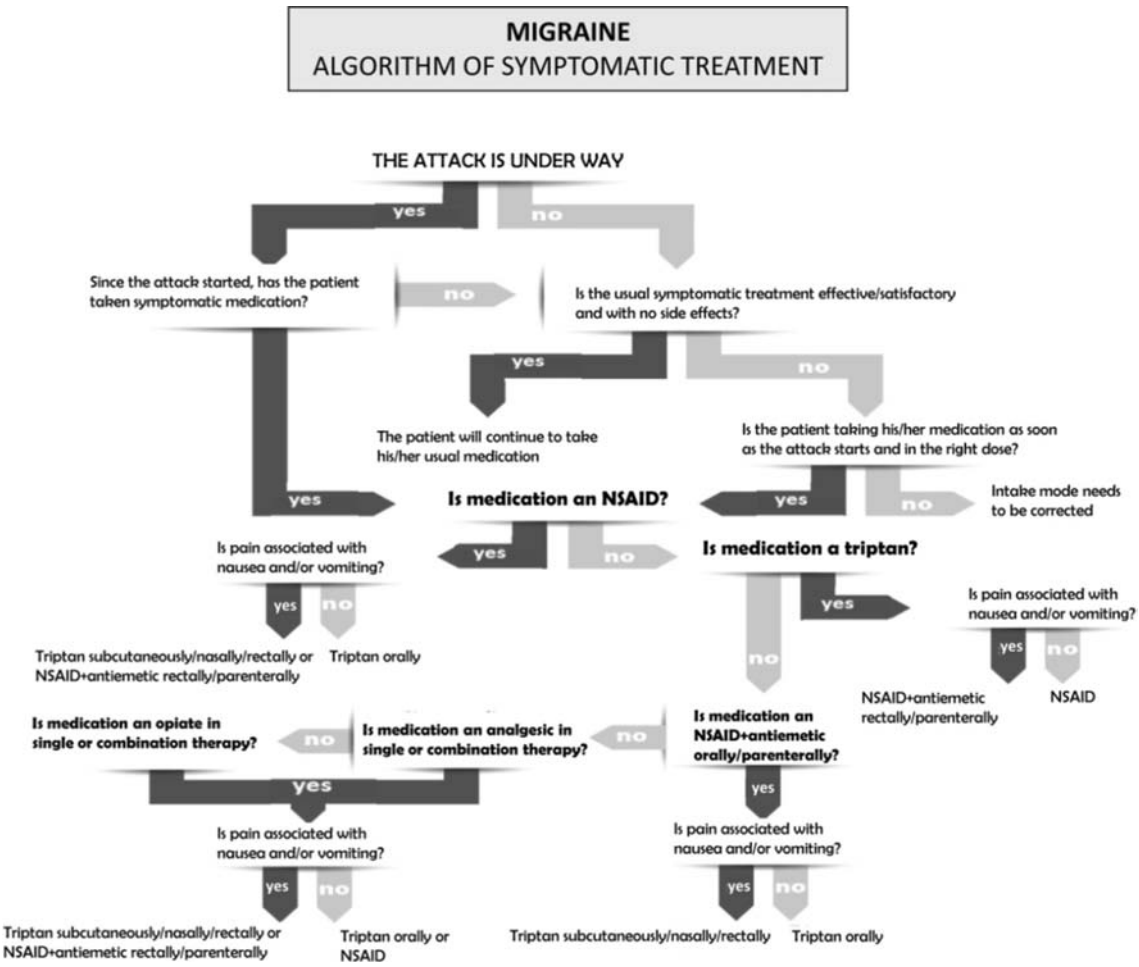



**Fig. 3** Algorithm for the treatment of migraine attacks

tablets and even more so in the form of effervescent tablets and suppositories, is an ideal combination for migraine attacks because indomethacin exhibits a vasoconstricting as well as pain-relieving action [10], while prochlorperazine has an antimigraine as well as antiemetic effect [11].

## A diagnostic and a therapeutic algorithm for GPs

Patients should be referred to a neurologist or a headache clinic for the symptomatic treatment of their migraine attacks only when the frequency of attacks is very high and they tend to overuse symptomatic drugs or when they have not responded well to the symptomatic drugs prescribed by their GPS, even if attacks are not very frequent (Fig. 1). In those cases, medical specialists will base patient management on the existing guidelines and on their personal clinical experience.

The different guidelines published in the literature are specifically devised and structured to be used by headache experts, but are not easy to use for GPs. GPs do not have tools that can support them in their therapeutic approach to patient management during migraine attacks.

Therefore, we thought it useful to devise a simple algorithm that could be easily used by GPs when they have to take the best possible decision after they are sure that the attack their patient is suffering from is unmistakably a migraine attack (Fig. 2). Obviously, the therapeutic course will depend on the moment when the patient is observed and will have to vary depending on the kind of medication that the patient may have taken previously and on whether nausea and/or vomiting are present (Fig. 3).

**Conflict of interest** The authors certify that they have no conflict of interest in this paper.

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# Treatment of tension-type headache: from old myths to modern concepts

**P. Barbanti · G. Egeo · C. Aurilia · L. Fofi**



**Abstract** Tension-type headache (TTH) is the second most common human disease, accounting for intense disability, high costs and numerous workdays lost. Tension-type headache is less simple and easy-to-treat than commonly thought. Antidepressants, despite their poor tolerability, are still the first-choice drugs for preventing TTH. The most widely studied non-pharmacological approach to TTH, cognitive-behavioral techniques, effectively relieve pain only in selected patients. The most frequently used and recommended treatments for acute TTH, NSAIDs and paracetamol have scarce efficacy as documented by their low therapeutic gain over placebo in the 2-h pain-free response. Their effectiveness may be increased by a more proper use and by the adjunction of caffeine, antiemetics, myorelaxants or tranquillizers but the risk of medication-overuse headache must be considered. Hence, the need for more effective and tailored treatments in TTH remains.

**Keywords** Tension-type headache · Prophylaxis · Acute treatment · Disability

## Introduction

Tension-type headache (TTH) has long been seen as the paradigm of common, mild, not disabling headache, successfully treatable with simple analgesics and, when needed, with tricyclic antidepressants. Research over recent years more clearly delineating its pathophysiology, epidemiology, burden and costs now underline the need to reappraise TTH-related disability, evaluate its impact on social and working life and reconsider the therapeutic approach. In this paper, we review major recent advances in the options for treating TTH.

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## TTH is the second most prevalent human disorder

TTH is the most common human health problem after dental caries in permanent teeth, affecting almost 1.5 billion people worldwide [1]. Its prevalence varies by continent, sex and age. According to epidemiological studies, from 24 to 37 % of the general population have TTH attacks several times a month, 10 % have them weekly and 2–3 % have chronic TTH. Women are affected slightly more than men. The age at onset is 25–30 years, prevalence peaks between 30 and 39 years and declines only slightly with increasing age [2]. Risk factors for TTH include poor self-rated health, stress, sleep loss and fatigue.

The high TTH prevalence causes a substantial burden to both individuals and society, accounting for a significant productivity loss. TTH causes at least as much disability as migraine [3]. A European study reported that the number of workdays lost due to TTH was three times higher than that lost due to migraine [4]. A study on 385 headache sufferers showed that 17 % of patients with TTH consulted the emergency department and 12 % the neurologist during the 3 months before the survey [5]. A survey on 1,788 employees at a Dutch manufacturing company showed that 8.9 % of patients with TTH had visited the company doctor for headache during the 4 weeks before the questionnaire and disclosed a total economic loss for TTH of 4,318$ [6].

## TTH treatment

All the foregoing findings explain why medical professionals are increasingly aware that today we still need to seek more effective and tailored treatments for TTH.

### Prevention

TTH prevention includes pharmacological agents, behavioral approaches (biofeedback and counseling) and physical methods (physical therapy, manipulative treatments, acupuncture, osteopathy) [7].

#### *Pharmacological treatment*

The current mainstay drugs for preventing TTH are antidepressants [7]. According to the EFNS guidelines, the first-choice drug (recommendation level A) is amitriptyline 30–75 mg, followed by venlafaxine 150 mg and mirtazapine 30 mg (level B), whereas third-choice drugs (level B) are chlorimipramine 75–150 mg, maprotiline 75 mg and mianserin 30–60 mg [8]. Recommendations to prevent TTH with muscle relaxants and antispasticity agents such as baclofen or tizanidine to increase muscular tone currently rely upon anecdotal evidence [7]. In a small controlled study, memantine, an *N*-methyl-D-aspartate antagonist acting on central pain mechanisms, failed to show a significant difference from placebo [9].

Botulinum toxin A is ineffective in TTH [10], despite a few isolated successful reports especially in patients with pericranial muscle tenderness [11]. Recently, a randomized placebo-controlled study on 108 patients with episodic TTH reported that 0.5 % lidocaine injected into head and neck muscles significantly reduced headache frequency and intensity [12]. The benefit lasted several months and was more evident when more muscles were injected and lidocaine was used at higher doses.

#### *Non-pharmacological treatment*

For patients with TTH in whom pharmacological options are limited, non-pharmacological approaches may prevent episodic TTH transforming into chronic TTH. They can also be useful in managing chronic TTH [13].

EMG-biofeedback helps to relieve TTH attacks by controlling muscular over-reactivity. A meta-analysis of 53 studies [14] indicates that biofeedback has a medium-to-large long-lasting effect in TTH; combining biofeedback with relaxation therapy enhances it efficacy [15]. Cognitive-behavioral therapy can decrease TTH activity by 40–50 % or more [16] and is most effective when used with relaxation training, especially in patients with higher stress levels and psychiatric comorbidities [17]. Relaxation training alone seems relatively ineffective in TTH [8].

The most beneficial preventive treatment, especially in patients with unremitting TTH or concurrent mood disorders, is probably combining antidepressants with psychological therapy [18]. The psychological approach can occasionally exceed pharmacological therapy in efficacy. For example, when they compared three sessions of hypnotic relaxation with amitriptyline (up to 75 mg) in 90 patients with TTH, Ezra et al. [19] observed a 50 % reduction in headache frequency in 67 % of the hypnotic relaxation group and 58 % of the amitriptyline group. When follow-up ended, 53 % of the amitriptyline-treated patients and 80 % of hypnotic relaxation patients reported improved global health feeling ($P = 0.027$).

Standard TTH treatments in primary care settings include physical and manual therapy [20]. The EFNS guidelines recommend physical therapy as a valuable option for TTH therapy, despite limited evidence for its effectiveness [8, 21]. Manual therapy may be beneficial in patients with chronic TTH, especially in those with coexisting migraine, higher headache intensity, absence of multiple site pain, greater cervical mobility and greater neck flexor muscle endurance [22]. Castien et al. [23] demonstrated a 50 % headache days reduction in 87.5 % of patients treated for 8 weeks with manual therapy but in only 27.5 % of those continuing their usual medical care. Though a review of chiropractic manipulation in TTH suggested a trend toward a benefit [24], others reported insufficient evidence regarding their efficacy [21, 25].

The efficacy of Chinese acupuncture in TTH remains debatable [26]. A Cochrane analysis concluded that acupuncture may be "a valuable non-pharmacological tool in patients with frequent episodic or chronic TTH" [27]. In a recent review, Hao [28] listed as crucial outcome factors for acupuncture in TTH stimulation mode, needle retention, and treatment frequency, suggesting that the ideal acupuncture treatment in TTH could be electro-acupuncture with 30-min needle retention and twice-weekly treatment.

Another increasingly widespread non-pharmacological option involves managing mental stress with meditation and yoga. Yoga reduces stress and improves fatigue, and some authors suggested that it seems to be more effective than pharmacotherapy in the treatment of chronic TTH [29].

#### *Others*

A trial conducted in 138 patients with chronic TTH [30] demonstrated that intermittent low-frequency high-intensity transcutaneous electrical nerve stimulation (TENS) administered to the temporal and occipital region for 10 weeks induces a visual analog scale (VAS) scores

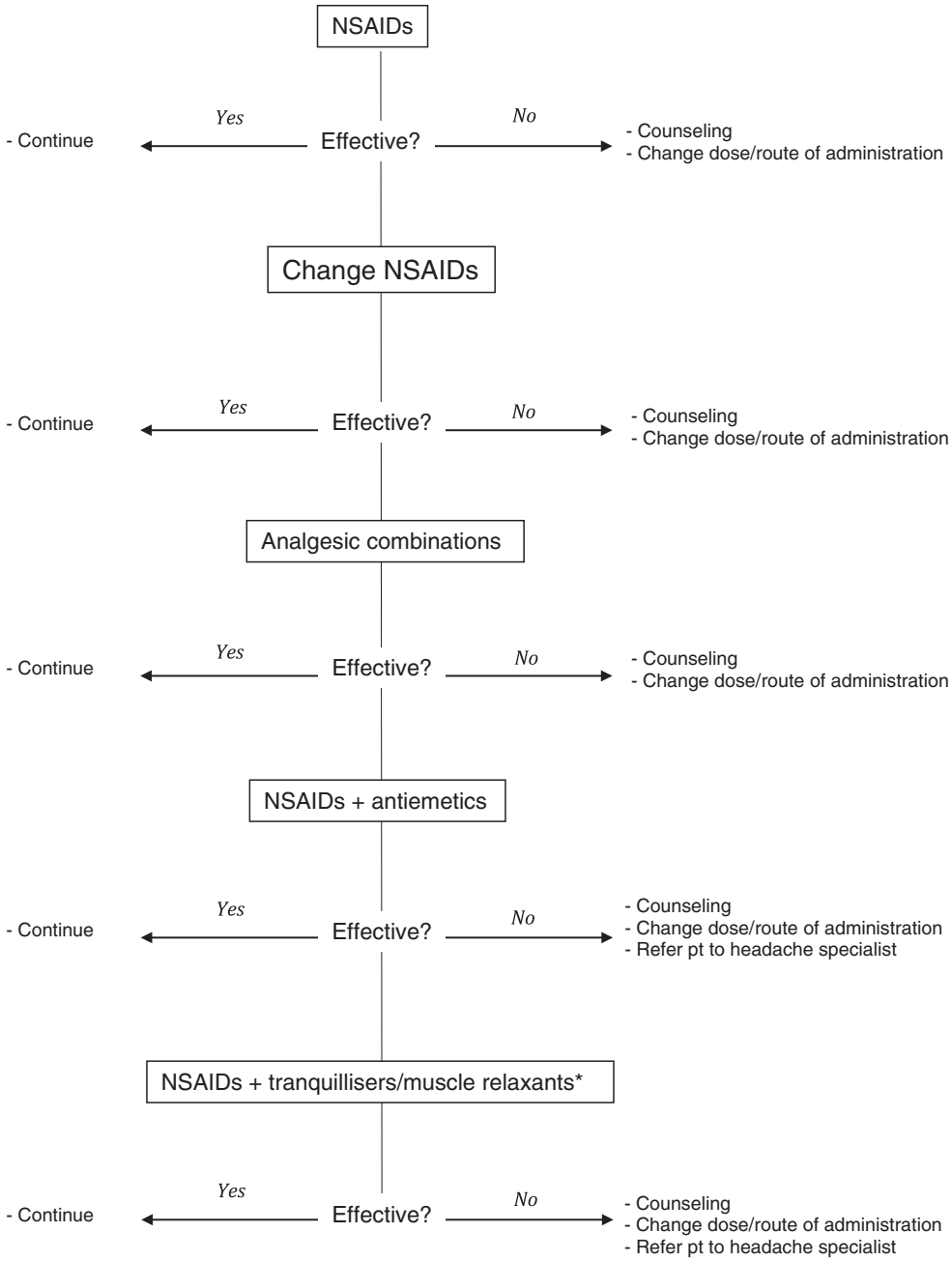


**Fig. 1** Algorithm for acute treatment of tension-type headache

reduction comparable to that of imipramine 50 mg/day for 3 months. A year ago, a consensus article from the European Headache Federation nevertheless subsequently reaffirmed that the use of TENS in headache is not supported by convincing scientific data [31].

A retrospective study on a miscellaneous population of 90 headache sufferers tested the effectiveness of transcranial direct current stimulation delivered to various scalp locations. The investigators reported a beneficial clinical effect in episodic TTH but not in chronic TTH, effectiveness being strictly linked to the scalp site where the stimulating electrodes were located [32].

## Acute treatment

Acute TTH is usually treated with simple analgesics and NSAIDs. First-choice drugs (recommendation level: A) are ibuprofen 200–800 mg, ketoprofen 25 mg, aspirin 500–1,000 mg, naproxen 375–550 mg, diclofenac 12.5–100 mg and paracetamol 1,000 mg [8]. A meta-analysis of 41 trials [33] on the efficacy of paracetamol and NSAIDs in patients with TTH showed that NSAIDs and paracetamol are more effective than placebo, NSAIDs are more effective than paracetamol, all NSAIDs have similar efficacy and ibuprofen has fewer short-term side effects than other NSAIDs.

These data have been partially questioned by a recent meta-analysis of six randomized placebo-controlled trial studies on the efficacy and safety of NSAIDs and acetaminophen in TTH [34], which reported that low-dose NSAIDs (ketoprofen 12.5 mg, naproxen 375 mg, aspirin 500 mg) and acetaminophen have similar efficacy in TTH treatment, whereas high-dose NSAIDs (ibuprofen 400 mg, ketoprofen 25 mg, aspirin 1,000 mg) are more effective but also more poorly tolerated. Despite their common use in acute TTH treatment, in the 2-h pain free response, paracetamol and NSAIDs have a low therapeutic gain over placebo, ranging from 6 to 11 % for paracetamol 1,000 mg, 6 % for naproxen 375 mg and 12 % for ketoprofen 25 mg [35, 36]. The findings in this review therefore agree with those who underline the need to seek more effective treatments for patients with episodic or acute TTH [37].

What should be done when treatment for acute TTH fails? First, physicians should reconsider the diagnosis to exclude secondary forms. Equally important, they should obtain a more detailed medical history focused on concomitant migraine headaches to exclude TTH-like headaches in patients with chronic migraine [37]. The physician should then adjust suboptimal analgesic doses or change administration routes. Another possibility is to use of combination analgesics, adjunction of caffeine (65–200 mg, level recommendation: B) or antiemetics (which improve gastric emptying and analgesic absorption) [8]. Selected patients, i.e., those with overt postural problems or anxiety, could receive tranquillizers or muscle relaxant (Fig. 1). Analgesic combinations should nevertheless be cautiously used, given that excessive use could result in induce medication-overuse headache.

## Conclusions

TTH is an extraordinarily common disorder associated with physical or mental stress. Its disability and social and economic burden is far higher than expected. Our review underlines the need to widen the range of pharmacological and non-pharmacological treatments. Selected patients with acute TTH might receive/may benefit from treatment options other than simple analgesics.

**Conflict of interest** I certify that there is no actual or potential conflict of interest in relation to this article.

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# Difficulties in work-related activities among migraineurs are scarcely collected: results from a literature review

**A. Raggi · V. Covelli · M. Leonardi · L. Grazzi · M. Curone · D. D'Amico**



**Abstract** Migraine affects work productivity in terms of missed workdays and days with reduced productivity. In this literature review, we looked for papers addressing specific difficulties in work-related activities. Twenty-three papers were included in the review, reporting data on 51,135 patients. Results showed that there is some evidence for limitations in skills such as problem solving, and activities such as speaking and driving. However, the way in which problems with remunerative employment are addressed is limited to concepts such as reduced performance or inability to work as usual. Given the paucity of data, a return to patient-derived data will be needed to develop an assessment instrument that is able to collect information on headache-related problems in work activities.

**Keywords** Disability · Migraine · Work · Employment · Job

## Introduction

Studies show that headaches, and migraine in particular, significantly impact on work activities [1, 2]. Given its high lifetime prevalence (18.5 %, 13 % in men and 25.6 % in women) [3], migraine determines huge social security problems. Recent estimates of migraine cost in Europe reported an annual cost per case of 1,222€, 93 % of them (i.e. 1,136€) being indirect costs due to absenteeism and reduced productivity [4]. Research results generally address the impact of migraine on work activities in terms of reduced productivity, i.e. in terms of lost workdays. Regarding chronic migraine, there are even less data than those on episodic migraine, and those available showed that the impact of chronic migraine is greater than that of episodic migraine [5, 6].

A review on available literature was performed: due to the presumed paucity of published data on job-specific difficulties, we moved from a previous research experience from our team [7], in which the International Classification of Functioning, Disability and Health (ICF) [8] was used as a term of reference to describe a set of difficulties that are relevant to migraineurs.

## Methods

ICF-based data showed that 25 activities were judged as limited by a sample of migraineurs [7]: however, not all of them are job relevant. The decision on relevance was taken by expert consensus: three blinded authors revised the list of activities, and those considered as relevant by at least two authors were used as keywords for the literature search.

### Search strategy and papers' selection criteria

We used the selected keywords, expressed as medical subject headings (MeSH) terms, and searched for papers in MedLine. We preferred to rely on MeSH terms as they should enable to capture most of the terminology

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**Table 1** Retained ICF categories and corresponding MeSH terms

| ICF category | MeSH terms |
|---|---|
| d110–Watching | Vision |
| d175–Solving problems | Problem solving |
| d310–Receiving spoken messages | Comprehension |
| d330–Speaking | Speech; communication |
| d350–Conversation | Speech; communication |
| d410–Changing basic body position | NA |
| d415–Maintaining a body position | NA |
| d430–Lifting and carrying objects | Lifting |
| d450–Walking | Walking |
| d475–Driving | Automobile driving |
| d730–Relating with strangers | Nurse–patient relations; physician–patient relations; professional–patient relations; interprofessional relations |
| d740–Formal relationships | Nurse–patient relations; physician–patient relations; professional–patient relations; interprofessional relations |
| d750–Informal social relationships | Friendship; interprofessional relations; public relations |
| d850–Remunerative employment | Work; workload; employment |

*NA* not available

variations. The health condition should be described as 'migraine', 'chronic migraine', 'chronic daily headache' or 'medication overuse headache': the search for the health condition was performed in papers' titles and abstracts. Clinical trials and observational studies (both cross-sectional and longitudinal), published in 2000–2013, in English and with abstract available, were included. Primary prevention studies, systematic reviews, case report/case series, qualitative studies, commentaries, letters editorials and conference reports were excluded.

Papers were selected if reported data referred to the impact of headaches on work, in terms of reduction, or of specific activities that were deemed to be relevant for the purpose of remunerative employment. For quality control, 20 % of abstracts and 10 % of full texts were double checked. An evaluation of the paper's quality was performed using the National Institute for Health and Clinical Excellence guidelines [9]: papers that were judged of poor quality were excluded.

### Data extraction

Data on sample composition and prevalence of headaches type were collected. Information on absenteeism or presenteeism was directly collected if available: in case data were categorical, median values were used to provide reasonable estimates of missed or reduced workdays.

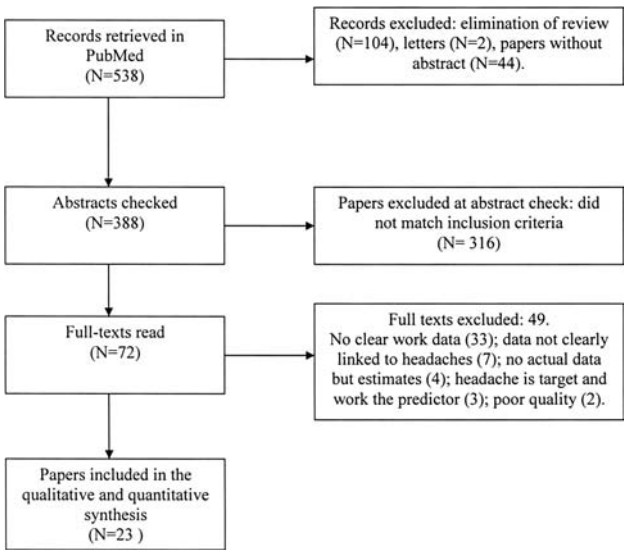


**Fig. 1** Flow chart of paper selection

Data on the kind of activity that was limited by presence of headaches were referred to ICF categories using standardised liking rules, an established procedure requiring the content of items in assessment instruments to be connected to the most precise ICF category possible [10]. To judge the level of evidence, we followed an approach already used in other literature reviews on other brain disorders [11, 12], including migraine: evidence was judged as strong if there are at least two good papers reporting the same results; partial if there are at least one good paper and some acceptable papers reporting similar result; poor if there is only one paper.

## Results

Fourteen out of the 25 ICF categories were maintained connected to seventeen MeSH terms (Table 1). Based on these keywords, a total of 538 records were found. A total of 388 abstracts were checked (double check agreement: 84.4 %) and 72 full texts were read: 23 were maintained for the qualitative and quantitative syntheses (Fig. 1), with full consensus at double check [13–35].

Table 2 shows the main patients' features, information on work limitations and work-specific difficulties. Studies' samples were quite heterogeneous in terms of composition, as there were both clinics based and population studies. As a whole, mean age was 43.2, and most of enrolled subjects were females (86.4 %) and employed (81 %): four studies were on females only [16, 20, 26, 32] and five studies were

**Table 2** Summary data

| Patients features | |
|---|---|
| Total sample (min–max) | 51,135 (44–12,053) |
| % Females (min–max) | 86.4 % (68–100 %) |
| Average age (min–max mean age) | 43.2 (28.6–47.7) |
| % Workers (min–max) | 81 % (56.5–100 %) |
| Migraine, not specified | 72.1 % |
| Migraine without aura | 3.0 % |
| Migraine with aura | 1.3 % |
| Chronic migraine | 4.3 % |
| Headaches, not specified | 19.3 % |
| MIDAS score (min–max) | 38.8 (26.9–101.9) |
| Work data | |
| Average missed workdays, year basis | 4.3 (2.4–103.2) |
| Average workdays with reduced efficacy, year basis | 10.2 (6.4–47.2) |
| ICF-linked data | |
| d110–Watching | Poor evidence |
| d160–Focusing attention | Poor evidence |
| d166–Reading | Poor evidence |
| d175–Solving problems | Partial evidence |
| d240-Handling stress | Poor evidence |
| d350–Speaking | Strong evidence |
| d360–Using communication devices | Poor evidence |
| d430–Lifting and carrying objects | Poor evidence |
| d475–Driving | Strong evidence |
| d850–Remunerative employment | Strong evidence |

carried out in workplace settings [25, 26, 28, 30, 32]. The most common diagnosis was unspecified migraine and unspecified headaches. The most used assessment tool was the MIDAS (Migraine Disability Assessment Schedule) [36]: MIDAS scores were reported in eight studies [13–17, 19, 24, 25].

The average number of workdays lost on a 1 year basis varied between 2.4 and 103: however, one study focussed on chronic migraine and on patients discharged from hospitals, which lost approximately half of their workdays in the reference period. Excluding this study, the average number of workdays lost on a year basis was 3.5, and varied between 2.4 and 9.2, and the average number of days worked with reduced efficacy was approximately threefold.

Most of the ICF-linked data showed poor evidence. There is partial evidence that headache sufferers have difficulties in problem solving activities and strong evidence for difficulties in speaking, driving and, of course, remunerative employment: in this case, the difficulty is generally expressed in terms of reduced ability to perform job activities or reduced ability to work as usual.

## Discussion

This review showed that, although it is widely accepted that migraine are likely to determine problems with work-related activities, there is a paucity of information on the actual impact of the disorder on work activities. On average, a migraine sufferer looses 3.5 days of work, but presenteeism is much more common, as the average number of days worked with reduced effectiveness is around 10. There is very scarce information on what kind of activity is mostly affected by headaches: some kind of result was found for skills such as problem solving, and activities such as speaking and driving. In addition to this, the way in which problems with remunerative employment were addressed in included papers was restricted to concepts such as "reduced work performance" or "inability to work as usual". However, this way to address the construct is largely inadequate, as the meaning of "work as usual" may represent very different concepts—according to respondents' work tasks—and, similarly, what a full work performance is expected to be is a function of the job tasks and the amount of demand from the workplace. The result is that in available literature, the actual meaning of both "usual work" and "full performance" was never clarified.

In our opinion, the main reason for the paucity of data on this topic lies in the absence of a specific assessment instrument and of a standardised methodology to collect work limitations in migraineurs. This is particularly problematic if we take into account the huge impact of work difficulties in the determination of migraine costs: more than 90 % of them are indirect costs, and those connected to presenteeism are around 50 % in medication overuse headaches—where, however, the period of hospitalisation is to be taken into account—and around 67 % in episodic migraine [4]. Unfortunately, the amount of data collected with this literature review alone is not adequate to launch an initiative to develop a new assessment instrument. This is consequence of the search strategy that was based on MedLine only—a choice that was made to ensure higher quality of data with regard to the diagnosis of headache disorders—and, most of all, of the absence of reliable information on problems in work-related activities among headache sufferers.

In conclusion, we performed a literature review for the years 2000–2013 and found confirmation of the relevant impact of headaches in terms of loss workdays and of workdays with reduced effectiveness. Despite the relevance of work issues in terms of indirect costs, we found very few data addressing difficulties in specific activities. For further research, a return to patient-derived data is needed to get to a definition of core themes, also in view of the development of a new assessment tool. The availability of such an instrument could allow a better understanding of

the impact of migraine on single work activities: this, in turn, could help to assess the outcomes of treatment interventions and to assist the development of therapies with less side effects which may contribute to patient's difficulties in work activities (e.g. drowsiness, dizziness, confusion, visual and cognitive disturbances).

**Conflict of interest** We certify that there is no actual or potential conflict of interest in relation to this article.

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# Migraine in health workers: working in a hospital can be considered an advantage?

**M. Bartolini · G. Viticchi · L. Falsetti · A. Ulissi · M. Baldassari · A. Medori · S. Mattioli · F. Lombardi · L. Provinciali · M. Silvestrini**



**Abstract** Migraine is the most common form of headache, and is one of the most diffused pathologies in the world. Moreover, patients often lose years before obtaining a correct diagnosis. The aim of this study was to evaluate whether diagnostic delay differs between hospital workers, in theory more sensible to health problems, and common people. We compared our cohort of patients attending the headache center on which we put a diagnosis of migraine with and without aura with a sample of hospital workers investigated about headache presence and characteristics. Particularly, hospital workers were evaluated by ID-migraine test, a three-question test validated to formulate a migraine diagnosis. Continuous variables (age and diagnostic delay) were compared with *t* test for independent samples. Dichotomous and categorical variables were compared with Chi squared test. The mean difference between in-hospital workers and outpatients was analyzed with a GLM/multivariate model accounting for age and sex. The difference between the single subcategory of workers affected by migraine was explored with a GLM/multivariate model accounting of age and sex. Five hundred and ninety-nine patients affected by migraine with and without aura were enrolled. Demographical characteristics were comparable in the two study populations. In-hospital workers (99 patients) had a mean longer diagnostic delay (14.89 years; 95 % CI: 7.85–21.93 years) with respect to the outpatients (12.13 years; 95 % CI: 5.37–18.89 years). The difference resulted statistically significant at the multivariate model ($p < 0.05$). Single subpopulations of in-hospital workers did not have a statistically significant different delay in diagnosing migraine. Diagnostic delay was significantly longer in hospital workers with respect to outpatients. Then, we can conclude that our population of hospital workers did not present a particular attention to their headache, probably because of a tendency to self-treating. Moreover, we did not find differences among different typology of workers, underlining that different job experience and education did not contribute to a best management of headache. More information and informative initiatives are necessary to sensitize people about migraine, especially among hospital workers.

**Keywords** Migraine · Diagnostic delay

## Introduction

Migraine is one of the most diffused pathologies in the world. In Europe up to 15 % of the population complains of this form of headache [1]. Diagnosis can be quite easily obtained according to the International Headache Society (IHS) guidelines [2] and no radiological or laboratory exams are usually necessary. Moreover, several studies showed that the diagnostic delay is very relevant in migraine, and very often patients need years for a correct definition of their problem [3, 4]. Our group investigated the diagnostic delay for migraine in general population and

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found a mean time to achieve a correct diagnosis of 10.7 years [5]. Moreover, we observed that the wasting time for diagnosis is proportional to the increasing number of instrumental examinations performed by patients [3, 6]. Hospital workers are expected to be more sensitized to health problems and more favored in the possibility of a medical consultation in order to clarify any suspected condition. This should be especially true for doctors, nurses and clinical workers.

The large number of shift workers in the hospital staff makes this particular population at an increased risk for headache because frequent changes in work time involves sleepless nights.

Hughes and colleagues investigated headache occurrence in people working in hospital focusing their attention on therapies and drugs employment [7]. Instead, no data are available about the diagnostic delay for migraine in hospital workers.

The aim of this study was to evaluate if there is a difference in migraine diagnostic delay between hospital workers and common people. Moreover, we investigate if there were any differences among different typology of in-hospital workers.

## Methods

We evaluated the occurrence of headache in the hospital employers during their legal visits for ability to work, as routinely concerned by the law. Time of onset of headache symptoms was the core of our investigation. Moreover, we checked if headache patients had ever undergone a specialist visit. Particularly, we evaluated headache presence by a self-questionnaire including the ID-migraine test (a three-question test validated to formulate a migraine diagnosis) [8]. Moreover, we investigated the specific characteristics of the job activity including the work time and the demographic characteristics.

We compared this sample of hospital workers with our database of headache center about all patients of the last 5 years on which we put a first diagnosis of migraine with and without aura according to IHS criteria [2]. These patients performed a complete visit with a physical examination, a complete anamnesis about their clinical history and finally a complete questionnaire about headache characteristics.

In the statistical analysis, we recorded for each patient the number of years from symptoms onset to migraine diagnosis, age and sex. Age and diagnostic delay were treated as continuous variables, sex was treated as binary. The subgroups of workers were synthesized as ordinal variables. Continuous variables were compared with *t* test for independent samples. Dichotomous and categorical variables were compared with Chi squared test. The mean difference between in-hospital workers and outpatients was analyzed with a GLM/multivariate model accounting of age and sex. The difference between the single subcategory of workers affected by migraine was explored with a GLM/multivariate model accounting of age and sex. Statistical analysis was performed with SPSS 13.0 for Windows systems.

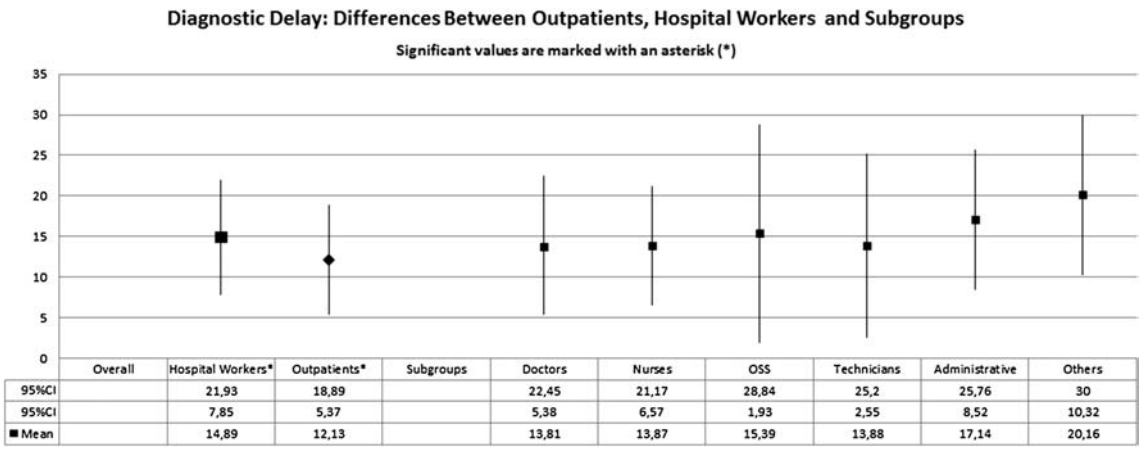
## Results

We considered a total of 639 hospital workers from September 2013 to February 2014: 377 subjects complained headache, but only 99 of them referred symptoms consistent with migraine with or without aura. In this subgroup, 16 (2.7 %) were doctors, 53 (8.8 %) were nurses, 3 (0.5 %) were sanitary operators, 6 (1 %) were technicians, 14 (2.3 %) were administrative employees, 8 (1.3 %) covered other positions. Five hundred subjects (83.3 %) were outpatients coming from our headache center.

Finally, a total of 599 patients affected by migraine with and without aura were enrolled. Mean age of in-hospital workers was 40.24 years (±9.72 years), mean age of our outpatients' population was 39.02 years (±13.60 years). *t* test showed a non-significant difference ($p = 0.393$) between the two subpopulations. Female sex was represented in 81 % of in-hospital workers and 78 % of the outpatients, and this difference did not result as statistically significant at Chi squared statistics ($p = 0.740$). In-hospital workers (99 patients) had a mean longer diagnostic delay (14.89 years; 95 % CI: 7.85–21.93 years) with respect to the outpatients (12.13 years; 95 % CI: 5.37–18.89 years), and this difference resulted statistically significant at the multivariate model ($p < 0.05$) (Fig. 1). Single subpopulations of in-hospital workers did not have a statistically significant different delay in diagnosing migraine: doctors (13.81 years; 95 % CI: 5.38–22.45 years), nurses (13.87 years; 95 % CI: 6.57–21.17 years), Sanitary operators (15.39 years; 95 % CI: 1.93–28.84 years), technicians (13.88 years; 95 % CI: 2.55–25.20 years), administratives (17.14 years; 95 % CI: 8.52–25.76 years) and other (20.16 years; 95 % CI: 10.32–30.00 years) showed a non-significant difference at multivariate model (Fig. 1).

## Discussion

Our data showed that diagnostic delay for migraine is surprisingly longer in hospital workers with respect to an outpatient population. These findings were largely unexpected because, as reasonably assumed, people working in a general hospital should be more sensitized about health




| | Overall | Hospital Workers* | Outpatients* | Subgroups | Doctors | Nurses | OSS | Technicians | Administrative | Others |
|---|---|---|---|---|---|---|---|---|---|---|
| 95%CI | | 21,93 | 18,89 | | 22,45 | 21,17 | 28,84 | 25,2 | 25,76 | 30 |
| 95%CI | | 7,85 | 5,37 | | 5,38 | 6,57 | 1,93 | 2,55 | 8,52 | 10,32 |
| Mean | | 14,89 | 12,13 | | 13,81 | 13,87 | 15,39 | 13,88 | 17,14 | 20,16 |

**Fig. 1** Migraine diagnostic delay: hospital workers presented a significant major delay in respect to out-patients. There are no significant differences among different sub-groups of in-hospital workers

problems and have more opportunities to undergo to medical evaluations or to obtain neurological consults.

A further interesting information from our study is that no significant differences in diagnostic delay derived from different job activities. In this respect, it was surprising that medical doctors and nurses shared the same diagnostic delay of the other workers who did not experience clinical activities. This finding is difficult to interpret. One hypothesis is that clinicians are inclined to use symptomatic therapies for a non-life-threatening condition without consulting a specialistic colleague. There are many studies about all the risks linked to uncontrolled use of symptomatic therapies [9, 10]. First of all, a non-specific treatment of migraine attacks tends to increase the risk of chronicization. Moreover, a relevant use (often till to a real abuse) of NSAIDs could cause severe consequences for health.

This study has two major limits: the first one is that the data of hospital workers were drawn by a self-questionnaire and not by a face-to-face visit. This fact could produce a possible bias, so we are planning to visit all these selected subjects in a second time to validate our data. The second limitation concerns the concept of delay: we considered the time between the day of our clinical diagnosis and the onset of symptoms as a diagnostic delay index. We recognize that it is an arbitrary assumption. However, we can underline that each of the 99 hospital workers have never had a previous diagnosis of migraine in spite of the fact that they presented typical symptoms from several years and usually they used symptomatic therapies. So, the gap between our assessment and the large amount of years with an unrecognized headache could be a reliable index for the waste of time.

In conclusion, our study demonstrates that for a fast recognition and effective management of migraine a strong engagement is still necessary. On the other hand, diagnostic work is essential for a rational therapeutic management in order to an uncorrected use of symptomatic drugs and useless investigations. More informative initiatives are necessary to sensitize people, including hospital workers about migraine.

**Conflict of interest** I certify that there is no actual or potential conflict of interest in relation to this article.

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# Headache in school age

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**Abstract** Headache, especially migraine and tension-type headache, is one of the most frequently reported somatic complaints by children and adolescents. Different population-based studies have been conducted to study the correlation between headache and lifestyles in pediatric age, nevertheless, the obtained results are often controversial and these relationship still remain unclear. Likewise, is still strongly debated the burden of headache during school age, its impact on school performances and on quality of life of children and their families. Consequently, larger studies are necessary to evaluate the degree of disability due to pediatric headache. We summarize the ongoing knowledge about these concepts, with the intent to provide useful data to neurologists but also to primary care providers, to further improve the management of pediatric headaches by preventing the headache progression, the disabling effects associated and improving the long-term outcome.

**Keywords** Headache · Migraine · Children · Adolescent

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## Introduction

Headache is one of the most common health complaints in the general population as well as in childhood and adolescents. The most common forms in school children are primary headaches defined according the International Headache Society (IHS) criteria as headaches not associated with underlying disorders [1]. Similar to adults, migraine and tension-type headache (TTH) represent the most frequent headaches among this group. Secondary headaches, such as those that develop alongside an injury or an infection, are possible in children but uncommon. Parents usually tend to underestimate the headaches of their children, also considering that the distinction between migraines, and TTH is difficult in this age group [2]. The prevalence of pediatric headaches has been studied across all ages starting in early childhood. The publication of the ICHD I-II, respectively, in 1988 and 2004 [3, 4] allowed a consistently increasing number of studies on epidemiology of pediatric headaches and a more accurate estimation of their impact on the child and their families. The environment of a child's world, which includes school, home and community, appears strongly affected by headache, mostly by migraine which is the primary headache most frequently brought to the attention of parents and primary care providers. Migraine commonly starts in childhood and adolescence and can even become chronic, inducing a heavy impairment in child's quality of life (QoL). The early recognition, the choice of acute and preventive therapies, the lifestyle adjustments and the early treatment of comorbid conditions, can affect the disease progression for the lifetime of the individual, preventing long-term discomfort and enhancing QoL of these children and their families.

## Epidemiology

The reported prevalence of headache among school children varies greatly, from 5.9 to 82 %, depending on the age and the definition criteria [5–11]. By age 3, headache occurs in 3–8 % of children, at age 5, 19.5 % have headache and by age 7, 37–51.5 % have headaches. In 7–15-year-olds, headache prevalence ranges from 57 to 82 %. Two recent reviews of cross-sectional epidemiological studies on headache in children and adolescents under the age of 20 years estimated the overall mean prevalence around 54.4 [12] and 58.4 % [13], respectively. According to Abu-Arafeh and colleagues, the overall estimated migraine prevalence is 7.7 % with a difference of 3.7 % between gender (respectively, 9.7 % in female children and adolescents and 6.0 % in males). Migraine is more frequent among boys up to 7 years of age; from 7–11 years, the frequency is the same for both genders and after 11 years of age, migraine predominates among girls. The headache and migraine prevalence increases also from childhood to adolescence. The estimated difference in both genders is significantly lower in subjects <14 years of age than in all subjects under the age of 20 years: 7.0 % < 14 years versus 9.7 % all ages under 20 years in females 4.7 % < 14 years versus 6.0 % all ages under 20 years in males [13]. This analysis shows that around 60 % of children are prone to experience headache at least once a life, over periods varying from 3 months to lifetime. Migraine is the more common disturb among children, with a geographical variability which shows higher prevalence in Europe and Middle East compared to Far East and USA. In spite of these differences among countries, it seems to be safe to fix prevalence around 8 % [13]. With regard to the onset age, the incidence of migraine without aura peaked between age 14 and 17 in girls and 10 and 11 in boys; migraine with aura incidence could be peak earlier [14].

## Comorbidities

Primary headaches, especially migraine, are positively associated with many other diseases in children and adolescents. The association of migraine with some disorders is not due only to a simple coexistence but implies a linkage in terms of causality. This combination induces a remarkable increase in the total burden of pediatric headache. However, some of these associations were confirmed by several studies, whereas others still remain uncertain or controversial [15]. In children, the relationship between headaches and psychopathology has been proved by several studies [16]. In a meta-analysis involving 406 patients, authors found that migraine children had more psychological symptoms, detected by Child Behavior Checklist than healthy controls [17]. Anxiety and depression resulted more prevalent in headache and migraine patients [18], and headache was the most frequent somatic symptom in children and adolescents referred for anxiety, depression and behavioral disorders, with a prevalence of females [19]. Moreover, it is well known that anxiety predicts the persistence of migraine and tension-type headache [20]. Higher frequency of suicidal ideation in young adolescents with migraine with aura or high headache frequency was reported, as well as nearly half of children with chronic daily headache (CDH) have been reported to be affected from one or more psychiatric disorders [21]. Among CDH patients, 29.6 % met criteria for at least one psychiatric diagnosis: Anxiety disorders were the most common (16.6 %), while mood disorders were less prevalent (9.5 %) [22].

Many studies have investigated the linkage between headaches and sleep disorders, especially the relationship between migraine and sleep has been investigated for a long time. Migraine might emerge during nocturnal sleep or following a brief period of daytime sleep; attacks can be preceded by a lack of sleep as well as sleep has been shown to relieve migraine, especially in children [23]. The relationship between headache and sleep complained in children and adolescents has also been widely studied by an Italian study, which confirmed that the most frequent triggering factor for migraine or non-migraine headache was "bad sleep". However, noteworthy, also the self-perception of disturbed sleep was prevalent in children and adolescents with migraine or other headaches [24].

A higher incidence of parasomnias, among which bruxism, somnambulism, sleep talking and nightmares, have been documented in children with migraine not only compared with controls but also with other headaches [24, 25]. A history of somnambulism was present in 32.8 % migraineurs referred to a neurological unit, in comparison with a prevalence of 2–7 % in the general population [26]. In a community sample of students aged 6–13 years, migraine resulted associated with bedtime struggle, teeth grindings, sleep vocalizations, nightmares and sleep walking [27]. On the other hand, Miller and colleagues showed that the frequency and the duration of migraine might predict the development of specific sleep disturbances, including sleep anxiety, parasomnias, co-sleeping with parents and bedtime resistance [28]. These data were confirmed by a recent population-based survey, which found that the reported relative risk of all sleep symptoms investigated, except enuresis, was significantly higher in children with migraine [29].

Among neurological disorders, the relationship between migraine and epilepsy remains uncertain. The higher prevalence of migraine in epilepsy patients individuated by some studies has not been completely confirmed by further

studies. In a recent Italian survey, 30 % of 142 epileptic children reported preictal headache, 62 % post-ictal headache and 57.6 % inter-ictal headache with prevalence of migrainous features [30]. The overall prevalence of migraine in children with epilepsy varies from 8 to 15 %. Also the increased risk of seizures in migraine with aura is still debated [15].

Migraine headache resulted four times more prevalent in children with Tourette syndrome than in the general pediatric population [31], while the association between primary headaches and attention-deficit/hyperactivity disorder, learning disabilities and stuttering is controversial [15].

Only few studies have investigated the relationship between migraine or other primary headaches and general medical conditions. Lateef et al. found a correlation between headache and asthma, high fever and frequent ear infections in a child population study [32]. It has also been found a higher comorbidity of migraine with atopic disorders (asthma, rhinitis or eczema) in small clinical studies, while an association between cerebrovascular or cardiovascular disease and migraine in children has not been recognized [15].

## Lifestyle and headache

Lifestyle factors, long implicated in the onset and exacerbation of headache disorders in adults have rarely been studied in children and adolescent. The HUNT study is a Norwegian large cross-sectional school-based study conducted on 13–18-year-old adolescents, to assess the relationship between lifestyle factors and the prevalence and the frequency of three types of headaches (migraine, tension-type and "non-classifiable headache"). Negative lifestyle factors examined were low physical activity (defined as students who exercised less than twice a week), obesity and smoking. When examined one at a time, each of these factors was associated with an increased prevalence of migraine, TTH and non-classifiable headache in both genders. Recurrent headache was found statistically significant associated with obesity (OR 1.4), low physical activity (OR 1.2) and smoking (OR 1.5). Non-significant differences were found among genders regarding these associations. Likewise, a significant correlation was found between all these negative risk factors and each headache type. The authors also demonstrated that there was a relationship statistically significant between the number of negative factors presented and the frequency of headache (very poor lifestyle and headache weekly or daily, OR 5.0, $p < 0.0001$). The authors hypnotized the role of these negative lifestyle factors both as risk factors which might increase the incidence of headache and as exacerbating factors with an effect on headache frequency in exposed individual [33].

A recent study investigating the association between diet and different types of headache in adolescents revealed that high consumption of cocktails (OR 3.4) and coffee (OR 2.4) was significantly associated with migraine plus TTH episodes. They did not find any correlation between headache and skipping of meals [34]. Regarding specific meal habits, a population-based Italian study revealed that among 800 studied students who suffered from headache, those with the "more painful headache attacks" were irregular meal consumers ($p < 0.0001$), especially patients used to skip breakfast ($p < 0.0001$) [35]. Even the excessive chewing gum use has been reported associated with an increase in headache frequency and severity (both migraine and TTH) in adolescents [36]. Finally, with specific regard to migraine, among the common precipitating factors in children and teenagers, there are stress, tiredness, videogames, noise, sunlight and the menstruation in girls [37, 38].

## QoL and disability

Pediatric headaches might often generate a leak of QoL in children and a consequent disability mainly due to a loss of school and family activities and to an impairment of psychological aspects. To evaluate the disability of pediatric migraine, PedMIDAS, was developed considering that school work is the major work responsibility for children, with a lower emphasis placed on household chores [30]. Three similar domains to PedMIDAS were evaluated: the school, the home and the social involvement [39, 40].

Health-related quality of life (HRQL) is the instrument used to assess the impact of a disease. The assessment of QoL in children is difficult, since measures must consider children's changing cognitive and social development. In addition, there is the question of who should provide the information, the parent or the child. The pediatric QoL inventory, version 4.0 (PedsQL 4.0) is a valid, developmentally appropriate measure of QoL in children between the ages of 2 and 18 years [41]. It is an useful tool used for many pediatric chronic disease including headache [42]. The PedsQL 4.0 (17) is a brief 23-item measure that evaluates QoL in four areas of functioning: physical functioning (eight items), emotional functioning (five items), social functioning (five items) and school functioning (five items). The PedsQL 4.0 has four age ranges: preschool age (2–4 years), small children (5–7 years), children (8–12 years) and adolescents (13–18 years). The instrument evaluates the perception of HRQL in children and parents, except for toddlers (2–4 years), where only report by parents is obtained.

In a recent study to determine QoL of migraines aged 6–12, Ferracini and colleagues found that children with migraine lost on average 13.9 days over the last 3 months considering the overall performance (school, household tasks and leisure), without significant difference between gender (boys 13 days vs. girls 15 days). Regarding absenteeism from school, the children lost 3.5 full days and 4.9 partially days on average without difference between genders. Finally, about presenteeism, the situation in which the child does not show a good performance at school because of physical or mental health problems, they found on average a loss of 5 days over 3 months in the children with migraine [43]. These data confirmed previous studies [44, 45] that did not find gender difference regarding absenteeism and presenteeism.

The assessment of disability showed a degree of severe and moderate disability in 14 %, of patients, a mild disability in 34 % and absence of disability in 38 %. Noteworthy, according to children perception, none impairment was noticed in the QoL total score by children with migraine compared to those without migraine. Instead, according to parents' perception, there was a worse general QoL ($p < 0.01$). The analysis of each separated aspect revealed an impairment of different QoL items: emotional and school aspects were mainly affected according to children perceptions, and physical and psychosocial aspects according to parents perceptions [43].

The cross-sectional comparisons within the migraine sample found differences in functional impairment among age groups. Adolescents (ages 13–18 years) reported more impairment in school functioning than children (ages 8–12 years) and young children (ages 5–7 years). In contrast, young children reported more impairment in social functioning compared with children and adolescents [46]. Despite of these evidences, these associations are weak and is still controversial the association between QoL and headache parameters across the age groups.

The study conducted by Ferracini in agreement with a previous datum reported by Gold et al. [47] has observed that children with headache do not realize to have a worse HRQL according to their self-perception. This evidence agrees with the behavior reported in children affected from cancer and rheumatologic diseases. Nevertheless, previous data reported in literature [46, 48, 49] partly disagreed, showing that also children and adolescents with migraine might have an impairment of HRQL in based on their self-perception. Anyhow, all studies agree and confirm there is a worse HRQL in children with migraine according the parents perceptions.

## Conclusion

Measuring the impact of headache in children in terms of epidemiology, health status, functioning and QoL is a fundamental necessity considering that headache is the most frequent neurological symptom and the most common manifestation of pain in childhood. Rigorous studies are necessary to quantify this burden using measures valid and reliable. Modifications of lifestyle habits play an important role in prevention and in the treatment strategy of headache disorders, especially in childhood and adolescence, but large scale longitudinal studies are necessary to clarify their role as risk factors, exacerbating factors or triggers factors. Regarding the causality between migraine and HRQL, the relationship is complex and still unknown. Few longitudinal studies are available to assess the effect of HRQL across age in migraine and in other types of headache during childhood and adolescence. Moreover, although the present studies demonstrate that migraine interferes with some daily activities, especially at school it is still debated if and the extent to which children perceive this impairment in the QoL. This analysis is mandatory to understand the risks and consequences of pediatric headaches across the years.

**Conflict of interest** I certify, as corresponding author, that there is no actual or potential conflict of interest in relation to this article.

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# Botulinum toxin A: a new option for treatment of chronic migraine with medication overuse

**Licia Grazzi · Susanna Usai**



**Abstract** The application of Botulinum toxin for several pathological conditions has been largely debated in the last decades and its use has been definitively consolidated for disorders related to increased muscle tone and hyperidrosis. Botulinum neurotoxin (BoNT-A) is a potent toxin produced by an anaerobic bacterium, *Clostridium botulinum*, which presents several pharmacological proprieties, but also different and serious contraindications. As chronic migraine (CM) is commonly reported as a serious and debilitating condition and a big challenge from the therapeutic point of view, in the last decades, after isolated observations, BoNT-A has been applied as preventive treatment for CM patients and, after randomized and rigorous studies, it has been accepted among the most effective pharmacological treatments for these problematic patients. In the present report, a group of patients suffering from CM with medication overuse was treated with BoNT-A to verify its efficacy for CM. The results confirmed the efficacy of BoNT-A when used at the dosage of 155 UI, according with the PREEMPT study protocol. Although these results are preliminary, in a limited group of patients, they led to intense efforts to enforce the use of BoNT-A for CM and to assess its clinical applicability.

**Keywords** Onabotulinum toxin A · Chronic migraine · Medication overuse · Clinical indexes

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## Introduction

Patients suffering from chronic migraine (CM) are problematic to treat as this condition is debilitating and conditioning the affective and social life of individuals. CM affects 1.4–2.2 % of the general population [1]. These patients experience headache >15 days per month for >3 months, and often they overuse medications for aborting pain for more that 15 tablets per month (generally triptans or NSAIDS).

An effective prophylactic treatment, based on pharmacological and also multidisciplinary measures, often after an adequate withdrawal from offending medications, can improve significantly the clinical condition of these patients by reducing the medication consumption [2].

Onabotulinum toxin A has been reported helpful in several pain conditions, in particular patients treated by Onabotulinum toxin A for increased motor disturbances noted a decrease in pain and consequently the use of Onabotulinum toxin A to improve pain in pain conditions including migraine has been applied [3–5].

Concerning migraine treatment, different studies with different protocols of treatment have been applied with results not always significant from the clinical point of view. Only recently, studies and the PREEMPT protocol evolved from preceding paradigms, by showing definitely that Onabotulinum toxin A is a safe, well-tolerated and effective headache prophylactic treatment for CM [6].

The mechanism of action of Onabotulinum toxin A in antinociception has not been clearly clarified yet: probably, as demonstrated in some studies, Onabotulinum toxin A inhibits the release of nociceptive mediators (glutamate, substance P, CGRP) from peripheral terminals of primary afferents [7, 8].

Blocking the release of these neurotransmitters, inhibits neurogenic inflammation and consequently the peripheral

sensitization of nociceptive nerve fibers. As result, peripheral pain signals to the central nervous system are reduced and central sensitization is blocked [7–9].

The problem concerning treatment of patients with CM and medication overuse is challenging for physicians involved in this field and, as the significant population of CM patients refractory to common therapeutic prophylaxis, Onabotulinum toxin A can be considered a new option for these problematic patients.

At our headache centre, clinical experiences evidence that treatment of CM with medication overuse need a multimodal strategy where behavioural, social and affective components have to be considered and also innovative pharmacological therapies have to be developed.

On the basis of the most recent clinical experiences, with specific paradigms, Onabotulinum Toxin A has been used at our headache centre at the Besta Institute of Milan as preventive treatment to treat patients suffering from CM with medication overuse after an adequate withdrawal program.

Aim of this study was to evaluate a group of patients treated with 155 UI of BoNT-A to verify its efficacy for CM with medication overuse.

## Patients and procedure

A group of 23 patients, 18 females and 5 males, mean age 51.1 ± 7.9 suffering from CM with medication overuse (diagnosis made according with the HIS criteria 2004 revised in 2006) [10, 11] were treated.

Patients underwent to a withdrawal program in a day hospital regimen for 5 days in order to stop the overuse of symptomatic medications. After that, patients were treated by Onabotulinum toxin A injection, in multiple sites, according with the protocol proposed by the PREEMPT study [6] at the dosage of 155 UI for 31 sites.

Every session of local injection (155 UI per 31 sites; 5 UI per each site) has been repeated every 3 months for a period of 1 year. Totally five injections of Onabotulinum toxin A were performed.

Clinical indexes, number of medication intake per month and days of headache per month, were recorded by using an headache daily diary.

Patients until now achieved the 6th month of treatment.

## Results

Data concerning this group of patients evidenced that days of headache/month decreased significantly during the period of treatment from the first session of therapy to the third session, 6 months later (pre 22.2 ± 6.9, post 13.8 ± 9.2, $p < 0.005$). Also medication intake decreased significantly (pre 20 ± 6.9, post 13.7 ± 9.2, $p < 0.0005$).

## Discussion

As CM is a serious clinical condition for patients, very disabled and at risk of medication overuse, and the moderate response to treatment, so common for this category of patients, the possibility to use new therapeutic options is crucial, also if the necessity of a multimodal treatment program, based on different kinds of therapeutic measures for these patients, has been confirmed in the last clinical experiences [2].

In the past, basic science data strongly support an analgesic effect of BoNT-A. According with these evidences, many headache clinicians have seen patients with CM who have responded significantly to BoNT-A treatment.

In the past decade, data from different studies were not conclusive due to the erroneous selection of patients and to the different protocols of treatment. On the other side, the most recent clinical trials have shown more positive results as more selective criteria for inclusion of patients were used.

The correct selection of patients is the key to the successful use of BoNT-A in CM management [12].

Although results of our study are preliminary, as patients were treated until the 6-month follow up, they led to intense efforts to evaluate analgesic properties of Onabotulinum toxin A and to assess its clinical applicability.

Moreover, the pharmacological profile of Onabotulinum toxin A makes it a good candidate for migraine prevention at the adequate dosage as proposed in the PREEMPT study. Its long duration of action (3 months) makes it particularly attractive for patients who are not compliant with the daily use of preventive medications, or if they cannot tolerate them or when they are refractory to preventive medications.

Although we did not assess it specifically, all patients accepted the treatment without referring any significant side effects or unpleasant events; moreover, they reported improvement in quality of their life as they did not assume medications every day for long period of time.

In conclusion, data from recent studies show encouraging results: BoNT-A seems to be effective for patients with CM; in particular the long duration of action and favourable adverse events make it a suitable therapeutic alternative for patients not compliant with oral preventive medications. The application of BoNT-A is indicated also in the early stage of the disease and this may result in better treatment outcome.

Future studies have to be performed to better understand the mechanism of action of BoNT-A and to identify possible predictors of response to this innovative treatment.

**Conflict of interest** I certify that there is no actual or potential conflict of interest in relation to this article.

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# Technique of injection of onabotulinumtoxin A for chronic migraine: the PREEMPT injection paradigm

**P. Liberini · E. Pari · S. Gazzina · S. Caratozzolo · R. Rao · A. Padovani**



**Abstract** In 2013 the Italian Pharmacy Agency (AIFA) approved onabotulinumtoxin A injection to prevent headaches in adult patients with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine) that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse. In the present paper we report the method of injection of Onabotulinumtoxin A for chronic migraine based on the PREEMPT paradigm as described by Blumenfeld et al. (Headache 50:1406–1418, 2010) adapted to our clinical setting.

**Keywords** Chronic migraine · Onabotulinumtoxin A · Technique of injection

## Introduction

Botulinum toxin type A is a purified neurotoxin complex, which is derived from the bacterium *Clostridium botulinum* and blocks peripheral acetylcholine release at presynaptic cholinergic nerves. The presumed mechanism for headache prophylaxis is the blockage of peripheral signals to the central nervous system, which inhibits central sensitisation; however, the actual mechanism of action for headache prophylaxis is not known.

Italian marketing provides authorisation for the prophylaxis of headaches in adults suffering from chronic migraine. Its efficacy erases from two randomised controlled trials, known as PREEMPT 1 and PREEMPT 2. Both evaluated botulinum efficacy on a 56-week treatment time period. In the first step (24 double blinded weeks) a series of 31–39 intramuscular injections of botulinum toxin type A or placebo at day 0 and week 12 were administered to patients. In the second step, all patients received botulinum toxin type A at weeks 24, 36 and 48. PREEMPT enrollment criteria were chronic migraine (at least 15 headache days in the 28 days before week 0, and at least 50 % of headache days had to be migraine or probable migraine days) in patients aged 18–65 years.

Reduction in frequency of headache days (primary endpoint) was statistically significant in both the trials [1]. In PREEMPT 1, there was a reduction of 7.8 headache days from 20.0 at baseline for patients treated with botulinum toxin type A, compared with a reduction of 6.4 headache days from 19.8 at baseline for those in the placebo arm ($p = 0.006$) [2]. In PREEMPT 2, there was a reduction of 9.0 headache days from a baseline of 19.9 in the botulinum toxin type A arm, compared with a decrease of 6.7 headache days from a baseline of 19.7 days for those in the placebo group ($p < 0.001$) [3]. As secondary endpoints, total cumulative hours of headache, frequency of migraine days, and number moderate to severe headache days, were statistically significantly lower in the botulinum toxin type A group compared with the placebo group in both studies. Health-related quality of life was also analysed, with the headache impact test 6 (HIT-6) and the migraine-specific quality of life questionnaire (MSQ). At 24 weeks a statistically significant reduction of 7.4 headache days from 20.0 days at baseline in the pooled botulinum toxin type A group, was found compared with a reduction of 4.7 headache days from 20.2 days at baseline in the pooled placebo group ($p < 0.001$).

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**Table 1** Botulinum toxin type A dosing by muscle for Chronic Migraine

| | Recommended dose |
|---|---|
| Head/neck area | Total number of units (U) (number of IM injection sites[a]) |
| Frontalis[b] | 20 U (4 sites) |
| Corrugator[b] | 10 U (2 sites) |
| Procerus | 5 U (1 site) |
| Occipitalis[b] | 30 U (6 site) up to 40 U (up to 8 sites) |
| Temporalis[b] | 40 U (8 sites) up to 50 U (up to 10 sites) |
| Trapezius[b] | 30 U (6 sites) up to 50 U (up to 10 sites) |
| Cervical paraspinal muscle group[b] | 20 U (4 sites) |
| Total dose range | 155–195 U |

[a] 1 IM injection site = 0.1 mL = 5 U

[b] Dose distributed bilaterally for minimum dose

The presumed mechanism for headache prophylaxis is by blocking peripheral signals to the central nervous system, which inhibits central sensitisation, as confirmed by clinical studies. Limited non-clinical data also suggest that TBA may reduce sensitisation processes, but the actual mechanism of action for headache prophylaxis is not known. Further studies are requested in order to fully understand the mechanism of action in TBA.

## Methods

In the present paper we shortly describe the Blumenfeld et al. [4] method of injection of Onabotulinumtoxin A (TBA) for chronic migraine based on PREEMPT paradigm.

The basic recommended dose for treating chronic migraine is 155 U administered intramuscularly (IM) using a 30-gauge, 0.5 in. needle as 0.1 ml (5 U) injections per each site. This dose could be increased up to 195 U using a pain paradigm according the physician prescription. Injections should be divided across seven specific head/neck muscle areas as specified in Table 1. With the exception of the procerus muscle, all muscles should be injected in right and left sides. If there is a predominant pain location or severe palpable muscle stiffness, additional injections to one or both sides may be administered in up to three specific muscle groups (occipitalis, temporalis and trapezius, up to 40 U of additional TBA, at the physician's discretion.

It is good practice to perform vial reconstitution and syringe preparation over plastic-lined paper towels to catch any spillage. To reconstitute vacuum-dried TBA injection, use sterile normal saline without a preservative; 0.9 % sodium chloride injection is the recommended diluent. Draw up the proper amount of diluent in the appropriate size syringe. Since TBA is denatured by bubbling or similar violent agitation, inject the diluent into the vial gently. Discard the vial if vacuum does not pull the diluent into the vial.

The safe and effective use of TBA purified neurotoxin complex depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques. Physicians administering TBA should be familiar with the relevant anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures, and care should be taken into account when injecting in or near vulnerable anatomic structures.

Serious adverse events including fatal outcomes have been reported in patients who had received TBA injected directly into salivary gland or in the oro-lingual-pharyngeal region. Serious and immediate hypersensitivity reactions such as anaphylaxis and serum sickness have been rarely reported, as well as other manifestations of hypersensitivity including urticaria, soft tissue oedema, and dyspnoea. As with all biological products, adrenaline and other precautions as necessary should be available should an anaphylactic reaction occur. Some of these reactions have been reported following the use of TBA either alone or in conjunction with other products associated with similar reactions. If such a reaction occurs, further injection should be discontinued and appropriate medical therapy immediately instituted.

## Conclusion

Botulinum toxin type A should be considered a safe and effective option for caring headaches in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies. This therapy has been approved in 2013 by the Italian Pharmacy Agency (AIFA).

The recommended reconstituted dose is 155–195 units, administered intramuscularly with injections between 31 and 39 sites around the head and back of the neck. The recommended re-treatment schedule is every 12 weeks.

According to our previous [5] and recent experiences, we suggest to Italian neurologists to follow the method of injection of Onabotulinumtoxin A as described by Blumenfeld et al. [4] based on the PREEMPT paradigm.

**Conflict of interest** I certify that there is no actual or potential conflict of interest in relation to this article.

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# The cost effectiveness of Botox in Italian patients with chronic migraine

**M. Ruggeri**



**Abstract** Migraine is a primary headache which World Health Organization ranks in 19th place in the list of disabling diseases. In Europe, in 2004, the total costs for migraine were quantified by Stovner and Berg, Eur J Neurol, 12(s1) (2005) at €27 billion. The objective of this study is to provide an estimate of the incremental cost-effectiveness ratio (ICER) of the treatment of chronic migraine with Botox compared to treatment with placebo in the perspective of the Italian National Health Service and society. To do this we studied the disease progression in a cohort of 688 individuals (patients enrolled in the study PREEMPT) via the application of a Markov model. Over a period of 2 years, the total costs of the experimental arm of the model amounted to €3,274 compared with a gain of 1.34 QALYs. In contrast, the costs of the control arm amounted to €2,395 with a gain of 1.24 QALYs. It follows that the incremental costs amounted to €889 compared to an incremental gain of 0.09 QALYs in favor of the experimental arm. The relationship between costs and incremental QALYs generated an ICER of €9,407/QALY. The incremental cost-effectiveness ratio, therefore, is favorable compared to the value usually considered by NICE as a threshold limit for reimbursement which ranges between €20,000 and €40,000/QALY.

**Keywords** Chronic migraine · Cost effectiveness analysis · Markov model

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## Introduction

Migraine is a primary headache which World Health Organization ranks in 19th place in the list of disabling diseases, like other diseases such as blindness, psychosis and quadriplegia. However, worldwide it is still a condition underdiagnosed, undertreated and generally there is a lack of awareness of the burden of disease as well as health resources actually used [9].

Globally it is estimated that the prevalence of chronic migraine is in the range of 1.4–2.2 % [6], but it is likely that these values are underestimated because of the difficulties in diagnosing the disease. The societal cost is enormous, according to the WHO the value associated with lost productivity for all types of headache is even higher than the health care costs incurred by each country associated.

In Europe, in 2004, the total costs for migraine were quantified by Stovner and Berg [1] at €27 billion. The average total cost per patient per year, according to the authors, was €590 euro. The 72–98 % of the costs of migraine in Europe was made up of indirect costs, which amounted to €554 per patient per year (due to 4.5 days of work lost per patient/year), while the direct costs were 36€ per patient per year.

## Objectives

The objective of this study is to provide an estimate of the incremental cost-effectiveness ratio (ICER) of the treatment of chronic migraine with Botox compared to treatment with placebo in the perspective of the Italian National Health Service and society.

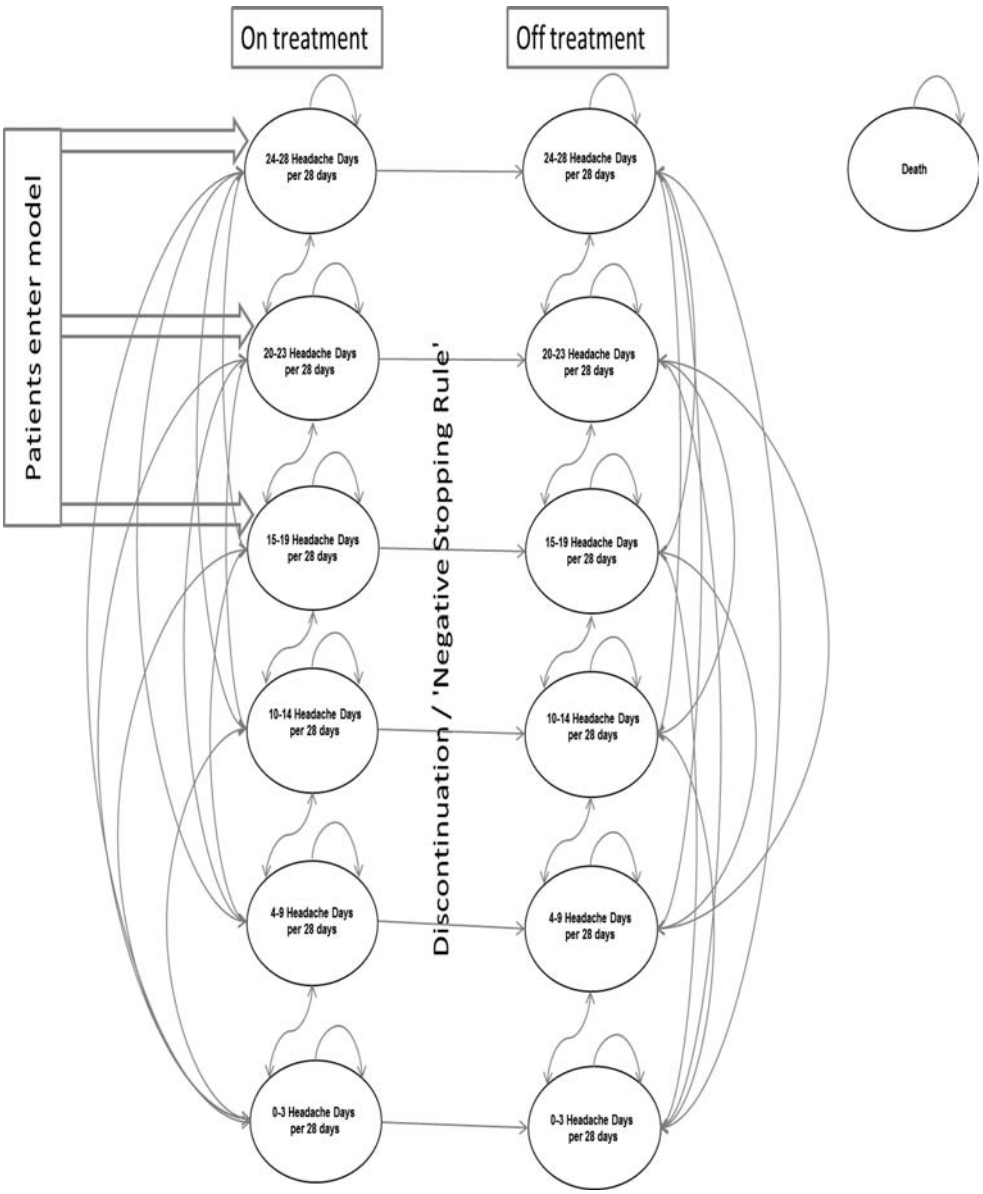


**Fig. 1** Markov model featuring patients with chronic migraine

## Methods

To do this we studied the disease progression in a cohort of 688 individuals (patients enrolled in the study PREEMPT [2]) via the application of a Markov model comprising two arms:

- arm "Botox";
- arm "Placebo"

We identified six states of health according to the frequency with which headache occurs in 1 month:

1. 0–3 days per month
2. 4–9 days per month
3. 10–14 days per month
4. 15–19 days per month
5. 20–23 days per month
6. 24–28 days per month

Figure 1 shows the Markov model which simulates the natural history of the disease and its changes as a result of the treatments used. The time horizon of the model is 2 years, while the duration of each cycle is equal to 12 weeks.

The transition probabilities used to populate the model were calculated starting from the PREEMPT clinical trial. The utilities associated with different health states were obtained from a study of Gillard et al. [3].

The estimation of the resources used for the implementation of the two treatment alternatives was carried out from the perspective of the Italian national health system (NHS) and the Italian society.

We considered the costs for medications, hospitalizations, visits to the general practitioner and emergency department access. We also included in the model the costs incurred for productivity losses [5, 7, 8] which we estimated from a median hourly wage for Italy amounted to €18.41 (ISTAT, 2008) [4].

## Results

Over a period of 2 years, assuming 688 patients treated with Botox, the total costs of the experimental arm of the model amounted to €3,274 compared with a gain of 1.34 QALYs. In contrast, the costs of the control arm amounted to €2,395 with a gain of 1.24 QALYs. It follows that the incremental costs amounted to €889 compared to an incremental gain of 0.09 QALYs in favor of the experimental arm. The relationship between costs and incremental QALYs generated an ICER of €9,407/QALY. The incremental cost-effectiveness ratio, therefore, is favorable compared to the value usually considered by NICE as a threshold limit for reimbursement which ranges between €20,000 and €40,000/QALY.

Adopting the perspective of the society and, therefore, by also including in the analysis the indirect costs associated with productivity losses, the ICER is reduced significantly and amounted to €815 over a period of 2 years. The univariate and multivariate probabilistic sensitivity analysis confirms the robustness of these results.

## Conclusions

The spread of the processes of economic evaluation to support decisions at various institutional levels of the system is a clear signal of the need to rationalize healthcare spending, in order to assure the population the best possible state of health in the face of available resources. The incremental cost effectiveness of Botox versus placebo for the prophylaxis of chronic migraine was favorable and below the threshold of acceptability implicitly used by NICE for reimbursement decisions. The sensitivity analysis conducted allowed us to explore the uncertainty in the model and confirm its robustness. In fact, by varying certain assumptions and certain parameters in the base case results in terms of ICER were always favorable to the use of Botox.

One limitation of the study is related to the choice of placebo as comparator. The cost-effectiveness or cost-utility evaluations are, in fact, generally conducted by comparing the benefits and costs of a new technology with those of the best alternative available. In addition to Botox, the other two drugs based on botulinum toxin type A currently approved and marketed in Italy are: XEOMIN and Dysport. However, these drugs approved for different indications and with different formulations are not interchangeable in terms of dosage units. Other alternatives for the prophylaxis of chronic migraine to be taken into account for future developments of the analysis carried out are the beta-blockers, calcium channel blockers, anticonvulsants, modulators of serotonin, antidepressants, although in many cases not have authorized indication.

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# The setting of a botulinum toxin treatment service

**Maurizio Cavallini**



**Abstract** The administration of botulinum toxin is an activity performed mostly by a specialist service for the management of a wide range of neurological conditions. For therapeutic purposes botulinum toxin type A is used, although in selected patients who develop antibodies specific for the serotype A botulinum toxin B can be used for the treatment. Hereby, we describe the organizational arrangements for the botulinum toxin treatment service at the Department of Neurology of Hospital Cardinal Massaia based in Asti. The diseases most frequently treated are movement disorders (primary and secondary focal dystonia, blepharospasm, facial emispasmo) spasticity and, more recently, chronic migraine. In particular, the latter application is one of the most promising expansions of the use of this drug in the few past years, although a larger number of patients are required to determine its efficacy and the related tolerability profile.

**Keywords** Botulinum toxin · Movement disorders · Chronic migraine

The administration of botulinum toxin is an activity performed mostly by a specialist service for management of a wide range of neurological conditions.

For therapeutic purposes is used botulinum toxin type A, which possesses greater potency and duration of action. In general, the first effects appear after 1–3 days, reaching a peak of maximum efficacy after 1–3 weeks and these remain constant for 30–45 days and then they gradually reduced. For this reason it is necessary to repeat the treatment after a variable time, that it has been identified around 3–6 months [4].

The collateral effects are usually transient and of a short duration (2–4 weeks), according to the duration of the therapy [7].

A small percentage of patients eventually develops antibodies to the botulinum toxin, especially those who have been treated with high doses at shorter intervals of time. The antibodies are specific for the serotype, and for this reason these patients may benefit from treatment with botulinum toxin B, with a profile of action comparable to the type A.

In order to better explain, we briefly describe the organizational procedures for botulinum toxin treatment service at the Department of Neurology of Hospital Cardinal Massaia of Asti.

The service is held 1 day a week and there are four dedicated doctors and a nurse.

Before being subjected to a treatment with botulinum toxin, the patient is usually submitted to a neurological evaluation at the movement disorders service; in other cases, he has been evaluated by the physiatrist at first, who sends him to our department service.

During the first visit at the botulinum toxin treatment service the charged doctor shows and details his patient the exact procedure of treatment, the extent of improvement that should be expected, the possible collateral effects and if there is any change for other supportive therapies.

Before treatment, patients are informed about the content of consensus where there are clearly highlighted: the kind of technique proposed, the infiltrative methods used and all the complications that may occur during the therapy.

The selection of districts to be treated is implemented by the use of instrumental methods, such as EMG and ultrasonography.

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Movement disorders mainly treated include:

- Primary and secondary focal dystonias
- Blepharospasm and facial hemispasm
- Spasticity

In the treatment of spasticity, the patient management is usually multidisciplinary and includes a physiatric evaluation and, where appropriate, the presence of a physical therapist who takes care of the post-inoculation treatment (stretching programs, prescription of orthesis, etc.).

In addition to the movement disorders, toxin has proven to be effective in other diseases such as sialorrhea (echo guided by infiltration of the major salivary glands).

After 3 months, post-treatment checks are carried on by the involved medical team to evaluate the clinical response of the patient and to focus on the potential collateral effects.

During the same visit, there is the chance that a further administration of toxin is injected to the patient, or a new schedule for a further dose is agreed with him.

According to the decree published in the Official Gazette No. 35 dated 11 February 2013, a new indication of botulinum toxin type A was recommended for the treatment of chronic migraine.

The new indication represents a therapeutic option in adult patients who fulfill the diagnostic criteria for chronic migraine: headache duration at least 15 days per month or longer, of which at least 8 days with migraine, showing an insufficient response and/or intolerance to drugs prophylaxis (Headache Classification Committee of IHS, 2013) [2, 5, 6].

In these cases, botulinum toxin would seem to act primarily through inhibition of the release of nociceptive mediators (CGRP, substance P, Glu) [1].

After the administration of informed consensus, for some selected patients, at least 155 U of BTX-A is inoculated in seven specific muscles of the head and of the neck, for a total of 31 injections, with the possible charge of 40 U (without exceeding the 195 U per patient) [3].

Therefore, we have added an extra weekly session for the treatment of these patients, who are previously selected from the Headache Center group and since 2009, 20 patients with chronic migraine have been treated with botulinum toxin.

The treatment of chronic migraine with botulinum toxin revealed to be one of the most promising extension of the use of this drug in the recent years, although a larger number of patients are imperatively required to determine and to clarify its effectiveness and its tolerability profile.

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KEY NOTE LECTURE

# The painful muse: migrainous artistic archetypes from visual cortex

**Marco Aguggia · Enrico Grassi**



**Abstract** Neurological diseases which constituted traditionally obstacles to artistic creation can, in the case of migraine, be transformed by the artists into a source of inspiration and artistic production. These phenomena represent a chapter of a broader embryonic neurobiology of painting.

**Keywords** Migraine · Visual aura · Art · Archetype

The history of migraines is probably as old as the history of mankind. It has been suggested [2] that the geometric earliest representations of migraine's auras might be the ornamental designs encountered in cave and rock of the paleolithic period of the Stone Age.

Migraine experiences can be shown to act as a source of artistic inspiration in a considerable number of contemporary artists, just like dreams, hypnagogic hallucinations, or drug-induced phenomena, the impact of which has been recognized for long in the history of art.

The term "migraine art," attributed to Derek Robinson, refers to the visual representations of both the symptoms and experience of migraine. It was Robinson who initiated the process that eventually leads to the British Migraine Association sponsoring four National competitions for migraine sufferers in the 1980s. An archive of 562 works [18] from these events has been the basis of numerous research articles by Podoll and Robinson and their associates.

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Drawings and paintings over centuries all bring us an understanding of migraine and migraine aura that we would never get from words alone.

Both the popular and the scientific literature abound with drawings and paintings of migraine auras; now let us go to visit this gallery of painters inspired by this painful muse.

## Hildegard von Bingen

This German abbess and mystic lived from 1098 to 1179, and some of her works have been preserved, including several books describing her visions and miniature drawings illustrating the visionary works. In 1917, Charles Singer, a British medical historian, suggested that Hildegard could have suffered from migraine [16]. He based this theory on some of Hildegard's descriptions of her visions and some of her illustrations. For example, he 'easily recognized' a description of a scintillating scotoma in her words: 'I saw a great star splendid and beautiful, and with it an exceeding multitude of falling sparks which with the star followed southward'.

The miniatures from the twelfth century can be compared with the drawing of a visual aura by a twentieth century migraine suffer.

*(Hildegard von Bingen, Scivias, vision III, Hildegard von Bingen, Scivias, vision II Migraine art collection).*

In several of her drawings, Hildegard depicts repeating square forms, such as the ramparts of a castle or walled city. Singer describes these as fortification spectra, but that is not correct as that term is commonly used for zigzag shapes seen on the map of a fortress, and not the square appearance of the fortress wall itself. So, although crenellations do sometimes occur, the drawings of Hildegard are

suggestive but not typical for migraine. This opinion is supported by Schott [15] after his systematic analysis of drawings of migraine auras.

## Blaise Pascal

There is documentation affirming that Pascal suffered from visual migraines with recurring headaches, episodes of blindness in half of his visual field, zigzag, fortification spectra, and other visual hallucinations [5].

From time to time, Pascal would imagine that a cavity or precipice was yawning on his left-hand side. Onfray suggest that this recurring precipice was actually a transitori left hemianopia.

A study of the manuscript writings of Pascal brings to light two features: quite often one finds an inordinately broad margin on the right half of the page; the second peculiarity concerns the interpolation here and there of zigzag designs reminiscent of a migraine aura.

*(Detail from Folio 20 of the original manuscript of Pascal's "Thoughts on Religion", Detail from Folio 251 of the original manuscript of Blaise Pascal's "Thought on Religion").*

It has been hypothesized that these migraine aura experiences acted as a source of inspiration for Pascal's philosophical reflections [6]. Pascal's sudden religious conversion, during the night of the 23rd to 24th of November 1654, was accompanied by a luminous hallucination that he interpreted as "fire" convincing him of God's "reality and presence", similar to religious vision of Hildegard von Bingen. This experience may have been based on the effects of a migraine aura attack.

## Lewis Carroll and Salvador Dalì

Lewis Carroll is renowned for his two novels, *Alice's Adventures in the Wonderland* and its sequel *Through the Looking Glass*. Because Carroll suffered from migraines, it was suggested that he had used his own migraine experiences as a source of inspiration for his two books.

In this figure, we show the frontispiece of Carroll's family magazine *Mischmasch*, compiled between 1855 and 1862. In the drawing of a standing man, parts of the head, shoulder, wrist and hand are missing on the right side of the picture, and the rounded border of the defect is similar to that seen with a negative scotoma on the visual field in migraine.

The name "*Alice in the wonderland*" *syndrome* was coined by Todd [17] to describe the phenomena of micro- or macrosomatognosia, i.e., altered perceptions of body image, which had first been described by Lippman in the context of migraine some years earlier.

(*Illustration by John Tenniel*).

These body schema perturbances are frequently encountered in Migraine Art Collection. In particular, macrosomatognosia was encountered more frequently than microsomatognosia and applied more often to the head and upper extremities, body parts particularly involved. Thus, the topological distribution of partial macrosomatognosia in migraine patients reflects the organization principles of the sensory maps in the human brain. So we can speculate that these migraine aura experiences represent a reversible modification of cerebral maps of somatosensation [9].

Salvador Dali (a self-reported migraineur) is also suspected of having created much of his bizarre images out of visual hallucinations associated with migraine aura. In 1969, a print run of *Alice In Wonderland* was released featuring the surreal illustrations of Salvador Dali. The book contained 12 heliogravures, one for each chapter. Only the cover was different, a sketched etching in muted tones.

His vision became an LSD-fueled daydream (or nightmare) with trippy, hyper-saturated marvelous pieces.

(*Salvador Dalì: Alice Frontispiece; Salvador Dalì Down the Rabbit Hole*).

## De Chirico

The Italian painter Giorgio de Chirico is one of the emblematic figures of twentieth century art. He has developed the style of "metaphysical art" and is seen as one of the forerunners of surrealism. In 1988, the British neurologist G. N. Fuller and the art historian M. V. Gale suggested, in a paper published in the British Medical Journal [4], that migraine with aura may have acted as a basis for several unusual and recurrent features of his "Pittura metafisica".

The same Andre Breton, the leader of the surrealists, recalled how the poet Apollinaire had said that "at that time he was painting these pictures [1914–5] Chirico was suffering from certain abdominal pains and migraines."

Fuller note as "In a set of prints illustrating Cocteau's Mythologie the jagged effect of the water is very similar to the advancing edge of a scotoma".

(*Giorgio de Chirico lithograph from "Mythologie", 1933*).

In a painting from the 1960s, the central silhouette of a man with a spiky edge is reminiscent of drawings of negative scotomata.

(*Giorgio de Chirico, The return to the castle, 1969*).

Reconsidering the notion of de Chirico's migraine aura as source of his artistic inspiration, Ubaldo Nicola and Klaus Podoll [14] have systematically examined his published works as painter and writer, including his

"Memoirs", the semi-autobiographical novels "Hebdomeros" and "Mister Dudron" and his collected essays. References to migraine aura symptoms were identified according to phenomenal similarities not only with clinical descriptions of such phenomena as established in neurological semeiology, but also with the paintings and drawings from the Migraine Art collection.

According to Podoll, De Chirico visually described not only typical visual auras, but also the variety of cenesthetic pain sensations arising from the hands of atypical aura [7]:

(*Self Portrait—Giorgio de Chirico, c.1925*).

Another phenomenon, which can occur as a migraine aura symptoms, out-of-body experiences (OBE) and heautoscopy, has been represented with extraordinary sensibility by de Chirico [8].

In this painting we can see depicted the feeling of being outside the physical body including the somesthetic sensations of a duplicate body (OBE).

(*Giorgio de Chirico: Self-portray with shadow. 1920*).

In heautoscopy or "seeing one's double", the subject remains identified with his own body and his normal point of view throughout, whereas during an OBE the subject is the observer who views his physical body from outside.

(*Giorgio de Chirico—Self Portrait, 1921*).

Blanke and Landis objected that the available evidence suggests a diagnosis of temporal lobe epilepsy (TLE) rather than migraine [1], but major criticisms can be raised against their selection and interpretation of data [14].

Probably, the best confirmation to the migranous origin of the Chirico inspiration is enclosed in the words of the same master, describing his conversion to the methaphysical art: "… let me recount how I had the revelation of a picture that I will show this year at the Salon d'Automne, entitled Enigma of an Autumn Afternoon. One clear autumnal afternoon I was sitting on a bench in the middle of the Piazza Santa Croce in Florence. It was of course not the first time I had seen this square. I had just come out of a long and painful intestinal illness [abdominal migraine], and I was in a nearly morbid state of sensitivity [hypersensitivity to light and noise; migraine aura phenomena]. The whole world, down to the marble of the buildings and the fountains, seemed to me to be convalescent. In the middle of the square rises a statue of Dante draped in a long cloak, holding his works clasped against his body, his laurel-crowned head bent thoughtfully earthward. The statue is in white marble, but time has given it a grey cast, very agreeable to the eye [photophobia]. The autumn sun, warm and unloving [photophobia; exposure to sun as trigger factor of migraine attack], lit the statue and the church façade. Then I had the strange impression that I was looking at all these things for the first time [jamais vu], and the composition of my picture came to my mind's eye. Now each time I look at this painting I again see that moment. Nevertheless the moment is an enigma to me, for it is inexplicable. And I like also to call the work which sprang from it an enigma."

(*Giorgio de Chirico, The Enigma of an Afternoon of Autumn, 1909*).

## Picasso

In a lecture delivered during the Headache World 2000 congress in London, Ferrari suggested a diagnosis of migraine aura without headache in the case of Picasso [3].

The lecture was livened up by a 'Migraine Picasso Quiz', which showed that 'participants of the congress repeatedly had great difficulties in distinguishing between several of Picasso's paintings and paintings of migraine patients, who had depicted their own visual auras'.

(*Migraine Art: Mosaic illusion. © 2007 Migraine Action Association and Boehringer Ingelheim. Pablo Picasso Portrait of Art Dealer Ambroise Vollard (1867–1939), 1910*).

But, Did Pablo Picasso suffer from migraine? Although the idea is fascinating, there is no proof of Picasso suffering from migraine with aura. But, as Ferrari suggests, this could have been overlooked if Picasso only suffered from migraine aura without headache.

In 2000, Podoll and Robinson described a peculiar phenomenon in paintings of migraine patients [10, 13]. They studied 562 paintings of patients who participated in a 'Migraine Art Competition' and found the so-called 'illusory splitting' in six of the drawings. In this type of illusion, 'objects or persons appear to be split, along fractured lines of varying form and orientation, into two or more parts that may be displaced and separated from each other'.

Illusory splitting as a part of bizarre visual migraine may have influenced his work, specifically paintings such as "*The Weeping woman*".

[*Pablo Picasso: "Weeping Woman" (donna in lacrime), 1937, Tate Gallery*].

## Contemporary artist

JJ Ignatius Brennan, renowned for his surrealist paintings, began his artistic career as a boy by painting the migraine experiences, which would plague him for the rest of his life. He experienced loss of vision, hallucinations of zigzags and triangles, and the visual field splitting into a mosaic. Faces, objects and parts of his body would appear deformed, grossly enlarged, or duplicated. His works not only show the visual hallucinations but also express the sensations that accompany the attacks.

(*J.J. Ignatius Brennan, The Sculpture You Want is Underneath, 1993*).

The live and work of J J Ignatius Brennann clearly document the significance of migraine experiences as a factor of artistic creativity [11].

Brennan won first prize in the fourth National Migraine Art competition in 1992, and the second prize in the 1992 "Migraine Images" competition, organized by the Migraine Trust and Glaxo Pharmaceuticals.

Sarah Raphael (1960–2001) was one of the leading British artists of her generation.

The history of Sarah Raphael's migraine with aura can be reconstructed from several articles [12].

First known during the 1980s as a figurative and portrait painter, from the mid 1990s her artistic development moved from naturalism toward abstraction.

It culminated in her series of ''Strip!'' paintings presented in her 1998 exhibition at Marlborough Fine Art Gallery, London, featuring a comic-strip format with hundreds of tiny images of brightly colored shapes, devoid of meaning and narrative.

In some ''Strip!'' pictures, the regular grids arranged by tiny boxes or repetitive images of unrecognizable objects are superimposed by large zigzags enclosing an oval-shaped area displaying some obscuration or alterations of color, reminiscent of the form and other phenomenal features of the so-called fortification spectra.

(*Sarah Raphael, Strip Page 7 (detail), 1998, acrylic on canvas with papier maché collage*).

Identifying Sarah Raphael's migraine experiences as a source of her artistic inspiration does by no means demystify or etiolate her art in a reductionistic way but rather enriches our appreciation of its complexities and beauty.

At least two other contemporary artist may correlate their migranous condition as source of artistic inspiration: Georgia O'Keeffe and Yayoi Kusama.

Georgia O'Keeffe (1887–1986) known for her striking flower paintings and other captivating works was one of the greatest American artists of the twentieth century and has been recognized as the Mother of American Modernism. Georgia O'Keefe once used a headache as inspiration. O'Keefe wrote: "Drawing No. 9 is the drawing of a headache. It was a very bad headache. Well, I had the headache, why not do something with it?"

(*Georgia O'Keeffe, Special Drawing No. 9, 1915*).

Yayoi Kusama is the artist who filled up her world up with brightly painted spots.

The origin of Kusama's artistic universe of dots, nets and accumulating patterns has prompted many interpretations both from neurologist, art critics and art historians: schizophrenia, obsessive compulsive, migraine with aura are some of the diagnosis formulated.

(*Yayoi Kusama, An Encounter with a Flowering Season, 2009*).

The artist has recorded her visual symptoms which have recurred ever since her childhood, in her 1975 autobiographical essay entitled *The struggle and wanderings of my soul* she wrote: "I was often troubled by a thin silk-like greyish-coloured veil that came to envelope me. On the day this happened to me, people receded far away from me and looked small". During these episodes, she experienced geometric hallucinations of nets and the visual illusion of teleopsia whereby objects appear further away, corresponding to her painting *Accumulation of Corpses*. She felt like being separated by a curtain from reality and people. These paroxysmal cerebral visual disturbances can occur as visual aura symptoms of migraine.

Yayoi Kusama, Accumulation of Corpses, 1950

Nonetheless, in many cases, specific knowledge of the artist's illness deepened an understanding of the work. The works offer us a rare opportunity to share the perceptions of extraordinary minds.

All of the works described in this paper show how the artist can exploit the paradoxical potential of pathology to liberate new powers of perception.

## Conclusions

But did Turner suffer from migraine too?

(*JMW Turner. The Piazzetta, Venice. National Galleries of Scotland*).

We can say that it is through illustration that the uniform nature of the various hallucinations has been so unequivocally documented with a visual constancy uniform over time.

The cause is that such geometrical form constants, then, are not dependent on memory or personal experience or desire or imagination.

In his post "Patterns" Oliver Sacks wrote: "What we can say, in general terms, is that these hallucinations reflect the minute anatomical organization, the cytoarchitecture, of the primary visual cortex, including its columnar structure—and the ways in which the activity of millions of nerve cells organizes itself to produce complex and ever-changing patterns. This activity operates at a basic cellular level, far beneath the level of personal experience. They are archetypes, in a way, universals of human experience".

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# Menstrual migraine: treatment options

**L. C. Newman · M. S. Yugrakh**



**Abstract** More than half of women with migraine note an association of headache attacks and their menstrual cycles. Headaches associated with menses are often more severe and disabling than headaches that occur other times of the month. First-line therapies include acute agents used for migraine in general; however, for many women, these therapies provide incomplete relief. In these situations, treatment options include short-term perimenstrual prevention employing nonsteroidal anti-inflammatory medications, triptans, or hormone-containing preparations. Should these options not suffice, or if menstrual cycles are irregular, continuous prevention using hormonal therapies or standard anti-migraine prophylaxis should be considered.

**Keywords** Pure menstrual migraine · Menstrually related migraine · Therapy · Short-term perimenstrual prophylaxis

## Introduction

It is well known that migraine affects women more often than men. The incidence and prevalence of migraine in women increases after menarche and continues to increase throughout the fifth decade of life [1]. It is widely believed that hormonal changes throughout a woman's lifetime play a major role in the increased prevalence [2].

As many as 60–70 % of women with migraine report an association with their menstrual cycle (menstrually related migraine) [3–6], whereas approximately 14 % of women with migraine report that they experience headaches only during their menstrual cycle (pure menstrual migraine, or menstrual migraine (MM)) [3, 6]. Migraines that occur during the menstrual cycle are much more likely to begin on the days just prior to and following the first day of menstruation [2–4, 7]. Diaries from population-based studies revealed the first 2–3 days of menstruation to be the time of highest risk of developing migraine [2, 8]. The pathophysiologic mechanisms responsible for the timing of these headaches are not completely known, but is probably in some part related to estrogen withdrawal as well as prostaglandin release [9, 10]. Although the literature is confusing to interpret, many clinicians (and patients) believe that migraines occurring during menses are different than non-menstrually related attacks. Differences in methodology and in the populations studied (general vs. clinic-based) may contribute to these discrepancies.

Studies in the general population suggest that MM are more severe [2, 12]. Although four clinic-based studies agreed with these findings [7, 13–15], an equal number reported no differences in pain intensity [8, 15, 16]. Three clinic-based studies and one population study noted that MM are longer in duration than attacks unassociated with the menstrual cycle [15, 16], but one study in the general population reported no difference [1]. Two clinic-based trials found that attacks of MM are associated with more nausea and vomiting [7, 14], but three other clinic-based and one study in the general population reported no differences in associated features between menstrual and non-menstrual attacks [1, 8, 15, 16]. All but two studies found that attacks of MM were more disabling and more resistant to acute treatment [15].

The ICHD 3 does not recognize MM per se, but has recommended criteria for diagnosis of both pure and

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**Table 1** ICHD-III criteria

| |
|---|
| Pure menstrual migraine |
| A. Attacks, in a menstruating woman[a], fulfilling criteria for migraine without aura and criterion B below |
| B. Documented and prospectively recorded evidence over at least three consecutive cycles have confirmed that attacks occur exclusively on day 1 ± 2 (i.e., days −2 to +3)[b] of menstruation in at least two out of three menstrual cycles and at no other times of the cycle |
| Menstrually related migraine |
| A. Attacks, in a menstruating woman[a], fulfilling criteria for migraine without aura and criterion B below |
| B. Documented and prospectively recorded evidence over at least three consecutive cycles have confirmed that attacks occur exclusively on day 1 ± 2 (i.e., days −2 to +3)[b] of menstruation in at least two out of three menstrual cycles and additionally at other times of the cycle |

[a] For the purposes of ICHD-3 beta, menstruation is considered to be endometrial bleeding resulting from either the normal menstrual cycle or from the withdrawal of exogenous progestogens, as in the use of combined oral contraceptives or cyclical hormone replacement therapy

[b] The first day of menstruation is day 1, and the preceding day is day −1; there is no day 0

menstrually related migraine in the Appendix (Table 1). These criteria mandate that MM are attacks of migraine without aura that occur between 2 days before the first day of menstruation and 3 days after the onset in 2 out of 3 menstrual cycles [17].

## Treatment options

### Acute therapies

Acute treatments that are used for all types of migraines can be employed to treat MM as well. Options include the use of nonsteroidal anti-inflammatory agents (NSAIDs), triptans, ergotamine, dihydroergotamine, and rarely opioids or other analgesics. Unless contraindications exist, most patients should be prescribed migraine-specific agents (triptans, ergots, dihydroergotamine) as first-line therapy.

Although many studies suggest MM are more disabling and resistant to acute therapies [15], data suggest that sumatriptan [3, 15], zolmitriptan [18], almotriptan [15], rizatriptan [11, 14], frovatriptan [19], eletriptan [11], and an over-the-counter analgesic containing aspirin/acetaminophen/caffeine [11] work equally well for attacks during or outside of the menstrual cycle.

Several of the triptans have also been studied in double-blind, placebo-controlled trials as acute therapies in MM. Sumatriptan [11, 14], sumatriptan-naproxen [14], zolmitriptan [14, 18], almotriptan [20], rizatriptan [11, 14], and naratriptan [11] all were superior to placebo.

### Perimenstrual prevention

When acute therapies fail to adequately abort attacks, preventive agents may need to be employed. Prevention can be given in a short-term, perimenstrual dosing strategy or on a daily basis. Short-term prophylactic strategies have the advantage that treatment is given around the patients' vulnerable time rather than on a long-term basis. This method should be utilized in women with regular, predictable, menstrual cycles. Agents used in this paradigm include NSAIDs, triptans, and hormonal therapies.

#### *NSAIDs—naproxen*

In a small open-label study of 25 women, naproxen 550 mg daily prevented MM [21]; a double-blind study, however, did not show statistical significance over placebo [22].

#### *Triptans*

The first study using perimenstrual dosing of a triptan as a treatment for MM was an open-label trial of sumatriptan 25 mg three times daily beginning 2–3 days prior to the expected onset of menses and continuing for a total of 5 days. Of the 126 treated cycles in 20 woman, 95 % of cycles were headache-free or >50 % reduced in intensity from baseline [23]. An open-label trial of naratriptan [24] also demonstrated efficacy. Subsequently, several double-blind, placebo-controlled studies using other triptans were conducted. Efficacy was demonstrated for zolmitriptan [14], naratriptan [14, 25], and frovatriptan [14]. All studies but one began therapy 2 days before expected menstrual onset; the study by Mannix et al. began treatment 2 days before expected onset of the headache. Allais et al. reviewed the efficacy and safety of frovatriptan vs. rizatriptan, zolmitriptan, and almotriptan in MM and concluded that frovatriptan was as effective as the other agents but had a more sustained effect [26]. A recent meta-analysis determined that the triptans are an effective, short-term prophylactic treatment for MM and that frovatriptan 2.5 mg BID and zolmitriptan 2.5 mg TID are preferred options [27].

A small pilot, open-label, non-randomized, parallel group study assessed the efficacy of 2.5 mg frovatriptan against 25 mg transdermal estrogen or 50 mg naproxen sodium each taken once daily for 6 days, beginning 2 days before the expected onset of menstrual headache [28]. Headache incidence was decreased on frovatriptan compared with the other two groups, but the drug doses used in the study were sub-therapeutic.

#### *Hormonal therapies—estradiol*

Perimenstrual application of transcutaneous estradiol gels has been reported to be efficacious in preventing MM. The

medication needs to be given at a dose of 1.5 mg applied 2 days prior to the onset of menses and continued for 7 days [5, 11, 29]. MacGregor et al. applied a 1.5 mg gel for 8 days, beginning on the ninth day following the LH surge through the second full day of menstruation. Although the headaches were decreased during treatment, there was an increased incidence of migraine when the patch was removed [14]. Studies of transdermal estradiol patches employed from days −2 through +5 were ineffective at doses below 100 μg [11].

*Miscellaneous therapies—magnesium*

A double-blind, placebo-controlled trial reported that 360 mg of oral magnesium pyrrolidone carboxylic acid daily beginning on day 15 of the cycle and continued until menstruation reduced the number of headache days, total pain index, and menstrual distress compared with placebo [3].

Continuous prevention

When MM is refractory to acute medications, short-term prevention, or when patients have irregular menstrual cycles, continuous prophylaxis can be instituted. Continuous prevention using medications that are typically used for high-frequency migraines, including antiepileptics, antihypertensives, and antidepressants, may be prescribed, but will not be discussed here.

*Continuous hormonal prevention*

The goal of hormonal prevention of MM is aimed at minimizing the premenstrual fall in estrogen levels [5]. In the only randomized, controlled trial of oral contraceptives (OC) for MM prevention, headaches worsened in 70 % and improved in 30 % [3]. Since women who use OC for birth control often report migraines during the placebo week (the result of estrogen withdrawal), strategies in which the placebo pills are not taken have been tried. An open-label trial successfully prevented MM in all 11 subjects using an OC containing 20 μg of ethinyl estradiol by substituting 0.9 mg of conjugated equine estrogen pills for the placebo pills [30]. Despite the absence of any trials, long-term prevention used instead of the usual regimen of 3 weeks of active followed by 1 week of placebo or no therapy has been recommended by some practitioners for their patients with MM [31]. The use of a transdermal contraceptive given for 84 consecutive days reduced the incidence of mean headache days compared with the standard 21/7 days regimen [11]. Sulak et al. treated 102 women with an OC containing 3 mg drospirenone/30 μg ethinyl estradiol continuously for 168 days and reported a decrease in headache severity and improvements in several quality-of-life measures [32].

An important consideration with continuous hormonal prevention is that estrogen increases risk of ischemic stroke and should not be used by women with migraine with aura who already have an increased stroke risk.

*Clinical recommendations*

All patients require an acute therapy for their migraine headaches. In the absence of contraindications, migraine-specific abortive medications should be used as first-line therapy. If acute medications are ineffective, and headaches occur with high frequency or with disability, preventive measures should be instituted. When considering preventive options, the clinician should consider whether the menstrual cycle is regular, whether the patient is already using OC, and whether other comorbidities are present.

For those women already using standard OC, consider changing to an extended dosing paradigm in which the placebo pills are eliminated for the first 3 months. For women with regular menstrual cycles, not on OC, short-term prevention with triptans or NSAIDs should be considered first, followed by short-term hormonal therapies. If the menstrual cycles are irregular, or if the above options are ineffective, the use of either standard anti-migraine prophylaxis or continuous hormonal therapy may be warranted.

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# Migraine in pregnancy and lactation

**E. Anne MacGregor**



**Abstract** Migraine in pregnancy can cause considerable concern to both patient and doctor, particularly if migraine starts for the first time during pregnancy or if the woman has her first attack with aura. There is often confusion regarding which medicines are safe to use during pregnancy and breastfeeding, leaving many women unable to control their attacks effectively. This paper reviews the diagnosis as well as the management of migraine, which is similar to the non-pregnant state, with a few exceptions.

**Keywords** Migraine · Pregnancy · Lactation

## Introduction

Migraine affects around 18 % of women, particularly during the reproductive years. Most women are able to control the symptoms of migraine with medication, using prophylactic drugs in addition, if attacks are frequent. When a woman is planning pregnancy, the potential effects of drugs on the fetus need to be considered, with careful review of all medication taken. Advice on safe and effective treatment of migraine during pregnancy is important as drugs have their greatest effects on the fetus during the first trimester, often before the woman knows she is pregnant. Medication needs further review if a woman is breastfeeding, due to the potential transfer of drugs in breast milk.

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## The effect of pregnancy and breastfeeding on migraine

Up to 60–70 % of women with preexisting migraine report improvement or cessation of migraine during pregnancy, particularly in women with a history of menstrual migraine [1]. If no improvement is seen toward the end of the first trimester, migraine is likely to continue throughout pregnancy and postpartum [2]. Aura can occur for the first time during pregnancy and requires careful assessment if the symptoms are atypical [3, 4]. In such cases, thrombocytopenia, cerebral venous sinus thrombosis or imminent eclampsia should be excluded.

Migraine following delivery is not uncommon, typically occurring a couple of days postpartum [2, 5, 6]. In women who bottle-feed, migraine tends to persist postpartum, whereas women who breastfeed maintain the protective effect of pregnancy until menstruation returns [2].

## Effect of migraine on pregnancy

Women can be reassured that there is no evidence that migraine has any significant adverse effect on the outcome of pregnancy [7, 8]. However, a number of studies have reported two to threefold increased risk of preeclampsia in pregnant migraineurs [9, 10]. Obesity was an additional risk factor carrying a 12-fold increased risk of preeclampsia in migraineurs compared with non-obese women without migraine.

There is also evidence that migraine is a risk factor for pregnancy-related stroke [11]. Additional research needs to identify which type of migraine affects this risk.

**Table 1** Drugs used for acute treatment of migraine during pregnancy

| | |
|---|---|
| FDA category B | |
| Acetaminophen | |
| Diclofenac | 3rd trimester: category D |
| Ibuprofen | 3rd trimester: category D |
| Naproxen | 3rd trimester: category D |
| Meperidine | Category D if prolonged use/high doses at term |
| Metoclopramide | |
| FDA category C | |
| Aspirin | 3rd trimester: category D |
| Indomethacin | 3rd trimester: category D |
| Mefenamic acid | 3rd trimester: category D |
| Codeine | |
| Morphine | |
| Tramadol | |
| Prochlorperazine | |
| Promethazine | |
| Almotriptan | |
| Eletriptan | |
| Frovatriptan | |
| Naratriptan | |
| Rizatriptan | |
| Sumatriptan | |
| Zolmitriptan | |
| Prednisolone | |
| FDA category X | |
| Ergotamine | |
| Dihydroergotamine | |

**Table 2** Drugs for acute treatment of migraine during breastfeeding

| |
|---|
| Minimal risk |
| Acetaminophen |
| Diclofenac |
| Ibuprofen |
| Cyclizine |
| Metoclopramide |
| Prochlorperazine |
| Promethazine |
| Sumatriptan |
| Benefits likely to outweigh risks |
| Indometacin |
| Naproxen |
| Codeine |
| Morphine |
| Meperidine |
| Tramadol |
| Eletriptan |
| Caution |
| Aspirin |
| Mefenamic acid |
| Contraindicated |
| Ergotamine |
| Dihydroergotamine |
| Insufficient data |
| Almotriptan |
| Frovatriptan |
| Naratriptan |
| Rizatriptan |
| Zolmitriptan |

## Investigations

The indications for investigation of the pregnant women with headache are the same as for a non-pregnant woman. X-ray exposure should be avoided in favor of MRI, which is considered safe in pregnancy [12]. Contrast imaging with gadolinium can be undertaken, if indicated. Iodinated contrast media should be avoided as it can depress fetal thyroid function, which should be checked during the first week of birth.

## Management

Trigger management, particularly encouraging regular meals, regular exercise, sleep hygiene and adequate fluids may help reduce the frequency of attacks without the need for medication.

### Acute treatment

Most drugs are not licensed for use in pregnancy and during breastfeeding and should only be considered if the potential benefits to the woman and fetus outweigh the potential risks. The options for drug treatment are shown in Tables 1 and 2.

Acetaminophen is the analgesic of choice for the short-term relief of mild to moderate pain during pregnancy and lactation. Ibuprofen can be taken during the first and second trimesters but should be avoided after 30 weeks of pregnancy because of increased risk of premature closure of the ductus arteriosus and oligohydramnios. NSAIDs can be taken during breastfeeding, and the amount of drug in breast milk is very low. Aspirin can be taken during the first and second trimesters but use in the third trimester is associated with premature closure of the fetal ductus arteriosus and can increase the risk prolonged labor, post partum hemorrhage and neonatal bleeding. Aspirin is

**Table 3** Drugs used for prophylaxis of migraine during pregnancy

| |
|---|
| FDA category C |
| Amitriptyline |
| Citalopram |
| Escitalopram |
| Fluoxetine |
| Sertraline |
| Venlafaxine |
| Metoprolol |
| Nadolol |
| Propranolol |
| Timolol |
| Gabapentin |
| Botulinum toxin |
| FDA category D |
| Atenolol |
| Topiramate |
| Candesartan |
| Lisinopril |
| FDA category X |
| Valproic acid |

**Table 4** Drugs used for prophylaxis of migraine during breastfeeding

| |
|---|
| Minimal risk |
| Amitriptyline |
| Nortriptyline |
| Propranolol |
| Verapamil |
| Nifedipine |
| Benefits likely to outweigh risks |
| Metoprolol |
| Escitalopram |
| Paroxetine |
| Sertraline |
| Venlafaxine |
| Gabapentin |
| Topiramate |
| Valproic acid |
| Concern |
| Citalopram |
| Fluoxetine |
| Atenolol |
| Nadolol |
| Timolol |
| Contraindicated |
| Lithium |
| Insufficient data |
| Candesartan |
| Lisinopril |
| Botulinum toxin |

excreted in breast milk and regular use during breastfeeding can increase the risk Reye's syndrome and impaired platelet function in susceptible infants.

Antiemetics such as metoclopramide, prochlorperazine and promethazine can be taken during pregnancy and lactation.

Sumatriptan may be used during pregnancy and breastfeeding if attacks fail to respond to the above treatment. Data from the sumatriptan/naratriptan/Treximet pregnancy registry (http://pregnancyregistry.gsk.com/sumatriptan.html) are reassuring and confirm that inadvertent exposure to sumatriptan during pregnancy has not been associated with adverse outcomes although a small increased risk of specific birth defects cannot be excluded. There are insufficient data regarding other triptans.

### Prophylaxis

Non-pharmacologic preventives such as acupuncture and biofeedback are useful during pregnancy [13, 14]. Coenzyme Q10 and magnesium supplements have the additional effect of reducing the risk of preeclampsia [15, 16]. The options for drug prophylaxis are shown in Tables 3 and 4.

The drugs of choice during pregnancy and lactation are propranolol or metoprolol in the lowest effective doses. These should be stopped 2–3 days before delivery to minimize the risk fetal bradycardia and decreased uterine contraction. The baby should be monitored for neonatal bradycardia, hypotension and hypoglycemia.

Low-dose amitriptyline 10–25 mg daily can also be taken during pregnancy and lactation. Although limb deformities have been reported following high-dose amitriptyline during pregnancy, there are no reports following doses of 10–50 mg daily used for pain management. Ideally, the dose is tapered 3–4 weeks before delivery to minimize neonatal drowsiness, jitteriness, hyperexcitability and suckling problems.

## Emergency treatment

Prochlorperazine 10 mg or chlorpromazine 25–50 mg by intramuscular injection together with intravenous fluids is usually sufficient to abort an attack. Intravenous magnesium sulfate 1 g given over 15 min is an alternative and can be given together with intravenous prochlorperazine 10 mg [17].

## Conclusions

Women with a history of menstrual migraine often report improvement of migraine during pregnancy, which is

sustained with breastfeeding. Migraine with aura is less likely to improve and may occur for the first time during pregnancy. Investigation of headache is the same as for the non-pregnant women, although routine investigations should be deferred until postpartum.

First-line acute treatment during pregnancy and breastfeeding is with non-opioid analgesics and antiemetics. Sumatriptan may be indicated for severe attacks that do not respond to first-line treatment. If prophylaxis is indicated during pregnancy or lactation, the lowest effective dose of propranolol or amitriptyline are options.

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# Migraine and the menopausal transition

**Vincent T. Martin**



**Abstract** The menopausal transition or "perimenopause" represents a time period of turbulent changes in ovarian hormones as middle-aged women progress into menopause. The purpose of this article is to review the literature to determine the effect of the menopausal transition on migraine headaches and to develop a rational treatment approach to these patients. The menopausal transition is divided into early and stages based upon patterns of menstruation and specific reproductive hormones. Studies would suggest that the prevalence of migraine and other climacteric symptoms tend to peak during the late menopausal transition particularly in those with a past history of premenstrual stress disorder. Treatment approaches vary by stage of the menopausal transition and include conventional daily preventatives, mini-prophylaxis and hormonal therapies.

**Keywords** Migraine · Menopausal transition · Perimenopause · Menopause

## Introduction

The menopausal transition, which is also called the perimenopause, represents a time period during which middle-aged women develop irregular menstrual periods and other climacteric symptoms as they evolve into menopause. The menopausal transition often represent a very turbulent time period for those with migraine leading to an increased frequency and disability of headache. This review will first discuss the classification, epidemiology, endocrinology, clinical symptomatology, comorbid disorders and pathophysiology related to the menopausal transition. We will then present the epidemiological studies linking migraine to the menopausal transition as well as the proposed mechanisms through which migraines might be triggered during this time period.

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## Classification

In 2001 a workgroup of international experts in reproductive medicine was convened to define the stages of the menopausal transition and it was called the Stages of Reproductive Workshop (STRAW) criteria [1]. In 2011 a second workgroup was convened to update the original criteria and their classification was termed the STRAW+10 criteria [2]. They divided the menopausal transition and postmenopausal time periods into early and late phases. Each phase was defined not only by the characteristics of the menstrual cycles (e.g., cycle length, amenorrhea), but also by specific serum levels of reproductive hormones. The "early" menopausal transition was characterized by cycle length variations of $\geq$7 days while the "late" menopausal transition was distinguished by periods of amenorrhea lasting $\geq$2–11 months. It was proposed that the "early" postmenopausal time period lasted for 5–8 years and was characterized by amenorrhea lasting $\geq$1 year, low and declining estrogen levels and rising follicular stimulating hormone (FSH) levels. The "late" postmenopausal time period persisted for the remaining lifespan of the women and represented a time of more stable, but low serum levels of ovarian hormones.

## Epidemiology

The mean age of onset of the menopausal transition is 47.5 years of age while that of menopause is 50–52 years of age [3–6]. An earlier onset of menopause has been associated with lower educational level, more physical activity and smoking [7–9]. In addition, polymorphisms of genes involving steroid hormone metabolism and biosynthesis pathways have been related to age of menopause [10].

## Endocrinology

The menopausal transition periods have a unique hormonal milieu that distinguishes them from other premenopausal times. During the "early" menopausal transition menstrual cycles remain ovulatory. Serum levels of estrogen are unchanged to slightly higher and progesterone levels are lower during these ovulatory cycles than those encountered in premenopausal women [11, 12]. Women may also experience aberrant menstrual cycles with luteal out-of-phase (LOOP) follicular events, which represent a second peak in estrogen that occurs during the luteal time period [13]. This second luteal peak resembles that typically seen during the late follicular phase as it is preceded by an LH surge and associated with very high serum levels of estrogen and very low levels of progesterone. Sometimes ovulation can occur with these LOOP follicular events. Anovulatory cycles predominate during "late" menopausal transition with the depletion of ovarian follicles. Serum levels of estrogen and progesterone are both low during these anovulatory cycles. Even if ovulation does occur serum levels of estrogen and progesterone are much lower than premenopausal time periods as these women approach menopause.

## Clinical symptoms

A variety of climacteric symptoms develop during the menopausal transition including hot flashes, night sweats, irritability, insomnia, joint aches, vaginal dryness, decreased libido and headache [14]. Women with a past history of premenstrual stress disorder (PMS), migraine, depression or atopy are at increased risk for the development of climacteric symptoms [14, 15]. Freeman and colleagues [14] reported that the severity of headache symptoms rated on a 0–3 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) varied with the stage of the menopausal transition. The proportion of patients with "moderate to severe" headache was lowest during postmenopausal time periods and highest during the early and late menopausal transition (24 vs. 36 and 32 %, respectively; $p < 0.002$). Premenstrual stress disorder symptoms were strongly related to the severity of headache (odds ratio [OR] = 1.71; $p = 0.001$) as well as that of all other climacteric symptoms (OR's 2.08–3.93; all $p$ values $\leq 0.001$). Therefore, the presence of PMS symptoms may indicate that a perimenopausal woman is "hormonally sensitive" and more vulnerable to develop "moderate to severe" climacteric symptoms.

## Comorbid conditions

Depression, anxiety and sleep disturbances are all more prevalent during the menopausal transition and postmenopausal time period. Bromberger and colleagues [16] found that depression was 2.2–3.6× more common during the menopausal transition and postmenopause as compared with the premenopause. Another study [17] found that with low anxiety at baseline was 1.5–1.6× more likely to develop severe anxiety during the menopausal transition and postmenopause. Sleep disturbances (e.g., frequent awakenings, trouble falling asleep, waking up early) were most prevalent during the late menopausal transition [18].

## Pathophysiology

It has long been assumed that the symptoms of the climacteric period are solely related to low serum levels of estradiol. However, more recent studies challenge this hypothesis and in some instances implicate other reproductive hormones. Randolph and colleagues [19] reported that higher serum levels of FSH and lower estrogen levels were both associated with hot flashes in univariate analyses. However, only FSH was independently predictive in multivariate analyses that included both variables. A greater risk of depression has been reported in perimenopausal women with higher serum levels of testosterone as well as fluctuations in estrogen and FSH [20–22]. Sleep disturbances were greatest on those days with higher urinary levels of FSH and progesterone metabolites in menstruating perimenopausal women [23]. Thus, there may be several different patterns of reproductive hormonal hormones that may predispose to climacteric symptoms.

## Migraine during the menopausal transition

There has only been one past study to date to ascertain the effect of the menopausal transition on the prevalence of migraine headache. Wang and colleagues [24] conducted a

cross-sectional study of 1,436 Chinese women to determine if the prevalence of migraine differs during the various climacteric time periods. Migraine was least prevalent in individuals after a spontaneous menopause (OR = 0.6 [0.4, 0.9; 95 % CI]) when compared to those in the early and late menopausal transition for the population as a whole. Migraine was significantly more common in the hysterectomy/oophorectomy group (hysterectomy alone [$n = 63$], hysterectomy + unilateral oophorectomy [=22] or hysterectomy + bilateral oophorectomy [$n = 19$]) as compared to those with a spontaneous menopause occurring in 27 and 7 %, respectively ($p < 0.001$). There was an increase in the proportion of individuals with migraine during the late menopausal transition as compared to the premenopause and early menopausal transition only in those with PMS (31 vs. 21–22 %).

## Mechanisms

The "estrogen withdrawal" hypothesis is the most commonly advanced theory to explain the mechanism through which migraine is triggered by ovarian hormones. This theory is supported by the fact that menstrual migraine occurs in 35–51 % of female migraineurs and can be prevented by perimenstrual administration of estrogen [25–27]. In the past "estrogen withdrawal" has been considered a transient event that only occurs for several days around menstruation. However, "estrogen withdrawal" may trigger migraine for weeks to months if estrogen deprivation is prolonged as may occur from the amenorrhea that occurs during the late menopausal transition or early postmenopausal time periods. This is supported by the results of the Medical Oophorectomy in Migraine (MOM) study [28] in which headache outcome measures tended to worsen or remain unchanged during a 2-month treatment phase with placebo while they improved in those receiving add-back estrogen therapy.

The hormone changes in the menstrual cycle that are encountered during the menopausal transition could theoretically provoke migraine. Greater mid-cycle fluctuations in estrogen as occur during the early menopausal transition may be more likely to trigger mid-cycle attacks of migraine. Past studies [26, 29] had not identified a mid-cycle pattern of migraine, but a more recent study [30] clearly demonstrated the existence of mid-cycle peak of headache that was related to PMS symptoms. Likewise, the bifid peaks in estrogen that occur with LOOP follicular events might trigger attacks of migraine in susceptible patients. Extremely high or low serum levels of progesterone during the mid-luteal time period as seen during the early and late menopausal transition might be provocative for headache [31].

The menopausal transition may be associated with a worsening of migraine secondary to an increase in the prevalence of comorbid disorders (e.g., depression, insomnia). The American Migraine and Prevention (AMPP) study found that depression conferred a 65 % excess risk of transitioning from episodic to chronic migraine. Another study [32] found that insomnia was related to an increased frequency of migraine headache.

## Management

There are three potential approaches to prevent "hormonally triggered" migraines during the menopausal transition. These include conventional daily preventative medications, mini-prophylaxis of menstrual migraine and hormonal therapies. Their use might vary depending upon the stage of the menopausal transition.

Conventional daily preventatives can be used during any stage of the menopausal transition. Topiramate has the best evidence in the prevention of menstrually related migraines and could be particularly effective during the early menopausal transition. Allais and colleagues [33] reported that topiramate was equally effective in reducing the frequency of migraine during perimenstrual and non-perimenstrual time periods in patients with menstrually related migraine. Gabapentin, fluoxetine and venlafaxine might also be considered since they have been shown to prevent both migraine and climacteric symptoms [34–36].

Mini-prophylaxis of menstrual migraine might be employed during the early menopausal transition if menses are regular and migraines predictably occur during perimenstrual time periods. Perimenstrual administration of triptans or estrogen gels/patches has been shown to reduce the frequency of menstrual migraine in past studies [25, 37, 38].

Contraceptive therapies such as estrogen-containing oral contraceptive pills (OCPs) or patches might be used to prevent migraine if patients have no contraindications (e.g., breast cancer, thromboembolic disease, cardiovascular risk factors). Generally these therapies are given continuously for extended durations only administering a placebo week every 3 months or not at all. Such approaches have been shown to reduce the frequency of menstrual migraine by decreasing time periods of "estrogen withdrawal" [39, 40]. These therapies could be employed during the early and late menopausal transition to prevent headache.

Hormone replacement therapy (HRT) is most commonly used during the late menopausal transition and early menopausal time periods to relieve climacteric symptoms. Transdermal estradiol patches or estradiol gels are preferred over oral therapies as they maintain more constant levels of estrogen. Estrogen preparations should be

administered daily as interruptions in therapy will create "estrogen withdrawal" and precipitate headache. Progestins must be used in women with an intact uterus to prevent endometrial hyperplasia. Daily progestin regimens are preferred as opposed to those that administer cyclic progestins for 10–12 days each month [41].

An important question is whether HRT can be used to prevent migraine headache in perimenopausal migraineurs. Cross-sectional studies [42, 43] suggest that HRT is associated with a greater prevalence of migraine headache. It is tempting to conclude that HRT increases the prevalence of migraine, but it is equally plausible that migraineurs receive HRT as a therapy to prevent worsening headaches during perimenopausal times. Studies [44, 45] have reported that daily oral conjugated estrogens + cyclic or daily progestins increase the frequency of migraine while daily transdermal estrogen + cyclic progestins do not change the frequency. A 100 mg transdermal estradiol patch by itself was found to decrease headache outcome measures by 34 % in premenopausal women after induction of a medical menopause [28]. Therefore, HRT regimens consisting of oral estrogen + progestins worsen migraine while transdermal formulations of estradiol ± oral progestins leave migraine unchanged or provide a modest preventative benefit. See a manuscript by Nappi [46] for a more comprehensive review of hormonal therapies during the menopause.

There have been rare instances in which attacks of migraine with aura have been triggered by estrogen-containing OCPs and estrogen replacement therapy [47, 48]. If this occurs then it may be necessary to discontinue these medications altogether or use lower dosages or potencies of estrogen preparations.

Another option for perimenopausal women is tibolone, which is a steroid hormone used to treat climacteric symptoms that binds to estrogen, progesterone and androgen receptors. It has been shown to reduce the number of hours of headache-related disability per month as compared to baseline in postmenopausal women with headache and climacteric symptoms [45].

## Conclusion

The menopausal transition represents a time of great change in ovarian hormones and the characteristics of the menstrual cycle. It is divided into early and late stages based on the patterns of menstrual bleeding as well as specific changes in reproductive hormones. The prevalence of migraine is greatest during the late menopausal transition, but only in those experiencing symptoms of PMS. The mechanisms through which the perimenopause might trigger migraine include "estrogen withdrawal", fluctuations in ovarian hormones, or secondarily through an increase in comorbid disorders. An understanding of these mechanisms may guide therapy for these women during their transition into menopause.

**Conflict of interest** I certify that there is no actual or potential conflict of interest in relation to this article.

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KEY NOTE LECTURE

# Strictly unilateral headaches: considerations of a clinician

**Gennaro Bussone**



**Abstract** The aim of the lecture is to draw attention to the role that clinical practice and clinical observation have had in stimulating research on the pathophysiology of cluster headache (CH) and other trigeminal autonomic cephalalgias (TACs). The symptoms of cluster headache—in particular the typical circadian periodicity of the headaches and the seasonal recurrence of cluster periods—were fundamental in shifting attention away from peripheral pathogenetic hypotheses to the idea that cluster headache could have a central origin. Initially, solid neuroendocrinological data pointed to hypothalamic involvement. For example, CH patients were shown to have alterations in biorhythms. Subsequently, modern functional neuroimaging techniques were able to demonstrate that the homolateral posterior hypothalamus is activated during TAC headaches, so implicating this region in TAC pathogenesis. It is known that the hypothalamus has a modulatory effect on nociceptive and autonomic pathways, particularly on the nociceptive trigeminovascular system. Future research should clarify whether the hypothalamus is the generator of TAC headaches, or whether it is activated in response to an alteration of the homeostatic equilibrium between limbic emotional-affective components and autonomic-nociceptive components modulated by the hypothalamus.

**Keywords** Cluster headache · Unilateral headache · TACs · Hypothalamus · Limbic system

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## Introduction

The so-called strictly unilateral headaches are a major group of primary headaches, about which we have learned a great deal in the last 50 years, thanks in large part to cross talk between clinical observation and pharmacological research.

When I became interested in these conditions back in the 1970s, the only strictly unilateral headache recognized by the Ad Hoc Committee classification of 1962 was cluster headache, which was then considered to be a form of migraine. The history of the emergence of this entity is instructive. The first description of what we would today recognize as cluster headache was by Romberg in 1840, although its clinical characteristics were more fully described by Mollendorf in 1867, who called the condition 'red migraine.' As the 20th century advanced, several similar conditions were recognized and named, based on variations in symptomatology, for example Sluder's neuralgia of the sphenopalatine ganglion (1913), Vail's vidian nerve neuralgia (1932), Harris' ciliary neuralgia (1936), and Horton's histamine headache (1952). All these conditions were violently painful, strictly unilateral headaches, typically occurring at fixed hours of the day or night and accompanied by prominent autonomic manifestations including lacrimation, conjunctival injection, eye reddening, rhinorrhea, facial and forehead sweating, and at times ptosis and miosis (Claude-Bernard-Horner syndrome, CBH), all ipsilateral to the pain. In 1952, Kunkle argued that these entities were symptomatic variants of a single condition for which he proposed the name cluster headache [1].

Cluster headache is characterized by phases (cluster periods) lasting weeks or months during which the headaches occur, followed, at least in the episodic form, by

attack-free periods. During a cluster period, the headaches occur with variable frequency, from once every other day to eight times a day, and last from 15 to 180 min. As noted above, the headaches are accompanied by prominent vasosecretive autonomic phenomena. Sometimes too, a headache is accompanied by transitory CBH, and in rare instances, this manifestation may persist after the resolution of a cluster period, particularly if headache frequency is high.

Around 80 % of cluster headache patients have the episodic form in which the cluster periods are separated by headache-free intervals lasting months or even years. The pain characteristically affects the same side of the head, not only within a cluster period but from one cluster period to the next.

The pain comes on unexpectedly and reaches its acme within a few min. Sometimes, however, an attack is preceded by sensations of heaviness or discomfort in the orbitofrontal region. The pain may be centered on the eye—'a needle or knife stabbing the eyeball'—or located periorbitally, temporally, or in other regions of the ipsilateral face. The pain is excruciatingly severe, having been described the most painful condition imaginable or ever experienced: typically, it provokes severe agitation and restlessness, sometimes inducing a patient to bang his head against a wall. Head fractures have been reported, so too have cluster headache-related suicides. The attacks may not only occur several times during the day, but also during REM sleep, waking the patient. It is not difficult to imagine that sufferers are often completely incapacitated, not only during the headaches, but also throughout the entire cluster period. Outside of cluster periods patients may be in terror of the onset of a new bout of attacks.

Around 20 % of cluster headache patients have a chronic form of the condition characterized by the absence of significant pain-free remission periods. In extreme cases, patients endure daily attacks without respite for years. Chronic cluster headache may present as such or may evolve from the episodic form.

The prevalence of cluster headache in the population has been estimated at about 0.3 %; it affects more men than women in the ratio of about 3:1 and usually appears in comparison in the third decade of life [2]. Mercifully, cluster headache frequency and severity tend to attenuate after age 60.

It should be evident that cluster headache is a serious condition that requires major commitment by the treating neurologist. The approach to a patient with suspected cluster headache begins with careful history taking and is followed by a neurological examination. Neuroimaging may be necessary to rule out secondary headache. The therapeutic approach should be decided with the involvement of the patient, and successful treatment is predicated on the establishment of good patient–physician relationship.

The clinical characteristics of cluster headache clearly distinguish it from other more common forms of primary headache like migraine, tension-type headache, and also the classical neuralgias. Up to the Classification of 1988, the International Headache Society (IHS) considered cluster headache as the member of the third major group of primary headaches.

In the years after the 1988 classification, rarer headache forms were described, with characteristics somewhat similar to those of cluster headache. One of these—chronic paroxysmal hemicrania—is diagnosed much more frequently in women than men and characterized by brief (5–30 min) unilateral, frequent (at least five per day) headaches that are resolved by treatment with indomethacin [3].

More recently, short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) has been recognized. Its characteristics are encapsulated in its name, and it is of shorter duration than any of the other strictly unilateral headaches; in most cases, the lacrimation and conjunctival injection are conspicuous. The pain is described as excruciating burning or stabbing, lasts 1–600 s and is located in orbital, supraorbital or temporal areas. The attacks recur from once to over 200 times per day. I have personal experience of SUNCT patient with around 500 attacks per day. SUNCT was first described by Sjaastad and is well described in his paper of 1989 [4] Differential diagnosis is against the similar condition called short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) [5].

The latest (2013) edition of International Classification of Headache disorders [6] introduced hemicrania continua at the latest of strictly unilateral headache group. Hemicrania continua are a persistent headache, associated with autonomic symptoms like those of cluster headache, but with milder and more-or-less continuous pain that is characteristically relieved by therapeutic doses of indomethacin. Photophobia and phonophobia may accompany hemicrania continua, suggesting the condition has affinities with migraine [7].

The headaches described above are all characterized by unilateral trigeminal distribution of pain that occurs with ipsilateral cranial autonomic manifestations.

For this reason, they are called trigeminal autonomic cephalalgias or TACs.

## Discussion of pathophysiology of TACs

Does the commonality of symptoms for TACs reflect a common or closely similar pathophysiology? Studies on

pathophysiology have been mainly confined to the most common TAC—cluster headache. The initial pathogenetic hypothesis for cluster headache proposed by Horton was the so-called vascular hypothesis, which in essence attributed the pain to vasodilatation of extracranial blood vessels. Vasodilatation was also considered the cause of the pain in migraine, and in fact, Horton considered that cluster headache was a variant of migraine. However, later studies demonstrated that vasodilatation is not specific for cluster headache or migraine, but is also present in experimentally produced cranial pain [8]. Furthermore, cluster headache pain attacks can re-occur after vasodilatation is blocked by trigeminal nerve sectioning [9].

Clues to a more realistic understanding of the pathophysiology of cluster headache come from consideration of the condition's principal clinical characteristics: the main trigeminal distribution of the pain, the homolateral autonomic symptoms, and the typical periodicity of the headaches and the cluster periods. It also has to be remembered that supratentorial intracranial pain receptors are located around the pial and dural blood vessels, including the large venous sinuses. This implies that the headache trigger must activate the perivascular trigeminal nerve endings. A theory that accounts for the pain and autonomic phenomena of cluster headache proposes that the former arises a result of activation of the trigeminal nerve, and the latter arise as a result of activation of craniofacial parasympathetic nerve fibers. Simultaneous activation of these structures is considered due to pathological activation of the trigeminofacial brainstem reflex.

Stimulation of branches of the trigeminal nerve results in liberation of vasoactive neuropeptides (by antidromic conduction) in the walls of blood vessels and meninges to stimulate nerve endings there, and also centrally, in the subnucleus caudalis (by orthodromic conduction) to cause neurogenic inflammation. The nociceptive information arriving at the subnucleus caudalis passes (trigeminovascular system) to integrating centers in the thalamus and subsequently to the cortex so that pain is perceived [10].

It is a characteristic of the trigeminovascular system that its stimulation causes the release of vasoactive neuropeptides such as substance P, calcitonin gene-related peptide (CGRP), neurokinin A, and other transmitters into the walls of innervated blood vessels supplying the meninges (antidromic activation). These substances provoke sterile inflammation with secondary vasodilatation and plasma protein extravasation, with consequent hypersensitisation of surrounding nerve endings, so that pain signals may occur even in the event of innocuous stimuli such as blood vessel pulsation. Drugs effective against cluster headache, such as triptans and ergotamine, very likely exert their pain-relieving effects by blocking the extravasation of these proteins [11].

Evidence that the trigeminovascular system and plasma protein extravasation are involved in cluster headache comes from the finding that during a cluster headache, levels of CGRP and also vasoactive intestinal polypeptide are increased in blood from the external jugular vein on the pain side. This increase indicates activation of facial nerve parasympathetic fibers originating from the superior salivary nucleus secondary to activation of the trigeminofacial brainstem reflex—itself a consequence of activation of the trigeminovascular system [12].

The fact that the pain of cluster headache is usually located in the territory of the distribution of the first branch of the trigeminal nerve suggested that that cluster headache trigger was inflammation or other disturbance affecting the cavernous sinus or intracavernous portion of the internal carotid artery, since the first branch of the trigeminal, the sympathetic pericarotid plexus, and parasympathetic nerves all pass through this sinus. Cavernous sinus involvement would also explain the sympathetic symptoms (Horner's syndrome) as well as the parasympathetic hyperactivity (manifest as lacrimation, nasal congestion, and conjunctival injection).

However, magnetic resonance imaging (MRI) studies have shown that the cavernous sinus is normal in cluster headache, so the hypothesis of its involvement in cluster headache pathophysiology has been abandoned.

On the other hand, a positron emission tomography (PET) study has revealed increased blood flow in the region of cavernous sinus during cluster headache attacks. But this also occurs when pain is induced by capsaicin injection in the distribution of the first trigeminal branch [13]. These data show that different types of painful stimulation of the ophthalmic branch of the trigeminal modify cavernous sinus blood flow via the trigeminofacial brainstem reflex [12]. According to this scenario therefore, the observed changes in cavernous sinus blood flow (likely due to changes in internal carotid blood flow) are a secondary reflex effect of the cluster headache pain, and not its cause.

While activation of the trigeminovascular system and trigeminofacial brainstem reflex can explain the pain and the autonomic manifestations of cluster headache, it is unable to explain the predominance in men and, above all, the typical periodic recurrence of the headaches and cluster periods. This rhythmicity is highly characteristic cluster headache and led to the suspicion that the hypothalamus is involved since it regulates biological rhythms and also regulates autonomic activity. Clinical evidence also pointed to hypothalamic involvement in the genesis of cluster headache. For example, lithium, which is an effective cluster headache prophylactic [14] accumulates selectively in the hypothalamus where it increases serotonin levels. Lithium is also affective against bipolar disorder, another

rhythmic disorder. Verapamil—today first choice drug for cluster headache prophylaxis and effective in bipolar disorder—also accumulates in the hypothalamus [15, 16].

One of the best-known functions of the hypothalamus is to control the activity of the neuroendocrine system, and this system has been used as a window onto the hypothalamus particularly as regards its role in cluster headache [17]. Circulating levels of several hormones directly under the control of hypothalamic releasing and inhibiting factors are altered in cluster headache patients, as are hormones of the hypothalamo-hypophyseal-adrenal axis. Increased basal levels of plasma cortisol, in conjunction with reduced cortisol and ACTH responses to insulin-induced hypoglycemia, and to challenge with ovine corticotropin-releasing-hormone, have been demonstrated in cluster headache patients, both in cluster period and remission, but are not observed in other pain conditions [18]. The circadian rhythm of plasma melatonin and its principal metabolite 6-sulphatoxymelatonin are also altered in cluster headache [19]. The fact that these alterations are present in both remission phase and cluster period suggests a primary hypothalamic dysfunction [20].

It is not clear, however, how the hypothalamus contributes to the clinical manifestations of cluster headache. There are several possibilities. Perhaps the functionality of the hypothalamic centers regulating biological rhythms are compromised so that when stimulated intrinsically or extrinsically, they do not respond appropriately, resulting in irregularities in the secretion of neuroendocrine agents and neurotransmitters, in turn resulting in altered responses of the autonomic system and impaired homeostasis of anti-nociceptive and emotional systems.

Studies in animals have shown that there is a direct neuronal connection between the trigeminal nucleus caudalis and the hypothalamus. It is therefore possible that periodic activation of this pathway, as a result of hypothalamic dysfunction, activates the trigeminovascular system.

Unequivocal evidence that the hypothalamus is involved in cluster headache came from PET studies which showed activation of the posterior hypothalamic gray matter on the pain side during a headache [21, 22], while a voxel-based morphometric MRI study documented increased neuronal density in the same area. This was the first time that a structural anomaly in the central nervous system been implicated in a primary headache [23] and directly inspired the use of hypothalamic stimulation as a treatment for chronic cluster headache.

Hypothalamic stimulation—deep brain stimulation, DBS—is now used to treat intractable drug-resistant cluster headache, chronic paroxysmal hemicrania, and SUNCT, and this efficacy has implications for the pathophysiology of the strictly unilateral headaches [24–26].

The posterior hypothalamus receives pain and other sensory information from the territories of the trigeminal by a direct pathway. It has also been shown that stimulation of the posterior hypothalamus is able to modulate the activity of the neurons of this pathway; in the same way, DBS of the posterior hypothalamus may modulate the activity of neurons in the trigeminal nucleus caudalis to restore normal function of the trigeminal nucleus caudalis in cluster headache, preventing activation of the trigeminofacial brainstem reflex [27–29]. A PET study using $H_2^{15}O$ in 10 cluster headache patients with a hypothalamic implant provided evidence for this scenario by showing—during stimulation—increased blood flow (activation) at the site of the implant, and also in the homolateral thalamus, insula, anterior cingulate cortex and somatosensory cortex—all parts of the pain matrix. More significantly, the ipsilateral trigeminal nucleus and ganglion were also activated, for the first time demonstrating simultaneous activation of the hypothalamus and trigeminal system [30]. This finding supports the hypothesis that hypothalamic stimulation improves chronic cluster headache, and other TACS, by modulating the activity of the trigeminovascular system. However, because hypothalamic stimulation takes weeks to months before it becomes effective, it would seem that hypothalamic and trigeminal activation are necessary, but not sufficient to provoke a cluster headache [31], and it is more likely that the hypothalamus interacting with the limbic system is not itself a generator of cluster headache, but a regulator of the duration and frequency of cluster periods and attacks [32].

## Concluding remarks

It has been observed that the onset of cluster headache may coincide with a highly stressful fife event, so perhaps the primum movens of cluster headache and other TACs are an alteration of the relation between emotion and nociception [33, 34], or more specifically an alteration in the homeostasis of the interoceptive system that integrates nociceptive information with emotional awareness mediated by the limbic system [35]. It is known that pain perception is closely related to affective state and that pain influences behavioral responses, contributing to maintaining homeostasis in the anti-nociceptive and emotional systems. This is no less the case in patients with cluster headache [35]. These considerations suggest a more holistic interpretation of the various primary headaches: as different outcomes of modifications in the equilibrium between emotional-affective aspects managed by the limbic system and autonomic pain aspect modulated by hypothalamus. It is expected that in vivo

imaging of the brain will soon more shed light on the altered relation between pain, behavior, and emotion in primary headaches.

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SESSION III LOCAL TREATMENTS

# Peripheral neurostimulation in primary headaches

**Giorgio Lambru · Manjit Singh Matharu**



**Abstract** Peripheral neurostimulation techniques have emerged as promising treatments for patients with medically intractable, highly disabling chronic daily headaches including chronic migraine (CM) and chronic cluster headache (CCH) besides other less common headache syndromes. Encouraging controlled and open label data in medically intractable CM and trigeminal autonomic cephalalgias (TACs) have suggested a meaningful therapeutic role for occipital nerve stimulation (ONS). In view of the frequent occurrence of pain in the first branch of trigeminal nerve, percutaneous supraorbital nerve stimulation alone or in combination with ONS has been used successfully in open label series of CM and CCH patients. In view of its connections with the trigeminovascular system, the stimulation of the sphenopalatine ganglion has been used as a therapeutic target for the treatment of acute cluster headache attacks, with promising results. Preliminary data in patients with epilepsy and migraine have suggested a potential efficacy of vagus nerve stimulation in the treatment of primary headaches. Non-invasive devices targeting peripheral nerves have been developed and initial experience is emerging for the acute and preventive treatments of primary headache disorders. This review analyses the available evidence on the efficacy and safety of the different peripheral neurostimulation techniques.

**Keywords** Occipital nerve stimulation · Sphenopalatine ganglion stimulation · Vagus nerve stimulation · Chronic migraine · Trigeminal autonomic cephalalgias

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## Introduction

Chronic daily headache is a major worldwide health problem that affects 3–5 % of the population [1] and results in substantial disability. Advances in the management of headache disorders have meant that a high proportion of patients can be effectively treated with medical treatments. However, a significant minority of these patients are intractable to conventional medical treatments. There is, therefore, a clear need for novel approaches for the management of this patient group. Neurostimulation therapies that entail peripheral or central nervous system targets are emerging as very promising approaches. The most widely used peripheral target is the occipital nerve. Open label studies in medically intractable trigeminal autonomic cephalalgias (TACs) have shown good tolerability and significant, long-term benefit of occipital nerve stimulation (ONS) [2, 3]. Encouraging open label results in chronic migraine (CM) patients have led to three multicenter randomized trials [4–6]. The benefits of ONS shown in these trials were less dramatic than hoped for. However, the studies had methodological flaws, unmitigated placebo effects and high rates of surgical complications, which may have obscured the full beneficial effect of ONS. More recently the use of different peripheral nervous targets, such as the sphenopalatine ganglion (SPG), supraorbital nerves and vagus nerves, has shown promising results. This

article reviews the available evidence for the use of stimulation of the occipital, supraorbital and vagus nerves as well as the sphenopalatine ganglion in the management of headache disorders.

## Occipital nerve stimulation

The rationale for the use of ONS in headaches came from animal studies showing the convergence of cervical, somatic and dural afferents on second-order nociceptors in the trigeminocervical complex [7]. In recent years, ONS has been used in various primary headache syndromes, including migraine, cluster headache (CH), hemicrania continua (HC), SUNCT (Short lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing) and SUNA (Short lasting unilateral neuralgiform headache attacks with autonomic symptoms) [2, 3].

Open-label studies on the use of ONS in medically intractable CM showed very encouraging outcomes. Forty-three of 51 patients treated (84 %) reported at least 50 % improvement [2]. Based on this initial experience, three randomized controlled trials (RCTs) in the use of ONS for the prevention of CM were undertaken. The ONSTIM feasibility trial (ONS for the Treatment of Intractable chronic Migraine) was a multicentre, randomized, single-blind, controlled study [5]. The study recruited 66 patients who met the revised International Classification of Headache Disorders (ICHD-II) criteria for CM [8] and had responded to occipital nerve blocks. Patients were randomized in a ratio of 2:1:1 to adjustable stimulation, preset stimulation and medical management. The responder rate was defined as 50 % reduction in headache days/month or at least a three-point drop (on VRS 0–10) in pain intensity at 3 months. The responder rate was 39 % in the adjustable stimulation group compared with 6 % in the preset stimulation group and none in the medical management group. Lead migration occurred in 12 of 51 patients (24 %). In the PRISM trial [4], available in abstract form only, 125 drug-refractory CM patients were treated with ONS or sham. The study showed a mean decrease of 5.5 migraine days/month in 63 patients who received active stimulation and a decrease of 3.9 days in 62 patients who received sham stimulation at 12 weeks. This difference was not statistically different. In the third RCT by Silberstein et al. [6] 157 CM patients were treated with ONS. Responders were defined as patients with a reduction of the mean daily pain intensity from baseline of 50 % or greater. The study failed to achieve the primary endpoint, with the proportion of responders in the active group (17.1 %) not differing significantly compared to the control group (13.5 %). However, the number of headache days was significantly reduced in the ONS group compared to the sham group (−27.2 % vs. −14.9 %). The migraine-related disability also decreased with active ONS.

These studies tried to explore the safety and efficacy of ONS in CM using rigorous study designs but have some methodological flaws. The follow-up of 12 weeks may not be a sufficient timeframe to assess the outcome of a surgical procedure in primary headaches. From the open label experience with ONS, some patients report meaningful improvement a few months after the implant [2]; hence a longer follow up period may be more appropriate. As part of the inclusion criteria of some of these studies, only patients with pain centred in the C2–C3 territory were included. This subpopulation of patients may not be representative of the CM population that report pain in the trigeminal territories as well as in the cervical ones in the majority of cases. Additionally, these studies included patients who have failed to respond to at least two classes of preventive treatments. One of them was the class of beta-blockers [6]. There is no evidence for efficacy of beta-blockers in CM. This raises the possibility that the subgroup of CM patients selected and treated in these trials may not have been medically intractable, as defined by international consensus [9]. Finally, the study by Silberstein et al. [6] cannot be considered double-blind, since the patients underwent a trial phase during which ONS-induced paraesthesia were induced before being randomized thereby potentially unblinding the study population.

Future studies should focus on selection criteria that include the highly disabled patients seen in tertiary care headache centres. The surgical treatment should be offered only to patients with CM that cannot otherwise be managed with medical treatments, thus defined medically intractable [9]. On this note, due to the demonstrated efficacy of Onabotulinum toxin A in the prophylaxis of CM [10], Onabotulinum toxin A should be included within the list of medication that CM patients must fail to respond to in order to be suitable for surgery. Patients with concurrent medication overuse headache need to be studied separately. In addition, the blinding process should be addressed more carefully; long-term follow-up should be reported to provide more stable estimates of outcome measures.

ONS seems to be slightly more effective in the treatment of chronic medically intractable TACs than CM. To date, open label data in 91 medically intractable CCH patients treated with ONS have shown a favourable outcome in 67 % of cases [2]. However, no RCTs have been performed yet. A novel study design in headache neuromodulation has been suggested for a double blind RCT in the prevention of medically intractable CCH [11]. Blinding in peripheral neuromodulation studies is difficult because stimulation is felt by the patient as paraesthesia in the occipital region; therefore, it is not possible to perform a blinded study in which active stimulation is compared to no (sham) stimulation. Using the same principle

of a vagal nerve stimulation study in epilepsy [12], the authors proposed a way to perform a blind study in neuromodulation by comparing high- and low-amplitude stimulation and establishing a dose–response curve in a blinded way. The study would compare patients treated with ONS at high stimulation intensity (100 %), which corresponds to the sub-pain threshold with patients treated at low stimulation intensity (30 % of the range between perception and sub-pain thresholds). Although innovative in trying to reduce blinding issues, it should be noted that this kind of design will ultimately be unable to answer the paramount question of whether ONS is more effective than placebo. The results of the study will only help clarify whether high-intensity stimulation is superior to low-intensity stimulation. Notably, studies using spinal cord stimulation (SCS) for the treatment of angina and neuropathic pain showed that even sub-threshold stimulation can lead to some degree of pain relief [13, 14].

ONS has also been shown to be effective in hemicrania continua (HC) [15, 16]. Lambru et al. [3] recently reported the outcome of nine medically intractable SUNCT ($n = 6$) and SUNA ($n = 3$) patients treated with bilateral ONS. Data on frequency, intensity and duration of attacks were obtained from headache diaries at baseline and after implantation, along with data on disability, anxiety and depression and quality of life scales administered pre and post implantation. At a median follow-up of 38 months (range 24–55 months), all but one patient showed substantial improvements: four patients became pain free, two almost pain free and two had a remarkable reduction in attack frequency and severity. The implant was well tolerated overall with only one patient developing lead migration and one patient developing erosion of the electrode.

## Sphenopalatine ganglion stimulation

The sphenopalatine ganglion is an extracranial parasympathetic ganglion located in the pterygopalatine fossa. Postganglionic parasympathetic fibres from the SPG innervate facial structures such as the salivary and lacrimal glands, the nasopharyngeal mucosa and the cerebral and meningeal blood vessels [17]. It has been suggested that the trigemino-autonomic reflex plays an important role in the pathophysiology of primary headaches [18]. The SPG is an important structure of this anatomo-functional reflex, responsible for the ipsilateral cranial autonomic features typical of TACs and, to a lesser degree, of other primary headaches such as migraine.

Based on this assumption, the SPG has been targeted over the years to treat CH by various lesional techniques (anaesthetic blocks, radiosurgery and gamma knife, alcohol injections, pulsed radiofrequency ablations). The success rates seem promising (varying from 46 to 85 %), but the benefits have been transient [19]. Because of this transient effect and the irreversible complications of the lesioning interventions, a non-destructive approach using acute percutaneous SPG stimulator with a removable electrode was examined in five patients with CH. SPG stimulation resulted in complete resolution of the CH attack in 11/18 attacks (61 %), partial resolution (>50 % VAS reduction) in 3/18 attacks and minimal to no relief in 4/18 attacks. Stimulation also resolved the associated autonomic features of CH [20]. Spontaneous or induced migraine attacks were treated with a percutaneous removable SPG stimulator in 11 migraine patients. Two patients had complete abolition of their induced headaches within 3 min of SPG stimulation, three had reduction in pain, five had no response and one was not stimulated [21].

Based on these preliminary findings, a new implantable microstimulator was developed and a multicenter randomised double-blind and sham-controlled trial has been conducted to examine the efficacy of acute SPG stimulation in refractory CCH [22]. This device is powered and controlled transcutaneously by electromagnetic waves. In this study, 32 CCH patients experiencing a minimum of four attacks per week were included. The design of the study consisted of a 4-week baseline period, followed by a post-implant stabilization and therapy titration period. The experimental period lasted until 30 CH attacks were treated or, if attack frequency was not high enough, for a maximum of 8 weeks. During this period, patients were instructed to use the stimulator to treat each attack for 15 min. The pain score was recorded using an electronic headache diary prior to each use and after the start of stimulation. Three stimulation doses were randomly applied when treatment was initiated by the patient for a CH attack: full stimulation, sub-perception stimulation and sham stimulation. The primary endpoint of pain relief after 15 min of stimulation was achieved in 67.1 % of full stimulation-treated attacks compared to 7.4 % of sham stimulation treated attacks. Remarkably, 43 % of patients experienced an attack frequency reduction of $\geq$50 % from baseline. Given the slight tingling sensation that accompanies stimulation of the SPG, a placebo effect cannot be excluded. In view of the apparent preventive effect of SPG stimulation, a multicentre trial currently underway aims to explore the efficacy of SPG stimulation in the preventive treatment of CM (NCT01540799).

## Vagus nerve stimulation

Vagus nerve stimulation (VNS) is a well-established treatment for intractable epilepsy and depression. The mechanism of action still needs to be fully elucidated. In

animal studies, it has been demonstrated that electrical, chemical and physiologic activation of vagal afferents produces analgesic effects. A study using left VNS in animal models showed a significant decreased of fos-immunoreactivity in trigeminal nucleus caudalis neurons [23]. Initial positive data on the efficacy of VNS in migraine was gathered from retrospective analysis of patients implanted for the treatment of epilepsy [24, 25]. In another study, two of four patients with refractory CM and depression improved significantly with VNS [26]. Similarly, a positive effect of VNS was reported in two CCH patients who also suffered from severe depression [27].

Initial experience using non-invasive VNS has been presented at the European Headache and Migraine Trust International Congress (London, 2012). The transcutaneous VNS device (tVNS Gammacore®) was used in 18 patients: 12 migraine, two CCH patients and two HC patients. The stimulation was applied 3 times/day for 90 s each time. Ten patients out of 13 with data available stopped tVNS due to lack of efficacy and/or side effects [28]. In another pilot study, seven episodic and seven chronic CH patients were treated with tVNS. An improvement after 13 weeks of trial was reported by 13 patients [29]. Two patients with HC initially treated with ONS, who subsequently had to have the stimulator explanted, were treated successfully with tVNS [30]. Currently, some RCTs are ongoing to validate this therapeutic approach in the acute and preventive treatments of chronic headaches (NCT01667250, NCT01701245, NCT01792817).

## Supraorbital nerve stimulation

Percutaneous supraorbital nerve stimulation (SON) produced almost complete resolution of symptoms in a patient with refractory CCH. The continuous stimulation led to a dramatic reduction in the frequency of attacks. Moreover, the patient was able to abort a CH attack by switching the stimulator programme [31]. In a retrospective study of five patients with refractory TACs (four patients had CH and one SUNCT), an implantable supraorbital and supratrochlear neuromodulation system led to a substantial reduction in pain intensity. Adverse events included skin erosion and wire infection [32].

Percutaneous SON has also been used in combination with ONS. The rationale of this combination was to try to cover the painful area as best as possible, according to the proposed mode of action of PNS [33]. Reed et al. [34] used combined ONS and SON in seven CM patients. All patients derived significant benefit and preferred the combined stimulation as opposed to the ONS stimulation alone. Recently, the efficacy of a novel transcutaneous supraorbital electrostimulation device (Cefaly, STX-Med, Liège, Belgium) in the prophylaxis of migraine was studied in a double-blind, randomized, sham-controlled trial [35]. Sixty-seven migraine patients with at least two attacks/month were recruited. Verum or sham stimulation was applied daily for 20 min during the three-month trial. The primary outcome measures were achieved. Patients treated with the verum stimulation obtained a significant reduction in the mean migraine days and the responder rate (50 % reduction of monthly migraine days between run-in and third month of treatment) was significantly higher in the verum compared to the sham group.

## Conclusions

PNS techniques have emerged as potential meaningful management options in primary headache disorders. A growing armamentarium of different devices is becoming available; however, their clinical use is limited by the lack of proper controlled data [36]. Since peripheral nerve stimulation is always perceived by patients, a proper sham group is practically impossible. For this reason, PNS should be considered only in patients with primary chronic headache disorders, in whom the therapies recommended by the international guidelines have failed to produce significant benefit. Candidates for PNS should be carefully evaluated in tertiary care headache centres, preferably with a multidisciplinary set up. More effective and less invasive procedures should be offered first [37].

Based on published evidence, the use of ONS and SPG are advisable for the preventive and abortive treatment, respectively, of medically intractable CCH [2, 22]. However, properly controlled double blind trials are needed to ultimately confirm the open label evidence, especially for ONS. The use of ONS in CM seems acceptable albeit that the treatment effect is relatively modest in the trials. Future trials in CM should only include patients that fulfill the definition of medically intractable chronic headache [9]. Additionally, since Onabotulinum toxin A is the only medication approved for the prophylaxis of CM in adults [10], future neurostimulation study designs for CM should consider patients that have failed or not responded adequately to Onabotulinum toxin A. Furthermore, since medication overuse headache is relatively common in CM the role of neurostimulation therapies in this subgroup of patients needs to be studied.

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SESSION III LOCAL TREATMENTS

# Endonasal mucosal contact points in chronic migraine

**V. Ferrero · G. Allais · S. Rolando · T. Pozzo · R. Allais · C. Benedetto**



**Abstract** Some anatomo-functional alterations of the nose may be considered as possible causes of headache: deviations of the nasal septum, abnormal turbinates, especially middle or superior, with consequent areas of mucosal contact with the septum. This study was performed on 100 subjects, 27 chronic migraine (CM) sufferers and 73 subjects who never suffered from migraine as control group. In the CM group, a direct endoscopic assessment was carried out in order to search for mucosal points of contact. Following the endoscopy, the patients underwent a computerized tomography (CT) in order to confirm the mucosal contact and for a better evaluation of its localization. The control group (C group) consisted of subjects who underwent a CT of the skull for various reasons. In CM group, a mucosal contact was highlighted in 14 patients (51.8 %); it was unilateral in 50 % of cases. In C group, the contact was present in 27 cases (36.9 %); in 81.5 % of them ($n = 22$), it was unilateral. A single site of contact was present in 6 (22 %) patients in CM group and 20 (27.3 %) patients in C group; more sites, in 8 (29.6 %) CM group patients and in 7 (9.5 %) patients of the C group. The connection between subjects and the number of single or multiple contacts in the two groups was statistically significant ($p = 0.049$). Furthermore, the frequency of the septum–middle turbinate was significantly ($p = 0.0013$) more frequent in CM sufferers (13/14) compared with control subjects (11/27). This study suggests, although with extremely early data, the need to select carefully patients for a possible surgical approach, using various parameters: in particular, the site of the mucosal contact, favoring the cases with multiple areas of contact, mainly between septum–middle turbinate and septum–superior turbinate.

**Keywords** Chronic migraine · Computerized tomography · Contact point headache

**Abbreviations**
CM Chronic migraine
CT Computerized tomography

## Introduction

Migraine unfortunately shows in some cases a complication, chronic migraine (CM); in this type of primary headache, the attacks occur over almost every day in a month. Chronic migraine is a pathological condition that appears more disabling than episodic migraine [1, 2]. The estimated prevalence of CM worldwide ranges widely, but the majority of studies estimate 1–3 % [1].

It is important to search for any associated factor that may somehow be linked to the process of transforming migraine from episodic to chronic.

Correlations between anatomo-functional alterations of the nose and the onset of headache [3] were already looked into in Sluder's first works (1927).

In 1988, Stammberger and Wolf [4] divided patients with headache symptoms in three groups:

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- patients with headache clearly attributable to nasosinusal pathology (sinusitis, barotrauma, tumors, etc.);
- patients with headache clearly not correlated with nasosinusal disorders, such as migraine, tension-type headache, cervical disorders, and vascular disorders;
- patients with headache that do not clearly fit into one of the two previous classes.

To cover all cases that are not clearly represented, the evaluation of a possible pathogenetical factor from mucosal intranasal contact would be correct, such as deviations of the nasal septum, abnormal turbinates, especially middle or superior, with consequent areas of mucosal contact with the septum [5, 6]. These areas of mucosal contact would be responsible for the release of substance P, able to cause vasodilation and to act as neurotransmitter for amielinic C fibers, with consequent onset of the headache [4].

Attention to these possible correlations allowed International Headache Society (IHS) to classify a particular form of headache already in 2004 [7], setting it only within the Appendix, since this picture was still supported by very limited data.

In fact, the last version of IHS classification [8], while acknowledging a possible correlation between headache and nasosinusal disorders, seems to be even less precise in diagnostic criteria, stressing how the studies in recent years do not allow a certain evidence. The diagnosis is possible within the classification when there is evidence of causation demonstrated by at least two of the following: (1) headache has developed in temporal relation to the onset of the intranasal lesion; (2) headache has significantly improved or significantly worsened in parallel with improvement in (with or without treatment) or worsening of the nasal lesion; (3) headache has significantly improved following local anesthesia of the mucosa in the region of the lesion; (4) headache is ipsilateral to the site of the lesion.

In the literature, the percentages of endonasal alterations with documented areas of mucosal contact in general population and in subjects suffering from headache are extremely variable, ranging from values of 4 % [9] to values higher than 55 % [5].

To our best knowledge, data are still missing in the literature about the possible influence of mucosal contacts specifically in subjects suffering from CM, in order to assess whether the intranasal trigger may participate in the process of headache attacks becoming chronic from episodic.

The goal of this study was to assess the presence of mucosal contact areas in a group of patients suffering from CM and in a control group.

## Patients and methods

The study was carried out from January 2012 until June 2013. The study was performed on 27 patients (24 females and 3 males) (mean age 44.77, range 16–77, DS ± 14.46) suffering from CM, diagnosed according to the IHS criteria [7].

Criteria for the inclusion in the study were: (1) history of CM for at least 2 years; (2) no rhinosinusal pathology as a possible cause of the headache; (3) having undergone at least four prophylactic treatments for migraine without significant therapeutic success.

In the CM group, a direct endoscopic assessment was carried out to search for mucosal points of contact.

Following the endoscopy, the positioning of decongestant (oxymetazoline) was carried out in order to exclude possible components due to mucosal edema; the local nasal mucosal anesthetic test was performed on patients with headache with the help of cotton soaked in a vasoconstrictor and anesthetic mix positioned at the level of the mucosal contact, highlighted with endoscopy, for 5 min.

In the CM group, a computerized tomography (CT) was also carried out as axial and coronal projection so as to confirm the mucosal contact and for a better evaluation of its localization.

The control group (C group) consisted of 73 subjects, 37 females and 36 males (mean age 50.26, range 16–88, DS ± 19.67), not affected by migraine, who for different reasons performed a CT of the skull.

We present here only the data regarding the comparison between CT reports of the two studied groups.

### Statistical analysis

Descriptive statistics are presented as count and percentages.

In order to verify the existence of significant differences between the distributions of mucosal contacts in CM group versus C group, a chi-square test was always applied; in case of low expected frequencies ($n \leq 5$), a Yates' correction was used.

Data were analyzed using the IBM SPSS Statistics Analysis System package for PC (version 21).

## Results

The certainty of the presence of mucosal contact was based on the outcome of the CT.

Of the 27 cases of the CM group, a mucosal contact was highlighted in 14 cases (51.8 %); the contact was unilateral in 50 % of cases.

In the C group, the contact was present in 27 cases out of 73 (36.9 %); in 81.5 % of them ($n = 22$), it was unilateral.

The percentage of subjects who showed a mucosal contact was not significantly different between the two groups (chi-square test $p = 0.18$).

The sites affected by a possible sinus contact considered in this study were as follows: contact between septal spur

**Table 1** Types of contact detected in the two studied groups

| | Septal spur | Septum–middle turbinate | Septum–superior turbinate |
|---|---|---|---|
| CM group | 3 | 13 | 7 |
| C group | 13 | 11 | 11 |

**Table 2** Distribution and association of the sites of contact in the two studied groups

| Site of contact | CM group ($n = 14$) | C group ($n = 27$) |
|---|---|---|
| Septal spur | 1 (7.1 %) | 8 (29.6 %) |
| Septum–middle turbinate | 5 (36.0 %) | 6 (22.2 %) |
| Septum–superior turbinate | – | 6 (22.2 %) |
| Septal spur + septum–middle turbinate | 1 (7.1 %) | 2 (7.4 %) |
| Septal spur + septum–middle turbinate | – | 3 (11.1 %) |
| Septum–middle turbinate + septum–superior turbinate | 6 (42.8 %) | 2 (7.4 %) |
| Septal spur + septum–middle turbinate + septum–superior turbinate | 1 (7.1 %) | – |

and inferior turbinate, between septum and middle turbinate, and between septum and upper turbinate.

The distribution of the number of sites affected by contact was: a single site in 6 (22 %) patients of the CM group and 20 (27.3 %) patients of the C group and more sites in 8 (29.6 %) patients of the CM group and in 7 (9.5 %) patients of the C group. In the CM group, seven patients showed two contact sites and one patient three sites, whereas all seven patients of the C group had only two contact sites. The connection between patients and the number of contacts resulted statistically significant when carrying out the chi-square test ($p = 0.049$) comparing single sites (CM: 6/14 vs. C: 20/27) to multiple sites (CM:8/14 vs. C: 7/27).

Table 1 shows the distribution in the two examined groups of the localization of the contact between septal spur and inferior turbinate, between septum and middle turbinate, and between septum and superior turbinate.

The presence of the septal spur, although being much more represented within control population compared with patients suffering from migraine, was not significantly different between the two groups ($p = 0.096$), as well as that of the septum–superior turbinate ($p = 0.57$); on the contrary, the frequency of the septum–middle turbinate resulted much more frequent ($p = 0.0013$) in patients suffering from migraine (13/14) compared with control subjects (11/27).

Table 2 details the distribution of contacts and their association in the two studied groups. When carrying out a statistical evaluation of the association of more sites of contact, no significant different distribution is highlighted between the two populations, except for the presence of the contact between septum–middle turbinate and septum–superior turbinate, which is significantly more represented in migraineurs than in the controls (6/14 vs. 2/27; $p = 0.021$).

The local nasal mucosal anesthetic test was negative in 19 over 27 cases but, as mentioned above, it was not considered an exclusion criteria for surgery.

## Discussion

The causes of headache are numerous and, in many cases, still unknown. Following this assumption, over the years, several authors have evaluated as a possible cause of headaches endonasal anatomical alterations able to support mucosal contact areas.

In this study, we tried to assess whether a possible role of mucosal contact in subjects suffering from CM is present.

As already shown in other studies [5] and confirmed by the evaluation of the present study, asymptomatic population frequently shows areas of mucosal contact, with a frequency that does not significantly differ from migraine patients. It was therefore thought that the areas of mucosal contact are able to act not in a direct manner, but as additional trigger areas and thus contribute to the occurrence of symptoms and their chronicity.

For this reason, it is difficult to think that mucosal contact is in itself a cause of headache, also considering the fact that in subjects suffering from headache the contact areas are always present and headache is often not continuous, at least in the subjects covered by the studies currently present in the literature. Furthermore Abu-Bakra et al. [9] showed how, when a mucosal contact area is present in patients with unilateral facial pain, this area of contact is often bilateral.

Moreover, the number and type of mucosal contacts are distributed in a significantly different manner between group CM and C: in particular, multiple contacts significantly prevail in CM patients in comparison with control subjects. Furthermore, the septum–middle turbinate is much more represented in people suffering from headache compared with the control subjects, as well as the association of septum–middle turbinate with septum–superior turbinate.

The difficulty in successful intranasal surgery is closely linked to the selection of patients: in the papers actually present in the literature [10, 11, 12], the selection criteria are unclear and each author uses particular techniques, often not well defined. Some authors [11, 13–16] consider

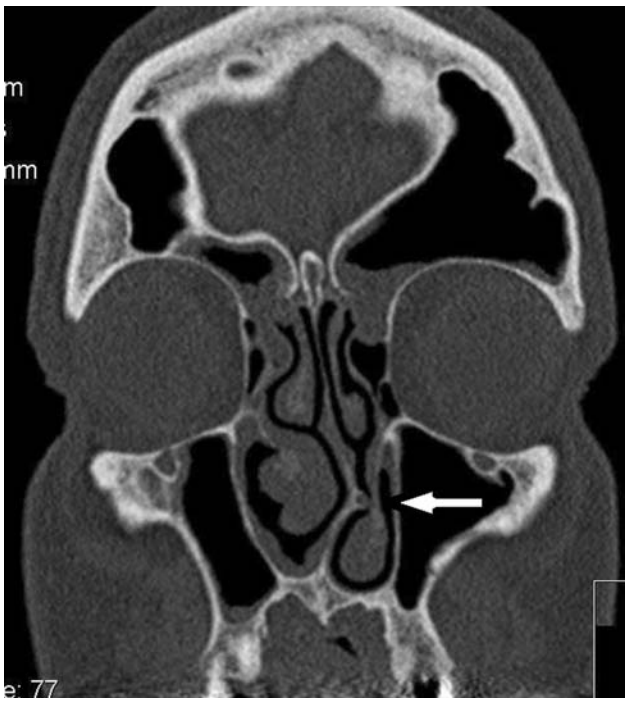

**Fig. 1** Nasal septal spur

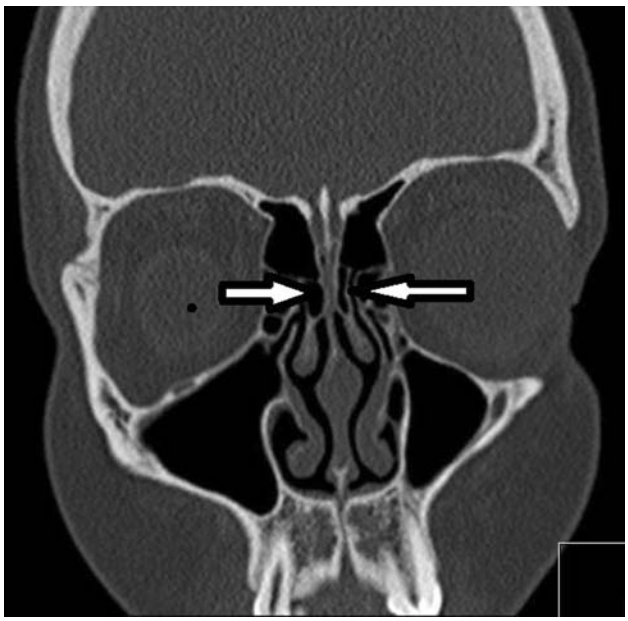

**Fig. 2** Septum–bilateral medium turbinate contact point

the local nasal mucosal anesthetic test as discriminating factor, but do not find a direct correlation between positivity of the test and the surgical outcome. On the other hand, Parsons and Batra [11] observed as this test does not predict the success of surgery. Furthermore, some authors select the type of headache according to the localization of pain, while other authors choose the headache patients on

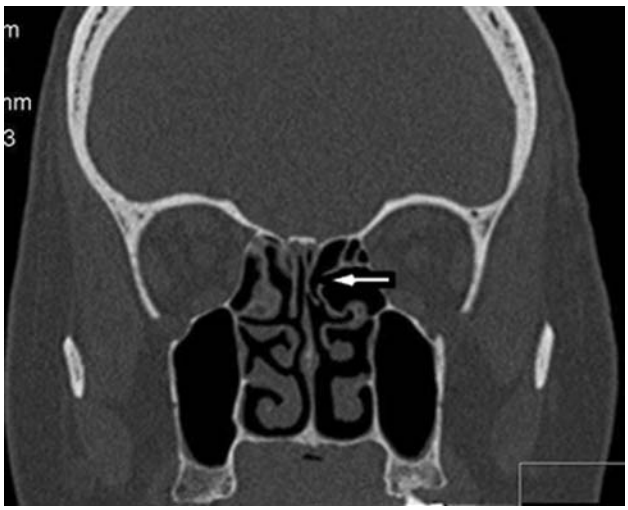

**Fig. 3** Septum–superior turbinate contact point

the basis of the diagnosis of primary headache, but they include different headache types in the same experimental group.

Other authors [17, 18] have also thought that mucosal contact areas as a possible cause of headache should be searched only in particular endonasal areas, excluding the most common ones, such as septal spurs (Fig. 1) and hypertrophies of the lower turbinates. In this way, only the mucosal contact areas between the upper component of the middle turbinate (Fig. 2) and the upper turbinate and septum (Fig. 3) should be considered important.

In our paper, focused on a very selected population with a specific diagnosis of CM, we demonstrate that the percentage of locations of mucosal contact at the septal spur level are higher, even if not in a statistically significant manner, in control subjects compared with patients suffering from headache; in this group, however, multiple locations are more frequent.

In the studies reported above, substance P would be the vehicle capable of supporting the headache, in the presence of mucosal contact areas. However, Baranuik [19] underlines how substance P is present in normal human mucosa and there is no evidence that its presence is unleashed from mucosal contact areas.

Hence, it is clear that currently there is still no certainty in selecting headache patients who would benefit with good probability from intranasal surgery in case of presence of mucosal contact areas, which are quite common. This study suggests, although with extremely early data, the need to select patients using various parameters: in particular, the site of the mucosal contact, excluding septal spurs, less frequent in CM, and favoring, on the contrary, the cases with multiple areas of contact, mainly between septum–middle turbinate and septum–superior turbinate, and positivity to the local nasal mucosal anesthetic test.

**Conflict of interest** All the authors certify that there is no actual or potential conflict of interest in relation to this article.

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KEY NOTE LECTURE

# New treatments for headache

**Sarah Vollbracht · Alan M. Rapoport**



**Abstract** Migraine and cluster headache are primary headache disorders commonly encountered in clinical practice. Despite the profound disability caused by these primary headache disorders, available acute and preventive treatment options are limited. Recent understanding of headache pathophysiology has led to the development of new drug formulations and novel drug targets that are extremely promising. This article will highlight several of the new treatments that are currently under investigation including novel delivery mechanisms of already existing medications, calcitonin gene-related peptide (CGRP) receptor antagonists, antibodies to CGRP and its receptor, serotonin receptor agonists, transient receptor potential vanilloid receptor modulators, orexin receptor antagonists, glial cell modulators, and neuromodulation. If data is supportive, these therapies will be welcome additions to the headache specialist's armamentarium.

**Keywords** Migraine treatment · Headache therapy pipeline · Novel delivery mechanisms · CGRP · Neuromodulation

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## Introduction

Migraine is a chronic neurovascular disorder with episodic manifestations that involves the cerebral cortex, trigeminal nerve and its central connections as well as the cranial vasculature [1]. It is characterized by episodic attacks of head pain and associated symptoms that cause significant disability. Although approximately 12 % of the adult population in the US suffers from migraine, treatment options are limited [2]. The most significant recent advancements in the treatment of migraine were the advent of the triptan class as an acute treatment in the early 1990s and the FDA approval of onabotulinumtoxinA for the prevention of chronic migraine in 2010. Treatment options for cluster headache, another primary headache disorder that is considered to be the most severe type of headache, are extremely limited. Only sumatriptan injection is approved by the FDA in the US for its acute treatment. Although not yet reflected in the number of approved available treatments, our understanding of migraine and cluster headache pathophysiology is rapidly expanding, which has led to new and exciting treatment targets. This review will briefly discuss many of the new and future therapies for headache that are currently being investigated.

## Novel delivery mechanisms

### Triptan reformulations

Triptans represent the mainstay of acute migraine therapy, but many migraineurs either do not experience complete and sustained pain relief, are unable to tolerate the adverse effects, have contraindications to their use, or cannot afford

them [3, 4]. Because of their overall safety, specificity, and efficacy, the most recent advances are novel delivery mechanisms that aim to address any shortcomings of the already existing medications.

**SUMAVEL® DosePro®** (Zogenix, San Diego, CA, USA) was approved by the FDA as a 6-mg needle-free sumatriptan injection in 2009. It is easy to use and, when administered in the thigh or abdomen, is bioequivalent to the existing needle auto-injector [5]. Active triptan users requiring a change in therapy or who were less than very satisfied with their current acute medication experienced a significant and sustained increase in efficacy, satisfaction, and confidence in therapy with Sumavel® DosePro® with no decrease in tolerability [6, 7]. A 4-mg dose was approved by the FDA in December 2013 and will be available in the US around June 2014.

**ALSUMA™** (Pfizer Inc., New York, NY, USA) was approved by the FDA in 2010. It is an epipen-type, preassembled, single-use sumatriptan injection system that can rapidly and effectively deliver a subcutaneous injection of sumatriptan succinate 6 mg for the acute treatment of migraine. It is easy to use and just as effective as the other sumatriptan injections, delivering 2-h headache response and pain-free rates of 93.7 and 60.3 %, respectively. Adverse events were comparable to those reported for other subcutaneous delivery mechanisms, with injection site bruising and pain reported in 15.9 and 6.3 % of patients, respectively. According to one study, more patients prefer ALSUMA™ (65.1 %) to the traditional auto-injector [8].

**ZECUITY™** (NuPathe Inc., Conshohocken, PA, USA) was approved by the FDA in 2013 and delivers sumatriptan transdermally with an iontophoretic patch, addressing the unmet need of medication delivery in the setting of migraine-associated gastrointestinal symptoms. At the time of writing of this manuscript, it appeared that the company will be purchased by Teva Pharmaceuticals (Petach Tikva, Israel). The patch utilizes an electrical current to drive sumatriptan through the skin into the subcutaneous tissue capillaries [9]. ZECUITY™ reaches plasma levels similar to the oral, nasal, and subcutaneous routes of administration, but provides a longer duration of therapy, maintaining therapeutic drug levels four times longer compared to the 6-mg injection and twice as long compared to the 50-mg tablet. It is an effective acute therapy, with significantly more patients treated with ZECUITY™ compared to placebo experiencing headache freedom, headache relief, and freedom from nausea, photophobia, and phonophobia at 2 h. Significantly more patients treated with ZECUITY™ attained sustained pain relief and required less rescue medication. The patch is well tolerated with few of the typical "triptan sensations." There were no serious adverse events, and the most common adverse events were mild and transient local skin reactions at the application site [10–12]. ZECUITY™ maintained its tolerability and efficacy with successive uses over a 12-month period [13]. It is expected to be available in the US in 2014.

**OPTINOSE™** (AVP-825) (Optinose US Inc., Yardley, PA, USA), a bi-directional, breath-actuated device to delivery sumatriptan intranasally in a fine powder formulation appears promising and the company has just recently filed for FDA approval. The device is activated by blowing into one arm of it with the other arm in one nostril. This releases a fine powder of sumatriptan into the nostril. It also causes the soft palate to rise and isolate the nasal cavity from the oropharynx allowing more sumatriptan to be absorbed across the nasal mucosa than with traditional nasal sprays [14]. A phase II trial showed both sumatriptan 10 or 20 mg delivered via the OPTINOSE™ device were statistically superior to placebo for pain relief at 1 and 2 h, pain freedom at 2 h, and sustained pain freedom at 48 h. No serious adverse events were reported and there were none of the customary "triptan sensations" including chest discomfort or pain, paresthesias, or asthenia. The most common adverse event was dysgeusia in 10 and 13 % of patients receiving the 10- and 20-mg dose, respectively [15]. Phase III data demonstrates that intranasal sumatriptan delivered via the OPTINOSE™ device is safe, effective, and well tolerated with no serious adverse effects with 2-h pain relief in 67.7 %, and 2-h pain freedom in 34 % of subjects compared to 45.2 and 17 % for placebo, respectively. Statistically significant pain relief was reached as early as 30 min [16, 17]. Avanir Pharmaceuticals (Aliso Viejo, CA, USA) and Optinose announced a licensing agreement in July 2013. Under the terms of the agreement, Avanir will assume responsibility for regulatory, manufacturing, supply chain, and commercialization activities for the investigational product, now named AVP-825. Both parties will work together on the remaining activities in support of the new drug application (NDA) submission.

**CAMBIA™** (Nautilus Neurosciences, Bedminster, NJ, USA, with rights recently bought by Depomed, Newark, CA, USA) was approved by the FDA in 2009 as buffered diclofenac potassium powder in a sachet for oral solution. In a head-to-head randomized, controlled, crossover trial, Cambia™ demonstrated an onset of analgesic effect within 15 min compared to 60 min for the same dose of the tablet formulation. Significantly more patients treated with Cambia™ (24.7 %) were pain free at 2-h compared to both tablets (18.5 %) and placebo (11.7 %). Cambia™ was also superior to tablets for sustained headache response, sustained pain freedom, and reduction in headache intensity within the first 2 h [18]. In a randomized, double-blind, parallel-group, placebo-controlled trial, Cambia™ was statistically superior to placebo in rates of pain freedom (25 vs. 10 %), nausea freedom (65 vs. 53 %), photophobia freedom (41 vs. 27 %), and phonophobia freedom (44 vs.

27 %) at 2 h, with reduction in pain intensity beginning within 30 min. The effect was sustained through 24-h post-treatment [19]. This medication is widely used by headache specialists in the US.

**LEVADEX® Tempo® Inhaler** (MAP Pharmaceuticals Inc., Mountain View, CA, USA, recently bought by Allergan, Irvine, CA, USA), delivers orally inhaled dihydroergotamine deep into the lungs after breath actuation via the Tempo® Inhaler. Intravenous dihydroergotamine has been the mainstay of inpatient headache management for decades, but outpatient use is limited. The currently available nasal spray formulation is less effective than intranasal sumatriptan and has low bioavailability, whereas intramuscular or subcutaneous dihydroergotamine is difficult for patients to self-administer and produces more adverse effects [20]. LEVADEX® is rapidly absorbed with a $T_{max}$ of 12 min, and provides similar, although 23 % lower, systemic exposure compared to a 1-mg intravenous dose, leading to a significantly fewer adverse effects, notably nausea and vomiting, compared to the intravenous formulation [21, 22].

Phase II data comparing the 0.5- and 1-mg doses with placebo-demonstrated onset of pain relief in a small number of patients as early as 10 min for the 0.5-mg dose. Significantly, more patients treated with both the 0.5-mg and 1-mg dose demonstrated pain relief and pain freedom at 2 h compared to placebo and sustained pain relief and sustained pain freedom at both 24 and 48 h also favored the 0.5-mg dose over placebo. Both LEVADEX® doses were well tolerated with no serious adverse events, but no additional benefit was observed with the higher dose [23]. A phase III trial demonstrated superiority over placebo in 2-h pain relief (58.7 vs. 34.5 %), pain freedom (28.4 vs. 10.1 %), photophobia freedom (46.6 vs. 27.2 %), phonophobia freedom (52.9 vs. 33.8 %), and nausea freedom (67.1 vs. 58.7 %). The medication was effective and well tolerated [24]. An additional benefit is that LEVADEX®, unlike triptans, is equally effective in patients with or without allodynia, suggesting that efficacy is maintained when taken late into the course of a migraine attack [25–27].

Allergan acquired MAP Pharmaceuticals Inc. in 2013 after NDA resubmission was accepted by the US FDA. It received a complete response letter from the FDA on April 15, 2013, postponing approval due to concerns over the manufacturing of the inhaler. Allergan has since acquired the company responsible for filling the canisters and is working to address the issue. It is hoped that the drug will be launched in 2014.

## Calcitonin gene-related peptide

Calcitonin gene-related peptide (CGRP) has been implicated in both migraine and cluster pathophysiology. CGRP first gained attention as a potent vasodilator, but is now understood to play a role in the modulation of neuronal activity in the trigeminocervical complex and brainstem signaling pathways and is found in high concentrations throughout the trigeminal ganglion and meningeal perivascular trigeminal neurons [28–33]. CGRP and its receptor are attractive therapeutic targets, but clinical development of the CGRP receptor antagonists to date has been disappointing.

Intravenous olcegepant (BIBN4096BS) was the first effective CGRP receptor antagonist, delivering statistically significant pain relief and pain freedom at 2, 24 h sustained pain relief, lower headache recurrence, and improvement in nausea, photophobia, phonophobia, and functional capacity compared to placebo. Although generally well tolerated with no serious adverse effects, drug development was terminated for unclear reasons, perhaps related to difficulty converting the intravenous product into an oral one and also to reduced bioavailability [34].

Telcagepant (MK-0974) and its more potent cousin MK-3207 were both superior to placebo and comparable to triptans in clinical trials. Generally well tolerated with fewer adverse events when compared to triptans, telcagepant appeared safe in patients with stable cardiovascular disease. Further development of both telcagepant and MK-3207 was abandoned when asymptomatic liver toxicity was detected while being studied as a preventive medication with daily use [35–46]. Three other CGRP receptor antagonists have shown promise, and further investigation into this class suggests that liver toxicity may not be a class effect. Both BI 44370 TA (Boehringer Ingelheim, Ingelheim, Germany) and BMS-927711 (Bristol-Meyers Squibb, New York, NY, USA) have phase II data showing efficacy superior to placebo and similar to triptans [47, 48]. MK-1602 (Merck Sharp & Dohme Corp, Whitehouse Station, NJ, USA) is listed as having completed a phase II trial on clinicaltrials.gov [49].

A novel way of targeting CGRP activity is through monoclonal antibodies (mAbs) directed against CGRP or its receptor. At the time of manuscript preparation, four companies are actively developing mAbs for migraine prevention.

LY2951742, a mAb against CGRP licensed to Arteaus Therapeutics (Cambridge, MA, USA) from Eli Lilly (Indianapolis, IN, USA), completed a phase I dose-escalating study tested single subcutaneous doses ranging from 1 to 600 mg along with 150 mg administered subcutaneously every other week for 6 weeks [50]. A phase 2a study has also been completed comparing 150 mg administered subcutaneously every other week for 12 weeks versus placebo for the treatment of moderate frequency episodic migraine [51]. Although the efficacy results have not been released, Eli Lilly has reacquired the drug suggesting its commercial viability.

ALD403, a mAb against CGRP developed by Alder Biopharmaceuticals (Bothell, WA, USA) for the treatment of frequent episodic migraine, is being tested in two-phase 1b studies evaluating the safety, pharmacokinetics, and efficacy of a single dose of ALD403 intravenously and subcutaneously over 12 and 24 weeks [52, 53].

LBR-101 (previously known as RN-307 or PF-04427429), a mAb against CGRP developed for the prevention of chronic migraine, was licensed to Labrys Biologics (San Mateo, CA, USA) from Pfizer (New York, NY, USA). Phase I data suggest that the drug is safe and well tolerated without obvious safety concerns when given as a single intravenous dose ranging from 0.2 to 2,000 mg or multiple intravenous doses up to 300 mg [54]. Another phase I study is ongoing to assess the safety, tolerability, and blood levels of two different doses of LBR-101 administered intravenously and subcutaneously in healthy volunteers [55]. A phase 2b study is ongoing comparing subcutaneous administration of high- and low-dose LBR-101 compared to placebo given monthly for 3 months for the prevention of chronic migraine, and another phase 2b study is investigating the drug as a possible treatment for high-frequency episodic migraine [56, 57]. LBR-101 has a reported half-life of 44–48 days, making monthly dosing intervals, or even one dose every 6 weeks, possible [58].

AMG 334, developed by Amgen (Thousand Oaks, CA, USA), is the only mAb developed against the CGRP receptor rather than the neuropeptide. Two separate phase 1b studies are assessing the safely and pharmacokinetics of single and multiple ascending doses given as subcutaneous or intravenous doses [59, 60]. A phase 2 study comparing low-dose, middle-dose, and high-dose AMG 334 with placebo for the treatment of episodic migraine is currently recruiting participants, and a separate phase 2 study comparing two separate subcutaneous doses of AMG 334 with placebo given monthly for the treatment of chronic migraine [61, 62].

## Serotonin receptor agonist

The triptans are high-affinity agonists at the 5-$HT_{1B}$ and 5-$HT_{1D}$ receptors, but some triptans also are agonists at the 5-$HT_{1F}$ receptor. Unlike the 5-$HT_{1B}$ receptor, which is found on intracranial blood vessels and coronary vessels and can cause vasoconstriction, activation of the 5-$HT_{1F}$ receptor, which is located in the trigeminal ganglion, trigeminal nucleus caudalis, and cerebral and peripheral blood vessels, does not cause cerebral vasoconstriction. It acts in part through inhibiting both dural neurogenic inflammation and neuronal activity in the trigeminal nucleus caudalis, which runs from the pons, through the medulla, into the upper cervical spinal cord [63]. COL-144, lasmiditan (CoLucid Pharmaceuticals Inc, Research Triangle Park, NC, USA), is a selective 5-$HT_{1F}$ receptor agonist [64]. Lasmiditan administered both orally and intravenously was superior to placebo in phase II studies in 2-h headache relief, but had a dose-dependent adverse event profile including dizziness, fatigue, vertigo, somnolence, paresthesia, heaviness, and nausea [65, 66]. Phase III studies are under development and if effective, 5-$HT_{1F}$ receptor agonists may represent a novel non-vasoconstrictive option for acute migraine treatment.

## Transient receptor potential vanilloid (TRPV1) receptor modulators

The transient receptor potential vanilloid (TRPV1) receptor, also known as the capsaicin receptor and the vanilloid receptor, is involved in nociception as well as body temperature regulation. Receptor activation leads to CGRP release in the central and peripheral trigeminal system, making it an attractive therapeutic target [67]. Civamide, a TRPV1 receptor agonist and calcium channel blocker, stimulates the release of excitatory neuropeptides CGRP and substance P, leading to their depletion in type-C nociceptive fibers and subsequent activity suppression. Civanex (Winston Laboratories, Inc., Vernon Hills, IL, USA) is a 0.01 % civamide nasal solution and has potential for the treatment of cluster headache. In a meta-analysis of two available studies, 1 week of treatment with civamide decreased cluster pain by 70 % by the third week post-treatment compared to 35 % in the control group. There were no systemic adverse effects or significant medication interactions since Civanex is not systemically absorbed. Many subjects did report a burning sensation in the nose that subsequently diminished after a few days [68]. 50 μg of civamide was modestly effective in the prevention of episodic cluster headache in a multicenter, double-blind, randomized, vehicle-controlled study of 28 patients [69]. A larger unpublished study of 112 patients using saline as a control demonstrated a decrease in cluster headache attacks that was not statistically significant, perhaps because saline in the control likely independently reduced cluster pain [68]. A phase III trial using only the vehicle as a control is planned [70].

Civamide 20 and 150 μg were studied for the acute treatment of a single migraine attack in a double-blind, randomized, pilot study. 2- and 4-h pain relief was reported in 55.6 and 72.7 %, respectively, and 2- and 4-h pain freedom was reported in 22.2 and 33.0 %, respectively. Again, there were no systemic adverse events. Almost all patients (91.2 %) experienced nasal burning and nearly half (44.1 %) experienced lacrimation [71]. Larger, vehicle-controlled studies evaluating the efficacy of civamide in the treatment of migraine headache are needed.

## Orexin receptor antagonists

Orexin A and orexin B are integral to sleep and eating, but also play a role in nociception. They are synthesized in the lateral and posterior hypothalamus and project widely to nociceptive areas of the brain and spinal cord and receptor activation can modulate responses of the trigeminovascular system to dural stimulation [72, 73]. MK-6096, a selective reversible antagonist of both orexin receptors, $OX_1R$ and $OX_2R$, was in clinical development for the treatment of insomnia; and a clinical study to evaluate it as a treatment for episodic migraine has been completed, but results have not yet been published [74, 75]. Its cousin, MK-4305, or suvorexant, is currently in development for the treatment of insomnia. In the summer of 2013, the FDA suggested that Merck study lower doses of the drug and resubmit their application.

## Glial cells

Glial cells have emerged as important therapeutic targets in the management of pain and migraine headaches due to their involvement in pain pathophysiology. In addition to the afferent trigeminal sensory neurons, the trigeminal ganglion contains satellite glial cells (SGCs) and Schwann cells. The SGCs are the most abundant cells in the trigeminal ganglion and surround the neuronal cell bodies in a functional network [30]. The SGCs in the trigeminal ganglion play an important role in neuronal modulation and influence trigeminal-mediated peripheral sensitization in migraine [76]. Trigeminal sensory neurons and SGCs communicate via gap junctions within the trigeminal ganglion. Neuronal CGRP regulates SGC cytokine expression that can feedback to modulate neuronal activity [77]. Additional evidence from in vitro studies shows enhanced release of CGRP from trigeminal neurons in response to capsaicin after treatment with conditioned medium from activated SGCs [78]. Pharmacologically targeting glial cells can perhaps prevent the development of peripheral sensitization.

Ibudilast (AV-411 or MN-166), currently used in Japan for the treatment of asthma and post-stroke dizziness, is a promising medication that crosses the blood brain barrier and suppresses glial cell activation. Ibudilast is a phosphodiesterase (PDE) inhibitor that also has anti-inflammatory properties, suppressing proinflammatory cytokines IL-1β, TNFα, and IL-6 while enhancing the anti-inflammatory cytokine IL-10. Ibudilast also enhances the release of glial-derived neurotrophic factor and nerve growth factor. Ibudilast can enhance the analgesic effects of opiates while reducing tolerance, and has potential utility in the treatment of neuropathic pain. Ibudilast was acquired by MediciNova, Inc. (San Diego, CA, USA) from Avigen, Inc. (Alameda, CA, USA) [79, 80] A phase I study of ibudilast in the prevention of chronic migraine and another phase I study of ibudilast in the treatment of medication-overuse headache are currently recruiting participants [81, 82].

## Neuromodulation

The treatment of patients with refractory chronic primary headache syndromes [such as refractory chronic migraine (CM) or refractory chronic cluster headache (CCH)] remains challenging. For those patients with refractory primary headache disorders who are either not responsive to or unable to tolerate available oral therapies, peripheral neuromodulation is a treatment option.

Cerena transcranial magnetic stimulator (TMS) was the first device approved by the FDA in December 2013 for the acute treatment of attacks of migraine with aura. The device is manufactured by eNeura Therapeutics (Sunnyvale, CA, USA). Cerena TMS utilizes single-pulse TMS (sTMS) to deliver a brief magnetic pulse to the occiput. In animal models, TMS can inhibit cortical spreading depression, thought to be the biological substrate of the migraine aura. The pivotal study was a multicenter, randomized, double-blind, parallel-group, sham-controlled trial investigating sTMS administered as two pulses separated by 30 s administered just below the occipital bone as soon as possible after the aura onset and always within 60 min of aura onset. 162 patients treated at least one attack with either Cerena TMS or sham stimulation. Pain freedom at 2 h was significantly higher with Cerena TMS compared to sham stimulation (39 vs. 22 %, respectively) and sustained pain freedom at 24- and 48-h post-treatment significantly favored Cerena TMS. Non-inferiority of Cerena TMS was shown for nausea, photophobia, and phonophobia at 2-h compared to sham stimulation. The device was generally well tolerated, and no device-related serious adverse events were reported [83]. A separate study demonstrated efficacy in both migraine with and without aura, but the response in patients with aura was more robust [84]. Although approved by the FDA only for the acute treatment of attacks of migraine with aura, we suspect that it may also be effective for attacks of migraine without aura.

Occipital nerve stimulation (ONS) is the best-known peripheral neuromodulation procedure in the treatment of refractory CM. Small open trials and case reports have suggested great benefit [85, 86], but larger randomized sham-controlled trials have not been as encouraging. In one large multicenter, randomized, blinded, controlled feasibility study, 39 % of patients treated with the active ONS device had at least a 50 % decrease in monthly headache days or at least a 3-point decrease in pain intensity from

baseline [87]. In another randomized, multicenter, double-blinded, controlled trial of 157 patients, the primary endpoint (responder rate) was not met, but a significant reduction in headache days was seen in the active ONS group compared to the sham group [88]. Interestingly, an uncontrolled small study suggested that combined ONS-supraorbital nerve stimulation may be beneficial in patients who did not respond to ONS alone [89]. The most frequent adverse events in all studies were lead migration, battery depletion, immediate or delayed infection of the surgical site and implantation bed, intolerance of paresthesias, and traction of the cable connecting the electrode lead to the battery. Although mostly mild, some adverse events required surgical revision or device removal. Further studies are underway to assess the safety and efficacy of ONS in the treatment of refractory CM.

Intermittent stimulation of the sphenopalatine ganglion (SPG) is a promising treatment modality in patients with CCH and potentially also with refractory CM. Autonomic Technologies, Inc. (Redwood City, CA, USA) has developed an implantable SPG neurostimulator that is implanted transorally in a minimally invasive procedure. Once implanted, the ATI device allows the patient to deliver stimulation with a hand-held rechargeable remote control at the onset of each cluster or migraine attack. A European multicenter, randomized, sham-controlled study treated 566 cluster headache attacks in 28 randomized patients with chronic cluster headache. Pain relief was achieved in 67.1 % of stimulated compared to 7.4 % of sham-treated attacks at 15 min. Overall, 68 % of patients experienced clinically significant improvement involving pain relief, attack frequency reduction, or both. Five device- or procedure-related SAEs occurred and most patients (81 %) experienced mild to moderate sensory loss in the maxillary nerve region that resolved within 3 months in 65 % [90]. Long-term follow-up is underway to assess the duration of benefit of the ATI neurostimulation system. A European study is currently underway using the same device to evaluate the safety and efficacy for the treatment of severe, disabling migraine attacks. Further studies are needed to assess the safety and efficacy of SPG stimulation in the acute and possibly preventive treatment of intractable CCH and CM. There are plans to repeat the chronic cluster and severe migraine studies in the US.

Several small open case series have reported that patients experienced migraine improvement after implanted vagal nerve stimulation (VNS) [91–95]. A novel device has been developed that is able to non-invasively deliver similar stimulation to implanted VNS. The gammaCore® device (ElectroCore LLC, Morris Plains, NJ, USA) stimulates the cervical branch of the vagus nerve transcutaneously in two 90-s stimulations separated by 15 min. Treatment with non-invasive vagal nerve stimulation (nVNS) in animal models resulted in a significant and prolonged increase in the trigeminal pain threshold, perhaps by inhibiting glutamate release within the trigeminal nucleus caudalis [96]. A pilot study demonstrated efficacy in the acute treatment of migraine attacks, with higher rates of 2-h pain relief and pain freedom achieved if the pain was rated mild rather than moderate to severe at baseline. The device was generally well tolerated with no serious adverse events. The most common adverse events were neck twitching, raspy voice, and neck redness [97]. In an open label study in the treatment 14 patients with intractable cluster headache, 93 % of treated patients reported improvement, and 86 % of patients were able to reduce or stop their previously used abortive therapy with a median device usage of 13 weeks. The device was well tolerated and all patients reported satisfaction with therapy [98]. Additional randomized controlled trials are currently ongoing to assess the safety and efficacy of nVNS with gammaCore® in the acute and prophylactic treatment of migraine and cluster headache.

Another potentially safe, non-invasive neurostimulation technique for the treatment of migraine headaches is transcutaneous stimulation using TENs technology to the supraorbital nerves with Cefaly® (STX-Med, Herstal, Belgium). Treatment consists of daily 20-min stimulation sessions. In a small pilot study of ten episodic migraine patients, daily treatment with Cefaly® for 3 months reduced monthly attack frequency by 1.3 [99]. A double-blind, randomized, sham-controlled trial of 67 patients treated for 3 months reported a statistically significant reduction in migraine days, monthly migraine attacks, monthly headache days, and monthly intake of acute anti-migraine medication in patients treated with the active Cefaly® device compared to the sham device. The 50 % responder rate was 38.1 % in the active group compared to 12.1 % in the sham group. No adverse events were reported [100]. A survey of 2,313 headache sufferers who had used the Cefaly® device for an average testing period of 58.2 days found that most patients were satisfied with the device and only 4.3 % of patients reported adverse events, none of them were serious [101]. Additional studies are needed assessing the safety and efficacy of Cefaly®.

## Conclusions

Recent scientific advances have led to the discovery of new headache specific drug targets and new therapies are being developed and investigated. Many of these new therapies show promise, and we are hopeful that the next several years will see these innovations become available to the headache patients who continue to suffer despite the currently available treatment options.

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SYMPOSIUM MIGRAINE AND ITS VARIETIES

# Gender and triptan efficacy: a pooled analysis of three double-blind, randomized, crossover, multicenter, Italian studies comparing frovatriptan vs. other triptans

**Flavia Franconi · Cinzia Finocchi · Gianni Allais · Stefano Omboni · Vincenzo Tullo · Ilaria Campesi · Giorgio Reggiardo · Chiara Benedetto · Gennaro Bussone**



**Abstract** Migraine is three times as common in females as in males, and attacks may be more severe and difficult to treat in women. However, no study specifically addressed possible gender differences in response to antimigraine therapy. The objective of this study was to review the efficacy of frovatriptan vs. other triptans, in the acute treatment of migraine in subgroups of subjects classified according to gender (men vs. women) through a pooled analysis of three individual randomized Italian studies. 414 patients suffering from migraine with or without aura were randomized to frovatriptan 2.5 mg or rizatriptan 10 mg (study 1), frovatriptan 2.5 mg or zolmitriptan 2.5 mg (study 2), frovatriptan 2.5 mg or almotriptan 12.5 mg (study 3). All studies had a multicenter, randomized, double-blind, crossover design. After treating 1–3 episodes of migraine in no more than 3 months with the first treatment, patients switched to the other treatment for the next 3 months. In this analysis, traditional migraine endpoints were compared between the 66 men and 280 women of the intent-to-treat population. At baseline, long-term and debilitating migraine attacks were more frequently reported by women than men. During the observation period, the proportion of pain-free attacks at 2 h did not significantly differ between frovatriptan and the comparators in either men (32 vs. 38 %, $p$ = NS) or women (30 vs. 33 %, $p$ = NS). Pain relief was also similar between treatments for both genders (men: 56 % frovatriptan vs. 57 % comparators; women: 55 vs. 57 %; $p$ = NS for both). The rate of relapse was significantly lower with frovatriptan than with the comparators in men (24 h: 10 vs. 30 %; 48 h: 21 vs. 39 %; $p < 0.05$) as well as in women (24 h: 14 vs. 23 %; 48 h: 28 vs. 40 %; $p < 0.05$). The rate of adverse drug reactions was significantly larger with comparators, irrespectively of gender. Although migraine presents in a more severe form in women, frovatriptan seems to retain its good efficacy and favorable sustained antimigraine effect regardless of the gender.

**Keywords** Migraine · Gender · Frovatriptan · Rizatriptan · Zolmitriptan · Almotriptan

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## Introduction

Migraine is a chronic neurovascular disorder occurring in both genders, although large surveys show higher

prevalence of this condition in women, with a female to male ratio in the order of 3:1 [1–4].

Although migraine acknowledges a complex pathophysiology, involving genetic and psychological factors [5], the disproportionate number of fertile women with migraine suggests that hormonal factors may indeed play an important role in the pathogenesis of migraine [6]. As a matter of fact, from adolescence migraine attacks are generally more common in women than in men, peaking during their 30 and 40 s, followed by a decline, particularly after menopause [7].This difference in migraine prevalence over a life time is mediated by the physiological fluctuation of estrogen level and consequently by its influence on cerebral vasculature, in women [8]. In addition, attacks are usually reported to be more severe and difficult to treat in women than in men [8].

The triptans, selective serotonin 5-$HT_{1B/1D}$ receptor agonists, are very effective acute migraine drugs; they are currently recommended as a first-line treatment for moderate to severe migraine, or for mild to moderate migraine that has not responded to adequate doses of simple analgesics [9–11]. Frovatriptan is an antimigraine agent of the triptan class, developed to provide a triptan with a clinical potential for a long duration of action and a low likelihood of side effects and drug interactions [12, 13]. Three direct comparative, prospective, double-blind, randomized, crossover studies have recently compared the efficacy and safety of frovatriptan with that of rizatriptan [14], zolmitriptan [15], and almotriptan [16]. The study showed a similar efficacy of the four triptans in the immediate treatment of migraine, but lower recurrence rates, and thus a better sustained relief, with frovatriptan. Retrospective analyses of the same studies proved the good efficacy of frovatriptan also in subgroups of female migraine patients, such as those with menstrually related migraine [17] or with oral-contraceptive menstrual migraine [18].

Although there is no reason to doubt that current drug options for migraine treatment should display a similar efficacy in male and female migraineurs, so far no study specifically addressed possible gender differences in response to triptan therapy. To this purpose, in the present paper, we report on results of a pooled analysis performed in subgroups of migraineurs classified according to gender (males vs. females) and enrolled in previous direct comparative studies of frovatriptan vs. other triptans.

## Methods

### Study population and design

This pooled analysis is based on the data from three studies sharing a similar design and whose details are extensively reported in the original publications [14–16]. Overall, the studies included subjects of both genders, aged 18–65 years, with a current history of migraine with or without aura, according to International Headache Society (IHS) criteria, and with at least one, but no more than six migraine attacks per month for 6 months prior to entering the study. In this retrospective analysis, patients were classified in two subgroups according to gender (men and women).

The studies had a multicenter, randomized, double-blind, crossover design. Each patient received frovatriptan 2.5 mg or rizatriptan 10 mg [14], frovatriptan 2.5 mg or zolmitriptan 2.5 mg [15], frovatriptan 2.5 mg or almotriptan 12.5 mg [16] in a balanced computer-generated randomized sequence (1:1), where frovatriptan had to be followed by the comparator or vice versa. After treating 1–3 episodes of migraine in no more than 3 months with the first treatment, the patient had to switch to the other treatment. Subjects were encouraged to treat 1–3 attacks for a maximum period of 3 months with each study drug and to visit the center three times during the study. Subjects having no migraine episodes during one of the two observation periods were excluded from the study.

### Data analysis

In this analysis, traditional migraine endpoints were compared between men and women of the intent-to-treat population, defined as all patients treating at least one attack in each treatment period. The study endpoints were qualified according to International Headache Society Guidelines [19] as: (a) the number of pain free episodes at 2 h (absence of migraine episodes at 2 h after the intake of one dose of study drug and without any rescue medication); (b) the number of pain relief episodes at 2 h (defined as a decrease in migraine intensity from severe or moderate to mild or none, after the intake of one study drug dose); (c) relapse after 24 h (namely an episode which is pain free at 2 h and headache of any severity returns within 24 h, or requires the use of rescue medication or a second dose of study drug); (d) relapse after 48 h (namely an episode which is pain free at 2 h and headache of any severity returns within 48 h, or requires the use of rescue medication or a second dose of study drug). Safety analysis was applied to the intent-to-treat population, by calculating the incidence of adverse events during the study. Continuous variables were summarized by computing average values and standard deviation (SD), while categorical variables by computing the absolute value and the frequency (as percentage). Study endpoints were separately assessed according to gender (men vs. women) and compared between attacks treated with frovatriptan and with the comparators by analysis of variance (ANOVA), in case of continuous variables, and by Chi-squared test, in case of

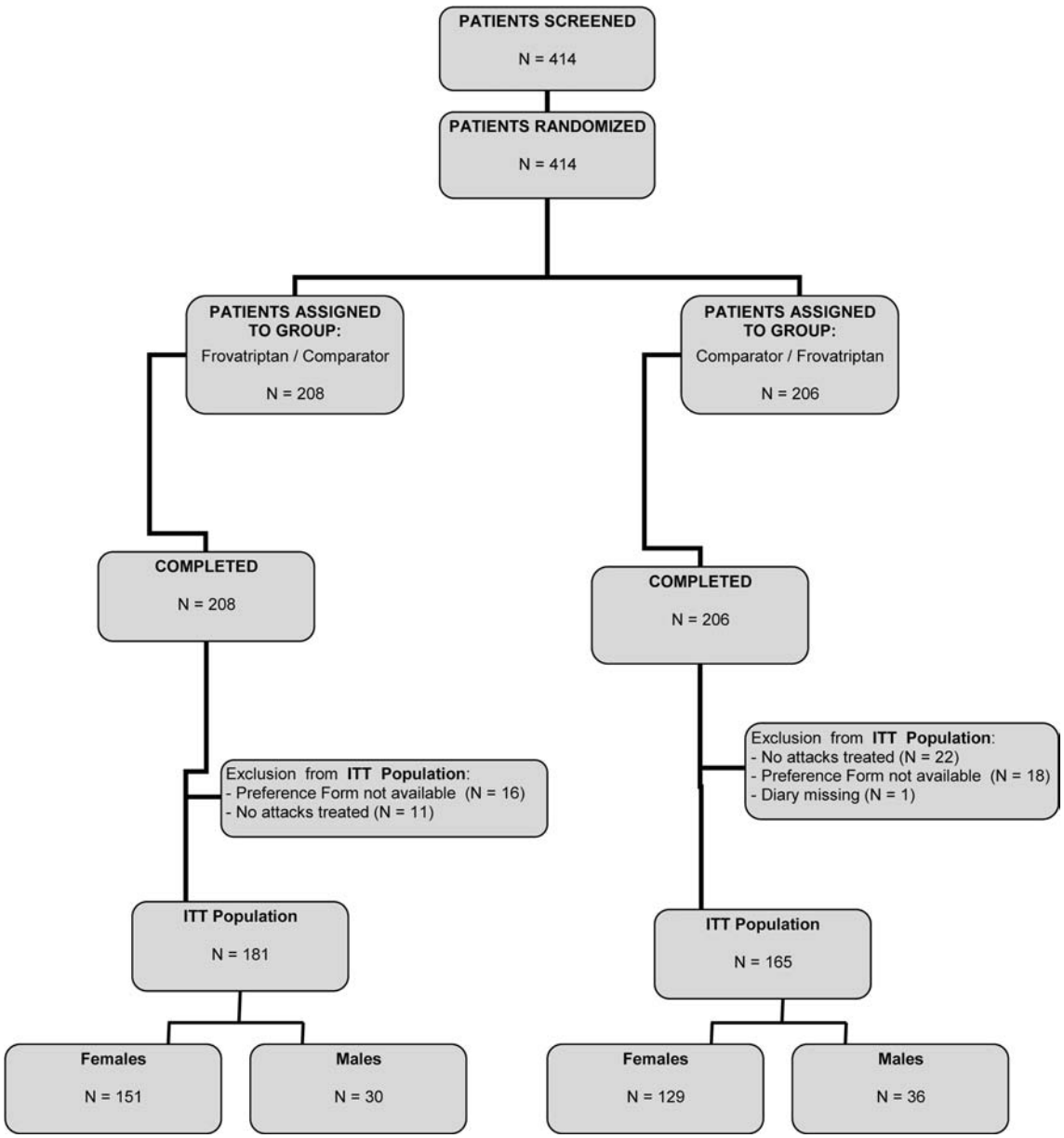


**Fig. 1** Flow diagram of the patients throughout the study

discrete variables. A subgroup analysis was carried out in postmenopausal and fertile women. All tests were two-sided and the level of statistical significance was kept at 0.05 throughout the whole study.

## Results

### Demographic and migraine feature of the study population

The intent-to-treat population consisted of 346 subjects, of which 66 (19 %) were men and 280 (81 %) women. A flow diagram of participants throughout the study is summarized in Fig. 1. Table 1 summarizes the main demographic and clinical characteristics of the intent-to-treat population at baseline, according to gender. The two study subgroups differed in several features at baseline, and particularly in those related to migraine severity. Women were younger, thinner and shorter than men. They reported their first attack earlier than men and the episodes were longer lasting and more debilitating (higher MIDAS score). Baseline intensity showed a statistically significant difference in the distribution of mild-moderate attacks between men and women, with attacks in women being more intense than in men.

**Table 1** Demographic and clinical data of women and men and of postmenopausal and fertile women of the intent-to-treat population at the time of randomization

| | Men ($n = 66$) | Women ($n = 280$) | $p$ value | Postmenopausal women ($n = 56$) | Fertile women ($n = 224$) | $p$ value |
|---|---|---|---|---|---|---|
| Age (years, mean ± SD) | 40 ± 10 | 38 ± 6 | <0.05 | 52 ± 5 | 34 ± 8 | <0.0001 |
| Height (cm, mean ± SD) | 178 ± 7 | 163 ± 7 | <0.0001 | 161 ± 8 | 164 ± 5 | <0.001 |
| Weight (kg, mean ± SD) | 78 ± 13 | 59 ± 10 | <0.0001 | 60 ± 10 | 59 ± 10 | NS |
| BMI (kg/m$^2$, mean ± SD) | 25 ± 3 | 22 ± 4 | <0.0001 | 23 ± 4 | 22 ± 4 | <0.05 |
| Age at onset of migraine (years, mean ± SD) | 20 ± 10 | 18 ± 7 | <0.05 | 22 ± 11 | 17 ± 6 | <0.01 |
| Migraine attack duration >2 days ($n$, %) | 4 (6) | 68 (24) | <0.01 | 16 (29) | 52 (23) | NS |
| Migraine attacks with aura ($n$, %) | 32 (5) | 102 (8) | NS | 39 (11) | 67 (5) | <0.0001 |
| MIDAS score (mean ± SD) | 19 ± 15 | 23 ± 18 | <0.05 | 25 ± 15 | 22 ± 19 | NS |
| Baseline migraine severity ($n$, %)[a] | | | | | | |
| Mild | 106 (28) | 303 (19) | <0.001 | 68 (17) | 255 (21) | NS |
| Moderate | 192 (51) | 954 (60) | | 249 (62) | 698 (58) | |
| Severe | 82 (22) | 346 (22) | | 85 (21) | 248 (21) | |
| No use of triptans in the previous 3 months ($n$, %) | 18 (27) | 118 (42) | NS | 22 (39) | 96 (43) | NS |

Data are shown as mean (±SD), or absolute ($n$) and relative frequency (%)

*BMI* body mass index, *MIDAS* migraine disability assessment

[a] Numbers refer to number and frequency of attacks as respect to overall number of attacks

Of the 280 women, 56 were postmenopause and 224 in fertile age. As expected, postmenopausal women were older than fertile women (Table 1). They also reported a higher rate of migraine attacks with aura and an older age at onset of the first migraine attack.

### Treatment efficacy of migraine attacks

During the observation period, a total of 1,978 attacks were recorded in the 346 migraineurs of the intent-to-treat population. Of these attacks, 331 (17 %) occurred in men and 1,647 (83 %) in women, 987 were treated with frovatriptan and 991 with comparators.

As shown in Fig. 2, at 2-h rate of pain-free episodes was not significantly different between frovatriptan and comparators, either in men (32 vs. 38 %; $p$ = NS) or women (30 vs. 33 %; $p$ = NS). Pain relief episodes at 2 h were also similarly distributed between the two treatments and both genders (men: 56 % frovatriptan vs. 57 % comparators; women: 55 vs. 57 %; $p$ = NS for both). Conversely, relapse at 24 h was significantly ($p < 0.05$) less likely to be reported in frovatriptan than in comparator-treated patients, with no between-gender difference (men: 10 vs. 30 %; women: 14 vs. 23 %). This was the case also for rate of relapse after 48 h (men: 21 vs. 39 % and women: 28 vs. 40 %, $p < 0.05$ between treatments).

No statistically significant differences were ever observed between men and women in response to study treatments, for all the considered endpoints.

The efficacy of frovatriptan and comparators on pain free and pain relief at 2 h was identical in the subgroup of postmenopausal and fertile women (Table 2). However, the risk of relapse at 24 and 48 h was higher in women treated with the comparators, with a statistically significant between-treatment difference for women of fertile age.

### Safety

A total of 133 adverse events were recorded in 2,033 treated attacks in the safety population (1,088 under frovatriptan and 945 under the other triptans), of which 55 occurred in men and 78 in women. The proportion of subjects with an adverse event was significantly ($p < 0.05$) lower with frovatriptan than with the comparators in both men (2 vs. 7 %) or in women (6 vs. 9 %).

## Discussion

In the present pooled analysis of three double-blind, randomized, crossover studies, acute treatment of male and female migraineurs with frovatriptan and with other triptans (rizatriptan, zolmitriptan and almotriptan) resulted in similar proportions of pain-free and pain relief episodes at 2 h, with no between-gender differences. However, frovatriptan showed a more sustained effect on relief of migraine symptoms than comparators, an effect that did not differ between men and women and such a finding is clinically

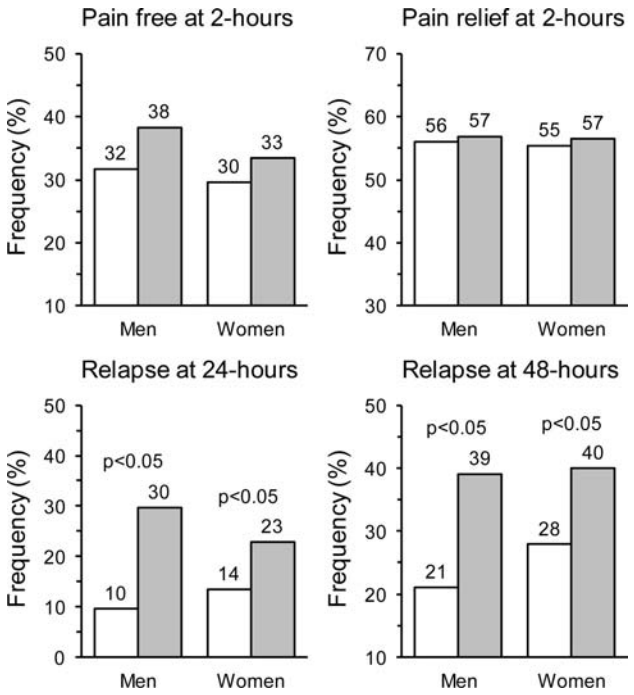


**Fig. 2** Proportion (%) of pain free at 2 h, pain relief at 2 h and relapse at 24 and 48 h in the 66 men and 280 women with migraine of the intent-to-treat population. Data are separately shown for frovatriptan- (*white bars*) and comparator-treated patients (*gray bars*). The *p* value refers to the statistical significance of the between-treatment difference

relevant because it has been shown that female patients have a twofold greater risk than male patients of experiencing headache return following pain-free response [20]. The particular pharmacokinetics of frovatriptan, characterizing its slower onset of action and longer duration as compared to other triptans, may explain its greater efficacy in preventing headache recurrence [12].

From adolescence women experience more frequent, long-lasting and more painful headaches as compared to men, and are potentially less responsive to specific migraine treatment than men [4, 7]. For instance, in a study of risk factors for headache recurrence after oral and subcutaneous sumatriptan, recurrence following oral sumatriptan was more frequent in female patients [21]. In our retrospective analysis, we showed for the first time that no difference in response to triptan treatment exists between the two genders. Notably, such a lack of difference occurred even despite the fact that women presented at enrolment with more severe migraine symptoms than men.

Our results obtained in women also confirm other retrospective analyses performed on the same pooled study sample. In 187 of the 346 women who treated at least one episode of menstrually related migraine, rate of recurrence was significantly lower with frovatriptan than with comparators, either after 24 or 48 h [17]. Frovatriptan showed a more sustained relieving effect on migraine, with lower headache relapses over 24 h and even more so over 48 h, also in a subgroup of 35 women with oral-contraceptive-induced menstrual migraine [18].

Our study also provides some additional matters for discussion. We replicated the evidence from previous large observational studies that the prevalence of migraine is much higher in women than in men, and that in the female gender attacks tend to present in a more severe and debilitating fashion than in men [1–4, 7]. The effect of frovatriptan on relapses was more consistent when the subgroup of fertile women was considered, suggesting that this more numerous group of migraine patients may particularly benefit from frovatriptan treatment. Notably, the tolerability profile of frovatriptan was better than that of the comparators, irrespective of the gender, adding a further positive feature to the good efficacy pattern of the tested drug.

Despite the interesting results, we must recognize the limitation of the post hoc nature of our analysis: we performed a retrospective analysis on a subgroup of patients which were not originally selected for a gender-related study. However, to our knowledge, our report stands as the first large comparative systematic analysis of head-to-head trials of frovatriptan vs. other triptans in male and female migraineurs. In addition, we did not evaluate plasma levels of the different triptans, which act as substrates for different enzymes (see Table 3): some of these enzymes (e.g. CYP3A4 and CYP2D6) are differently expressed in men

**Table 2** Study endpoints in men and subgroups of postmenopausal and fertile women of the intent-to-treat population treated with frovatriptan or the comparators

| | Men ($n = 66$) | | | Postmenopausal women ($n = 56$) | | | Fertile women ($n = 224$) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Frovatriptan | Comparators | *p* value | Frovatriptan | Comparators | *p* value | Frovatriptan | Comparators | *p* value |
| Pain free at 2 h (%) | 52/164 (32) | 64/167 (38) | NS | 56/173 (32) | 64/180 (36) | NS | 188/650 (29) | 211/644 (33) | NS |
| Pain relief at 2 h (%) | 62/123 (56) | 70/123 (57) | NS | 76/137 (56) | 82/148 (55) | NS | 294/531 (55) | 300/528 (57) | NS |
| Relapse at 24 h (%) | 5/52 (10) | 19/64 (30) | <0.05 | 9/56 (16) | 18/64 (28) | NS | 24/188 (13) | 45/211 (21) | <0.05 |
| Relapse at 48 h (%) | 11/52 (21) | 25/64 (39) | <0.05 | 20/56 (36) | 24/64 (38) | NS | 48/188 (26) | 86/211 (41) | <0.01 |

Data are shown as absolute values (number of attacks with the event and total number of attacks evaluated) and relative frequencies (%)

**Table 3** Enzymes involved in triptan metabolism, reported in order of importance

| Triptan | Enzyme involved in the metabolism |
|---|---|
| Almotriptan [23, 24] | MAO-A, CYP3A4, CYP2D6 |
| Frovatriptan [25, 26] | CYP1A2 |
| Rizatriptan [27, 28] | MAO-A |
| Zolmitriptan [29, 30] | CYP1A2, MAO-A |

*MAO* monoamine oxidase, *CYP3A4* cytochrome P3A4, *CYP2D6* cytochrome P2D6, *CYP1A2* cytochrome P1A2

and women [22] suggesting that plasma levels of the various types of triptans may differ in the two sexes [23–30]. We think that all these limitations of our study are at least partially contrasted by the large number of subjects and migraine attacks included in the analysis.

In conclusion, the results of our combined analysis of individual data of three double-blind, randomized, cross-over trials provide strong evidence that, in both men and women, frovatriptan seems to offer the advantage of a lower risk of recurrence as compared to other triptans. Our results might be helpful to stimulate the design and implementation of larger direct comparative randomized clinical trials evaluating triptan efficacy separately in men and women suffering from migraine.

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**Conflict of interest** All authors have occasionally served as scientific consultants for manufacturers of frovatriptan, rizatriptan, zolmitriptan or almotriptan. Deborha Pezzola and Dario Zava are employees of the manufacturer of frovatriptan.



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SYMPOSIUM MIGRAINE AND ITS VARIETIES

# Efficacy of early vs. late use of frovatriptan combined with dexketoprofen vs. frovatriptan alone in the acute treatment of migraine attacks with or without aura

**Gianni Allais · Vincenzo Tullo · Pietro Cortelli · Piero Barbanti · Fabio Valguarnera · Giuliano Sette · Florindo D'Onofrio · Marcella Curone · Dario Zava · Deborha Pezzola · Giorgio Reggiardo · Stefano Omboni · Fabio Frediani · Gennaro Bussone · Chiara Benedetto**



**Abstract** Early triptan use after headache onset may help improve the efficacy of acute migraine treatment. This may be particularly the case when triptan therapy is combined with a nonsteroidal anti-inflammatory drug (NSAID). The objective of this is to assess whether the combination of frovatriptan 2.5 mg + dexketoprofen 25 or 37.5 mg (FroDex25 and FroDex37.5) is superior to frovatriptan 2.5 mg alone (Frova) in the acute treatment of migraine attacks in patients who took the drug within 30 min from the onset of pain (early use) or after (late use). A total of 314 subjects with a history of migraine with or without aura were randomized into a double-blind, multicenter, parallel group, pilot study to Frova, FroDex25 or FroDex37.5 and were required to treat at least one migraine attack. In the present post hoc analysis, traditional migraine endpoints were compared across study drugs for subgroups of the 279 patients of the full analysis set according to early ($n = 172$) or late ($n = 107$) drug use. The proportion of patients pain free at 2 h in the early drug use subgroup was 33 % with Frova, 50 % with FroDex25 and 51 % with FroDex37.5 mg ($p = $ NS combinations vs. monotherapy), while in the late drug use subgroup was 22, 51 and 50 % ($p < 0.05$ FroDex25 and FroDex37.5 vs. Frova), respectively. Pain-free episodes at 4 h were 54 % for early and 34 % for late use of Frova, 71 and 57 % with FroDex25 and 74 and 68 % with FroDex37.5 ($p < 0.05$ for early and $p < 0.01$ for late use vs. Frova). The proportion of sustained pain free at 24 h was 26 % under Frova, 43 % under FroDex25 mg and 40 % under FroDex37.5 mg ($p = $ NS FroDex25 or 37.5 vs. Frova) in the early drug intake subgroup, while it was 19 % under Frova, 43 % under FroDex25 mg and 45 % under FroDex37.5 mg ($p < 0.05$ FroDex25 and FroDex37.5 vs. Frova) in the late drug intake subgroup. Risk of relapse at 48 h was similar ($p = $ NS) among study drug groups (Frova: 25 %,

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FroDex25: 21 %, and FroDex37.5: 37 %) for the early as well as for the late drug use subgroup (14, 42 and 32 %). FroDex was found to be more effective than Frova taken either early or late. The intrinsic pharmacokinetic properties of the two single drug components made FroDex combination particularly effective within the 2–48-h window from the onset of the acute migraine attack. The efficacy does not seem to be influenced by the time of drug use relative to the onset of headache.

**Keywords** Migraine · Frovatriptan · Dexketoprofen · Early intake · Late intake

## Introduction

Early triptan use after the onset of headache may help to improve the efficacy of acute migraine treatment, particularly in those patients with rapid pain onset and worsening, high frequency of pain recurrence and severe associated symptoms [1–3]. Despite their utility as migraine abortive medications, however, the triptans do not successfully treat all attacks of migraine or relieve all migraine associated symptoms, even when they are administered in the early phase of the acute attack [4].

A possible solution to increase the chance of successful treatment is to combine the triptan with a nonsteroidal anti-inflammatory drug (NSAID), which may help to effectively target the distinct vascular and inflammatory processes underlying migraine [4, 5]. Studies combining sumatriptan with naproxen [6–8], rizatriptan with rofecoxib [9] or almotriptan with aceclofenac [10] have all demonstrated an increase in the proportion of migraine patients with desirable treatment outcomes.

Recently, a randomized, double-blind, parallel group study documented an improved initial efficacy, but similar sustained pain free, when treating the acute attack with a combination of frovatriptan and dexketoprofen rather than with frovatriptan alone [11]. These results were most likely to be linked to the intrinsic pharmacokinetic properties of the two drugs: dexketoprofen is absorbed rapidly and contributes to the early efficacy of the combination whereas frovatriptan persists longer and so provides sustained efficacy with less recurrence [11–14].

In the present retrospective analysis of the aforementioned randomized, prospective study we made an initial determination of whether differences in the efficacy of the combination of frovatriptan with dexketoprofen over frovatriptan alone may exist with early or late use of the drugs (i.e. within or after 30 min from the onset of headache pain).

## Methods

### Study population and design

Full details of the study methodology are available in the original publication [11]. Briefly, the study enrolled male and non-pregnant and non-breast feeding female subjects, aged 18–65 years, with a current history of migraine with or without aura [15], and with at least one, but no more than six, migraine attacks per month for 6 months prior to entering the study. In the present retrospective analysis we separately selected subjects who treated headache pain within 30 min of its earliest onset, or when headache pain was established (late use, >30 min). This was a multicenter, randomized, double-blind, active-controlled, three parallel group, study, conducted in 25 different Italian Headache Centers. Following a screening visit eligible patients were randomized to frovatriptan 2.5 mg (Frova), or to extemporaneous combinations of frovatriptan 2.5 mg + dexketoprofen 25 mg (FroDex25) or frovatriptan 2.5 mg + dexketoprofen 37.5 mg (FroDex37.5). To ensure blinding the study drugs were overencapsulated. At the end of the randomization visit a headache diary was dispensed to the patient in order to document the characteristics of the headache pain and associated symptoms. The intensity of headache and the associated symptoms was graded according to a four-point rating scale, as recommended by International Headache Society [15]. Each subject was also given the study medication and was instructed to self-administer the drug at home and complete the diary, for the first migraine attack occurring during the study period (i.e. within 1 month from randomization).

### Data analysis

As in the original publication, this post hoc analysis was based on the full analysis set, including all subjects randomized and treated, for whom at least one post-dose headache attack was recorded. As aforementioned, the analysis was separately performed in the subgroup of patients reporting early or late study drug use.

The following efficacy endpoints were evaluated for each of the subgroups: (a) proportion of pain-free subjects at 2 h before any rescue medication (original primary study endpoint, estimated according to IHS Guidelines) [15]; (b) proportion of pain-free subjects at 4 h before any rescue medication [15]; (c) sustained pain free within 24 h (episode pain free at 2 h with no use of rescue medication or recurrence within 24 h); (d) relapse within 48 h (episode pain free at 2 h and headache of any severity returning within 48 h in a subject who did not take any rescue medication) [15]; (e) proportion of subjects taking rescue medication; and (f) subjects' preference for treatment.

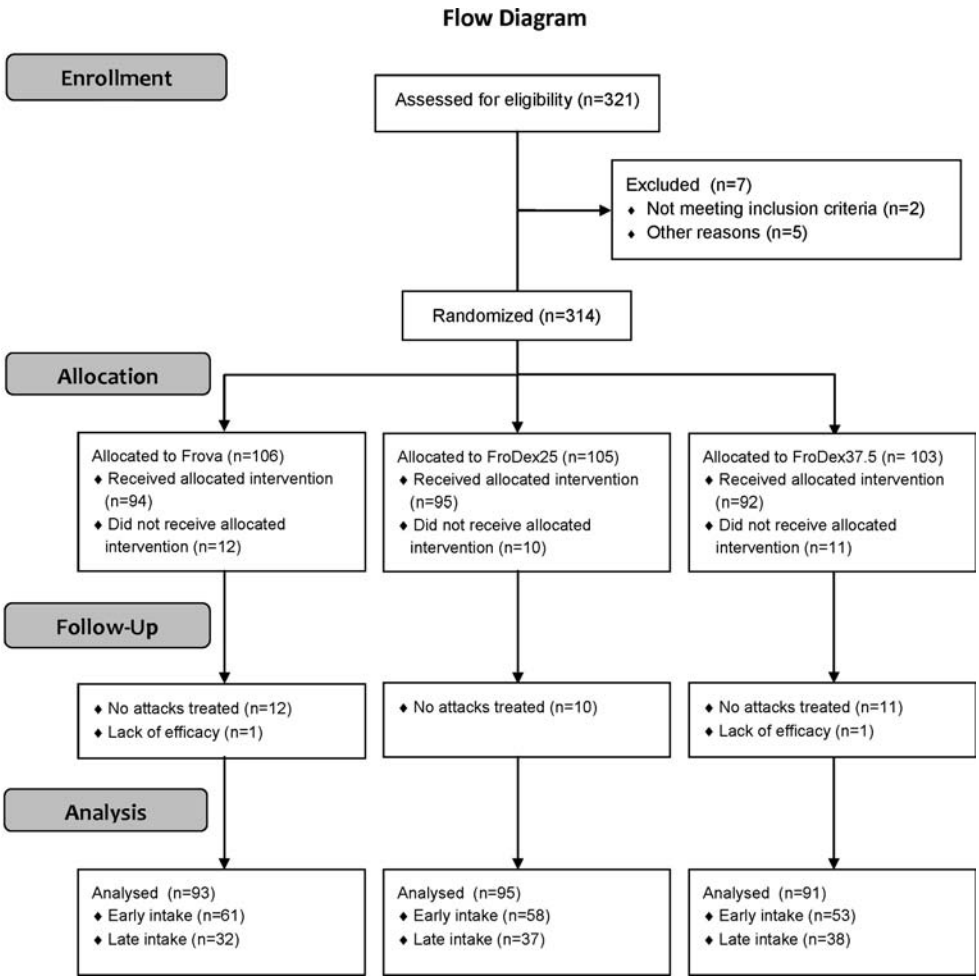


**Fig. 1** Flow diagram of the patients throughout the study

Continuous variables were summarized by computing average values and standard deviations (SD), while categorical variables by computing the absolute value and the frequency (as percentage). The primary study endpoint was assessed by the Fisher–Freeman–Halton Exact test statistics using either a $3 \times 2$ contingency table for testing association or a $2 \times 2$ contingency table for comparisons between treatments. The Fisher Exact test based on $2 \times 2$ contingency tables was applied also to secondary variables to check difference between pairs of treatments. A *t* test of Student was used to evaluate differences between continuous variables. All tests were two sided and the level of statistical significance was set at 0.05 for all analyses.

## Results

The flow diagram of the patients through the study is shown in Fig. 1. Of the 279 subjects of the full analysis set, 172 reported an early drug intake (61 Frova, 58 FroDex25 and 53 FroDex37.5) and 107 a late drug intake (32 Frova, 37 FroDex25 and 38 FroDex37.5). Table 1 shows the main demographic and clinical characteristics of the patients at randomization, by subgroups of patients according to time of first drug use and allocated treatment. No statistically significant difference was observed in any demographic or clinical characteristic, across the three study treatments for both the early and the late drug use subgroups. However, subjects in the early drug use subgroup had a significantly ($p < 0.001$) higher proportion of migraine attacks of severe intensity (39.0 vs. 16.8 % late drug intake), while those in the late drug intake group reported a higher rate of moderate intensity attacks (81.3 vs. 52.3 % early drug intake). Among the associated symptoms, phonophobia more frequently ($p < 0.05$) occurred in subjects in the early drug use group (66.9 vs. 54.2 %). Subjects with early drug use also reported a significantly ($p < 0.01$) lesser use of triptans prior to enrolment into the study (19.8 vs. 34.6 % late drug use).

Overall comparison among treatments for pain free at 2 h showed a statistically significant difference in favor of the combination therapy vs. the monotherapy for the late ($p < 0.05$, Fisher–Freeman–Halton Exact test on $3 \times 2$ contingency table), but not for the early drug use subgroup

**Table 1** Demographic and clinical characteristics of the 279 patients of the full analysis set at the time of randomization

| | Early drug use (≤30 min) | | | | Late drug use (>30 min) | | | |
|---|---|---|---|---|---|---|---|---|
| | Frova ($n = 61$) | FroDex25 ($n = 58$) | FroDex37.5 ($n = 53$) | All ($n = 172$) | Frova ($n = 32$) | FroDex25 ($n = 37$) | FroDex37.5 ($n = 38$) | All ($n = 107$) |
| Age (years, mean ± SD) | 38.5 ± 9.4 | 37.7 ± 10.7 | 40.0 ± 9.0 | 38.7 ± 9.7 | 39.6 ± 8.0 | 40.5 ± 9.5 | 41.6 ± 10.9 | 40.6 ± 9.6 |
| Females (*n*, %) | 58 (95.1) | 52 (89.7) | 44 (83.0) | 154 (89.5) | 30 (93.8) | 32 (86.5) | 30 (78.9) | 92 (86.0) |
| Height (cm, mean ± SD) | 164.9 ± 5.8 | 166.5 ± 6.9 | 166.7 ± 6.9 | 166.0 ± 6.5 | 163.3 ± 5.6 | 164.8 ± 8.5 | 165.8 ± 9.0 | 164.7 ± 7.9 |
| Weight (kg, mean ± SD) | 61.3 ± 8.3 | 61.8 ± 6.9 | 63.0 ± 11.2 | 62.0 ± 9.6 | 60.6 ± 9.6 | 60.9 ± 11.1 | 64.2 ± 13.6 | 62.0 ± 11.6 |
| MIDAS score (mean ± SD) | 25.6 ± 18.0 | 26.3 ± 10.7 | 24.1 ± 19.1 | 25.4 ± 23.7 | 18.2 ± 14.0* | 24.6 ± 25.4 | 21.3 ± 12.5 | 21.5 ± 18.4 |
| Presence of aura (*n*, %) | 6 (9.8) | 1 (1.7) | 1 (1.9) | 8 (4.7) | 3 (9.4) | 1 (2.7) | 4 (10.5) | 8 (7.5) |
| Intensity of baseline attack (*n*, %) | | | | | | | | |
| Mild | 8 (13.1) | 5 (8.6) | 2 (3.8) | 15 (8.7) | – | 1 (2.7) | 1 (2.6) | 2 (1.9)*** |
| Moderate | 32 (52.5) | 30 (51.7) | 28 (52.8) | 90 (52.3) | 26 (81.3)* | 32 (86.5)** | 29 (76.3) | 87 (81.3)*** |
| Severe | 21 (34.4) | 23 (39.7) | 23 (43.4) | 67 (39.0) | 6 (18.8)* | 4 (10.8)** | 8 (21.1) | 18 (16.8)*** |
| Presence of nausea (*n*, %) | 31 (50.8) | 32 (55.2) | 25 (47.2) | 88 (51.2) | 14 (43.8) | 15 (40.5)** | 17 (44.7) | 46 (43.0) |
| Presence of photophobia (*n*, %) | 42 (68.9) | 41 (70.7) | 39 (73.6) | 122 (70.9) | 22 (68.8) | 20 (54.1) | 24 (63.2) | 66 (61.7) |
| Presence of phonophobia (*n*, %) | 42 (68.9) | 37 (63.8) | 36 (67.9) | 115 (66.9) | 16 (50.0) | 25 (67.6) | 17 (44.7)* | 58 (54.2)* |
| Preventive therapy (*n*, %) | | | | | | | | |
| Antidepressant | 4 (6.6) | 2 (3.4) | 6 (11.3) | 12 (7.0) | 5 (15.6) | 6 (16.2) | 4 (10.5) | 15 (14.0) |
| Antiepileptics | 5 (8.2) | 5 (8.6) | 5 (9.4) | 15 (8.7) | 2 (6.3) | 1 (2.7) | 5 (13.2) | 8 (7.5) |
| Beta-blocking agents | 3 (4.9) | 1 (1.7) | 4 (7.5) | 8 (4.7) | 1 (3.1) | 2 (5.4) | 5 (13.2) | 8 (7.5) |
| Triptan users (*n*, %) | 14 (23.0) | 10 (17.2) | 10 (18.9) | 34 (19.8) | 9 (28.1) | 14 (37.8)* | 14 (36.8) | 37 (34.6)** |
| NSAIDs users (*n*, %) | 17 (27.9) | 9 (15.5) | 8 (15.1) | 34 (19.8) | 8 (25.0) | 6 (16.2) | 7 (18.4) | 21 (19.6) |

Data are separately shown for the early (≤30 min) and late (>30 min) drug intake and by type of treatment, and are summarized as mean (±SD), or absolute (*n*) and relative frequency (%). *Asterisks* refer to the statistical significance of the difference between the early vs. late subgroup (* $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$)

*Frova* frovatritpan, *FroDex* frovatriptan + dexketoprofen, *MIDAS* migraine disability assessment, *NSAID* nonsteroidal anti-inflammatory drugs

(Fig. 2). When pairs of treatments were compared, a statistically significant difference was observed in the late drug dosing subgroup between FroDex 25 and Frova ($p < 0.05$) and between FroDex37.5 and Frova ($p < 0.05$) (Fig. 2). In both study subgroups the proportion of pain free at 4 h was significantly better with FroDex37.5 than with Frova ($p < 0.05$ for the early and $p < 0.01$ for the late use subgroups, respectively) (Fig. 2). The proportion of sustained pain free within the 24 h was significantly ($p < 0.05$) larger under FroDex25 and FroDex37.5 than under the monotherapy in the late drug intake subgroup (Fig. 2). Finally, the proportion of recurrence within 48 h was similar between Frova and the combination therapy, either for the early or for the late intake subgroup (Fig. 2).

For pain free at 2 and 4 h, sustained pain free at 24 h and recurrence at 48 h, no statistically significant difference was ever observed between early and late drug users, although a trend was observed for a better efficacy in case of early intake for monotherapy-treated patients.

Recourse to rescue medication was not significantly different among the three treatment groups for patients with early drug intake (Frova: 25 of 61 patients, 41.0 %, FroDex25: 14/58, 24.1 % and FroDex37.5: 15/53, 28.3 %), while among those with late drug intake it was significantly ($p < 0.05$) lower with FroDex37.5 (11/38, 29.0 % vs. 17/32, 53.1 % Frova and 17/37, 46.0 % FroDex25).

Finally, treatment was judged excellent or good by significantly more patients under the combination treatment with respect to the monotherapy in the early intake (FroDex25: 37 of 58 patients, 63.8 % and FroDex37.5: 31/53, 58.5 % vs. Frova: 29/61, 47.6, $p < 0.01$ and $p < 0.05$, respectively) and in the late intake group (FroDex37.5: 27 of 37 patients, 73.0 % vs. Frova: 12/32, 37.5 %, $p < 0.01$) (Fig. 3).

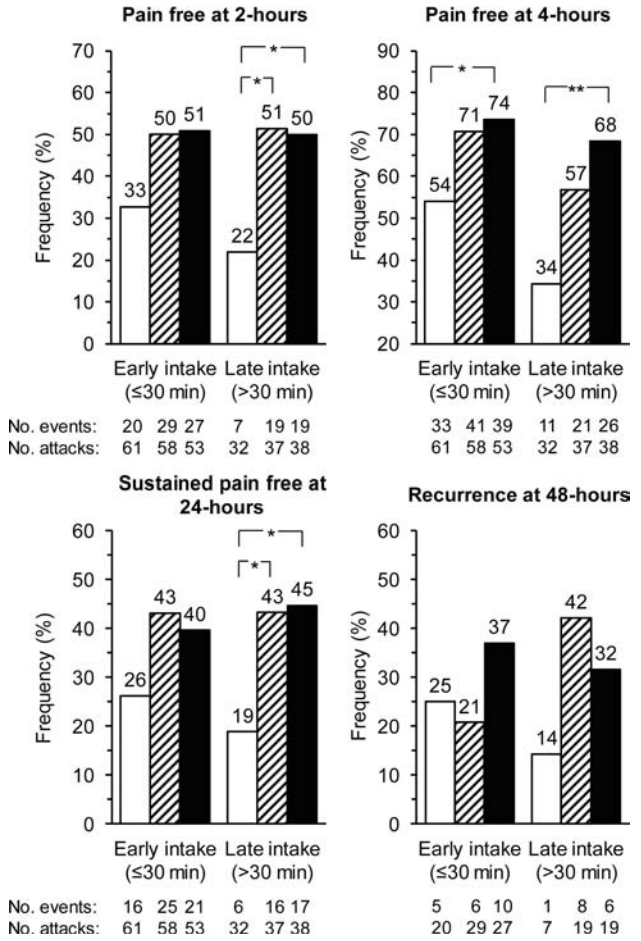


**Fig. 2** Proportion (%) of pain free at 2-h and at 4-h, sustained pain free at 24-h and recurrence at 48-h, after administration of frovatriptan 2.5 mg (*open bars*), frovatriptan 2.5 mg + dexketoprofen 25 mg (*striped bars*) and frovatriptan 2.5 mg + dexketoprofen 37.5 mg (*full bars*), separately shown for the patients reporting an early or a late drug intake. *Asterisks* indicate a statistically significant difference ($*p < 0.05$ and $**p < 0.01$) between the combination treatment and the monotherapy

## Discussion

In our post hoc analysis of a randomized, double-blind, active-controlled, dose comparison study [11], administration of the combination of frovatriptan 2.5 mg + dexketoprofen 25 or 37.5 mg showed a better efficacy than frovatriptan alone on the primary study end-point, pain free at 2 h, in the late drug, but not in the early drug users. Also the proportion of pain free episodes at 4 h was larger with the FroDex37.5 combination than with the monotherapy, in this case for both early and late drug users. In FroDex37.5-treated patients, the use of rescue medication was significantly lower than in monotherapy-recipients when the drug was used to treat the attack at a later stage. Sustained pain free within the 24 h was better in the combination treatment group, but yet only for patients in the late drug intake group. The proportion of relapse up to 48 h was similar in the three treatments arms and no differences were observed in early and late drug "dosers".

These results taken together suggest that, when dexketoprofen is used in combination with frovatriptan, early or late intake does not affect response to treatment, whereas this is not the case when frovatriptan is used alone. Such a finding supports current recommendations advising administration of a triptan monotherapy as early as possible at the time of headache onset in order to ensure the best effect [16–18]. It also adds an important piece of evidence on the effectiveness of a combination between a triptan and NSAID, also when taken later after the onset of pain. In the case of the combination used in the present study, it is likely that the short half-life of dexketoprofen and its rapid onset of action may contribute to the high pain free response, whereas the sustained effect of the combination may be largely driven by the long-half life of frovatriptan [13, 14]. We may hypothesize that using a combination of a drug with a fast action (dexketoprofen) and of a drug with a slow onset, but a prolonged effect (frovatriptan), may overcome the need to treat all attacks at the earliest opportunity. Indeed, there is controversy as to whether migraine patients should be advised to treat all attacks early with triptans [2, 19–23]. Rather, some authors suggest that patients should be free to take their medication as soon as they are sure they are developing a migraine headache, because this could reduce the risk of medication-overuse headaches and related adverse drug reactions [2, 20, 23]. In this regard a two-drug combination with synergistic activity, ensuring both quick and sustained pain free activity, should be regarded as a useful treatment option for migraineurs.

There are several additional interesting outcomes of our study which are worth discussion. The patients with late drug use had more frequently a history of migraine of moderate severity at baseline, whereas those with early drug intake reported more often severe attacks and associated phonophobia. Additionally, use of triptans was less often reported by early treatment patients. Both these findings may suggest that patients could be motivated to take the study drugs earlier because their attacks are usually more painful and because they are less used to a selective antimigraine drug, such as a triptan.

Patients taking the FroDex combination expressed a much better preference than those taking the monotherapy. Since the study had a double-blind design, such a finding further supports and strengthens the favorable efficacy results obtained with the combination.

The fact that significantly less patients in the late treatment group treated with FroDex37.5 needed rescue medication, as compared to patients taking frovatriptan alone, could be regarded as an additional beneficial treatment feature.

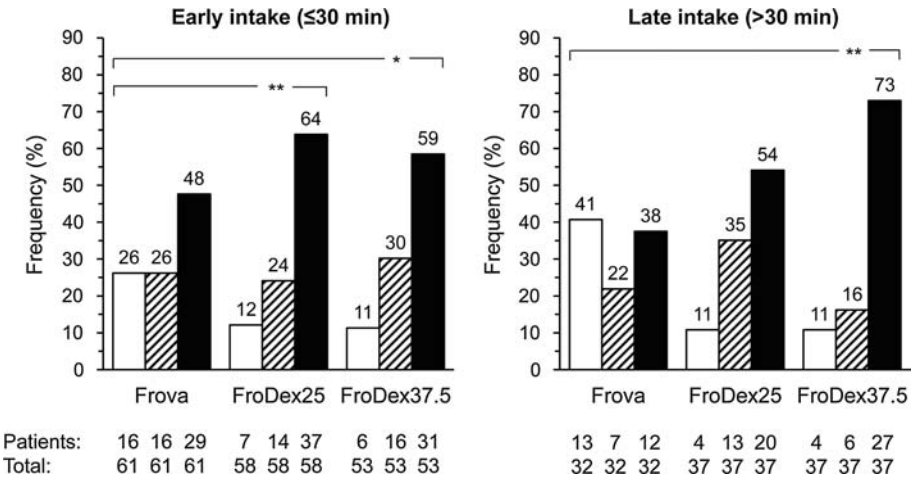


**Fig. 3** Proportion (%) of patients judging treatment poor or very poor (*open bars*), reasonable (*striped bars*) or good or excellent (*full bars*). Data are separately shown for the subgroup of patients reporting an early drug intake and for those with a late drug intake, and for the three different treatments (Frova: frovatriptan 2.5 mg; FroDex25: frovatriptan 2.5 mg + dexketoprofen 25 mg; FroDex37.5: frovatriptan 2.5 mg + dexketoprofen 37.5 mg). *Asterisks* indicate a statistically significant difference (*$p < 0.05$ and **$p < 0.01$) between the combination treatment and the monotherapy

The post hoc nature of the analysis represents the main limitation of our work. Although we acknowledge that further, prospective randomized trials are needed we also wish to point out that this is the first study demonstrating that the use of a combination therapy based on a triptan and an NSAIDs with particular pharmacological features, may not necessarily imply the need for an early use of the drug after the attack to ensure a prompt and sustained pain free response.

In conclusion, our results suggest that the frovatriptan plus dexketoprofen combination is effective in treating acute migraine attacks irrespective of the time treatment is started after the onset of pain.

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**Conflict of interest** All authors have occasionally served as scientific consultants for manufacturers of frovatriptan. Deborha Pezzola and Dario Zava are employees of the manufacturer of frovatriptan.



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SYMPOSIUM MIGRAINE AND ITS VARIETIES

# Efficacy of frovatriptan and other triptans in the treatment of acute migraine of normal weight and obese subjects: a review of randomized studies

**Maria Gabriella Saracco · Gianni Allais · Vincenzo Tullo · Dario Zava · Deborha Pezzola · Giorgio Reggiardo · Stefano Omboni · Chiara Benedetto · Gennaro Bussone · Marco Aguggia**



**Abstract** An association between obesity and migraine has been observed in recent studies and it is supported by plausible biological mechanisms. The objective of this study is to evaluate the efficacy of frovatriptan and other triptans in the acute treatment of migraine, in patients enrolled in three randomized, double-blind, crossover, Italian studies and classified according to body mass index (BMI) levels, as normal weight or non-obese (NO, BMI 18.5–24.9 kg/m$^2$) and overweight or obese subjects (O, BMI $\geq$ 25 kg/m$^2$). 414 migraineurs with or without aura were randomized to frovatriptan 2.5 mg or rizatriptan 10 mg (study 1), frovatriptan 2.5 mg or zolmitriptan 2.5 mg (study 2), frovatriptan 2.5 mg or almotriptan 12.5 mg (study 3). After treating up to three episodes of migraine in 3 months with the first treatment, patients switched to the alternate treatment for the next 3 months. The present analysis assessed triptan efficacy in 220 N and in 109 O subjects of the 346 individuals of the intention-to-treat population. The proportion of pain free at 2 h did not significantly differ between frovatriptan and the comparators in either NO (30 vs. 34 %) or O (24 vs. 27 %). However, the rate of pain free at 2 h was significantly ($p < 0.05$) larger in NO than in O, irrespective of the type of triptan. Pain relief at 2 h was also similar between drug treatments for either subgroup. Pain relapse occurred at 48 h in significantly ($p < 0.05$) fewer episodes treated with frovatriptan in both NO (26 vs. 36 %) and O (27 vs. 49 %). The rate of 48-h relapse was similar in NO and O with frovatriptan, while it was significantly ($p < 0.05$) higher in O with the comparators. Frovatriptan, in contrast to other triptans, retains a sustained antimigraine effect in NO and even more so in O subjects.

**Keywords** Migraine · Obesity · Frovatriptan · Rizatriptan · Zolmitriptan · Almotriptan

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## Introduction

Research increasingly suggests that an association exists between obesity and migraine [1–5]. Obesity also represents an exacerbating factor for migraine and some studies have found that overweight or obese migraineurs have more frequent episodes of headache and higher levels of disability compared to those who have normal weight [6–9]. Such an association is strongest in migraineurs with severe obesity, suggesting that greater adiposity contributes to greater exacerbation of headaches.

Obesity and migraine share common pathophysiological characteristics including a variety of physiological, psychological, and behavioral mechanisms [10]. Proinflammatory molecules such as calcitonin gene-related peptide

and cytokines that are increased in obese individuals have been implicated as pain mediators in neurovascular inflammation, which generates migraine pain [11, 12]. Various hypothalamic neurotransmitters and peptides involved in the regulation of eating behavior, adipocytokines regulating body weight through effects on metabolism and appetite and sympathetic dysregulation, all play a role in migraine pathophysiology [10].

Triptans are currently recommended for treating more severe forms of migraine, thus also potentially including episodes occurring in overweight or obese subjects [13–15]. However, presently there is no specific large-scale trial which assessed and compared the efficacy of different triptans for treating acute migraine attacks in overweight or obese individuals.

This retrospective analysis of three previously published randomized, double-blind, cross-over, Italian studies [16–18] sought to ascertain whether overweight or obesity can influence the pattern of response to triptan therapy in patients with migraine.

## Methods

### Study population and design

The three studies shared a similar design, whose details are extensively reported in the original publications [16–18]. Briefly, the studies included subjects of both genders, aged 18–65 years, with a current history of migraine with or without aura, according to International Headache Society (IHS) criteria [19], and with at least one, but no more than six migraine attacks per month for 6 months prior to entering the study. In the present retrospective analysis we separately selected lean and obese subjects. A body mass index (BMI) $\geq$ 25 kg/m$^2$ was used to classify overweight or obese subjects, while a BMI ranging from 18.5 to 24.9 kg/m$^2$ to select normal-weight subjects.

The studies had a multicenter, randomized, double-blind, cross-over design, and involved 33 different centers across Italy. Each patient received frovatriptan 2.5 mg or rizatriptan 10 mg (first study) [16], frovatriptan 2.5 mg or zolmitriptan 2.5 mg (second study) [17], and frovatriptan 2.5 mg or almotriptan 12.5 mg (third study) [18], in a randomized sequence. After treating 1–3 episodes of migraine in no more than 3 months with the first treatment, the patient had to switch to the other treatment and treated a maximum of three episodes of migraine in no more than 3 months with the second treatment. Subjects having no migraine episodes during one of the two observation periods were excluded from the study. Each subject was asked to visit the center three times during the study. Body weight and height were measured on subjects without shoes and wearing light clothing, using a calibrated, professional, electronic scale.

### Data analysis

As in the original publications, this pooled analysis was based on the intention-to-treat population, defined as all patients treating at least one attack in each treatment period.

The study endpoints were quantified according to IHS Guidelines as follows [19]: (a) pain free episodes at 2 h (absence of migraine 2 h after the intake of one dose of study drug); (b) pain relief at 2 h (decrease in migraine intensity from severe or moderate to mild or none 2 h after the intake of one dose of study drug); (c) relapse within 48 h (episode pain free at 2 h and headache of any severity returning within 48 h, or requiring the use of rescue medication or of a second dose of study drug).

Continuous variables were summarized by computing average values and standard deviations (SD), while categorical variables by computing the absolute value and the frequency (as percentage). Study endpoints were separately assessed according to BMI (normal weight vs. overweight or obesity) and compared between attacks treated with frovatriptan and with the comparators by analysis of variance (ANOVA), in case of continuous variables, and by Chi square test, in case of discrete variables. All tests were two sided and the level of statistical significance was kept at 0.05 throughout the study.

## Results

The intention-to-treat population of the three studies pooled together consisted of 346 subjects, of which 220 (67 %) were classified as normal weight and 109 (33 %) as overweight or obese (17 subjects with a BMI $<$ 18.5 kg/m$^2$ and classified as underweight, were not included in the analysis). A flow diagram of participants throughout the study is summarized in Fig. 1, while baseline demographic and clinical characteristics of the intention-to-treat population for the two BMI groups are reported in Table 1. Overweight or obese subjects were older and, as expected, with a higher weight than normal weight individuals. The average MIDAS score was greater in overweight or obese subjects, indicating a more disabling and severe form of migraine in this subgroup with respect to that of non-obese persons.

A total of 1,889 attacks were recorded, of which 1,295 (69 %) occurred in normal weight and 594 (31 %) in overweight or obese subjects: 948 were treated with frovatriptan and 941 with comparators.

As summarized in Fig. 2, at 2 h the rate of pain free and pain relief episodes did not significantly differ between

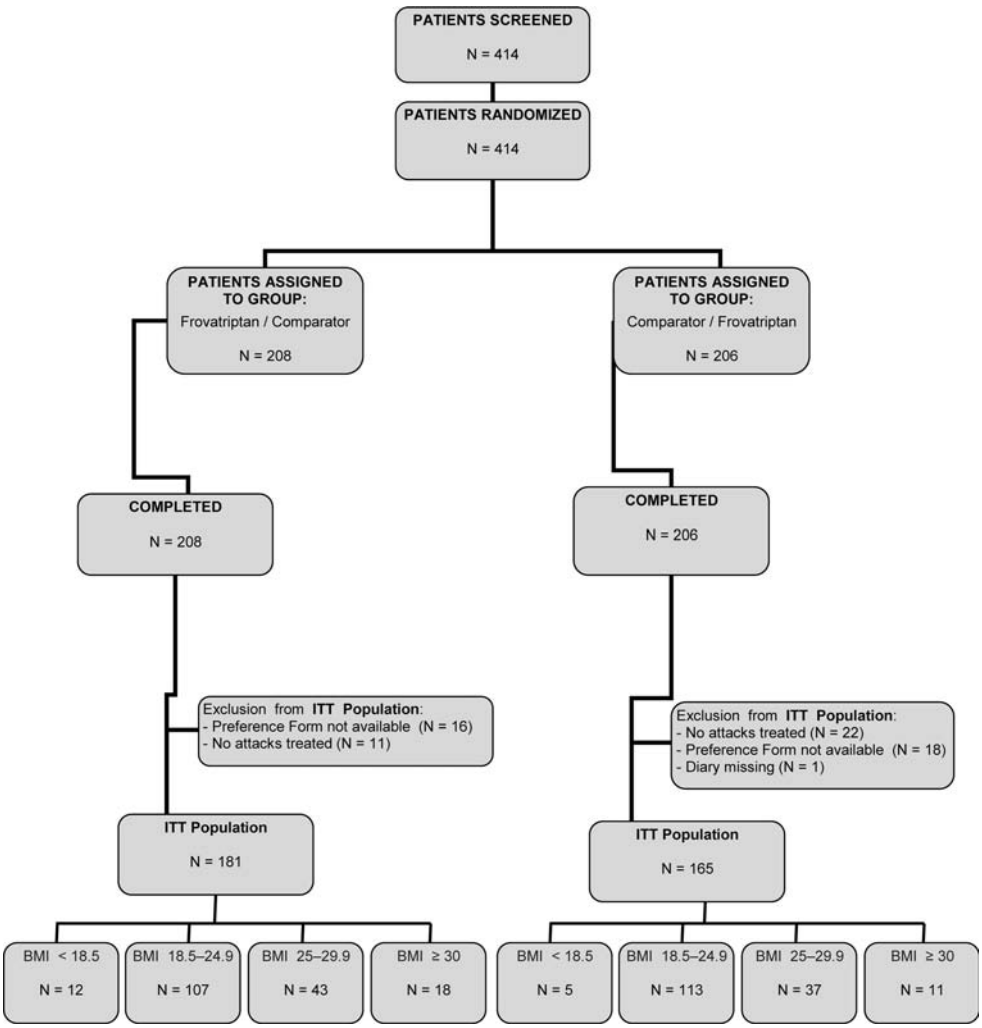


**Fig. 1** Flow diagram of the patients throughout the study

frovatriptan and the comparators in the two BMI subgroups. However, the proportion of subjects achieving pain free at 2 h was significantly ($p < 0.05$) larger in the normal weight than in the obese group either under frovatriptan (30 vs. 24 %) or the comparators (34 vs. 27 %).

Pain relapse occurred after 48 h in significantly fewer episodes treated with frovatriptan than comparators in both lean and obese subjects (Fig. 2). In addition frovatriptan showed a similar efficacy on 48 h relapse in both normal weight and overweight or obese subjects (26 and 27 %), while the comparators were significantly ($p < 0.05$) more effective in lean individuals (36 vs. 49 % overweight or obese).

## Discussion

In the present pooled retrospective analysis of three double-blind, randomized, direct comparative, cross-over studies we examined whether efficacy of frovatriptan and other triptans (rizatriptan, zolmitriptan and almotriptan) could differ according to patients' BMI level. Treatment of acute attacks with the study drugs resulted in no difference in the proportions of pain free and pain relief at 2 h between patients treated with frovatriptan or the comparators. Relapse at 48 h occurred less often in frovatriptan-treated patients, irrespective of the BMI level, suggesting that the long half life of frovatriptan may ensure a low rate of headache recurrence also in obese individuals. Interestingly, pain free at 2 h was more difficult to achieve and pain relapse at 48 h more easily occurred, in obese subjects, especially with the comparators. This finding may be related to the fact that obese subjects presented with a more disabling and severe form of migraine, as indicated by a higher baseline MIDAS score, and confirm that obese are more difficult to treat than non-obese migraineurs [6–9].

To the best of our knowledge this is the very first randomized study specifically investigating triptan efficacy in a large sample of obese and non-obese subjects with migraine, according to IHS criteria. In one recent non-

randomized prospective experimental study, the effects of weight on the preventive treatment of migraine headaches were studied in 203 migraineurs, treated for 8 weeks with nortriptyline and propranolol [20]. Response to treatment, in terms of pain frequency and duration, was better in patients with lower BMI and worse in severe obese patients [20]. A population-based longitudinal study, followed for 1 month 176 subjects with episodic or chronic migraine, or transformed migraine, seeking care in a headache clinic [21]. In this study BMI did not account for changes in disability, headache frequency, or in the number of days with severe headache per month [21].

Our study also confirms that obesity is not uncommon among patients with migraine. In fact, we reported a 33 % rate of overweight or obese migraineurs in our sample, a prevalence which is slightly higher than the 20–30 % observed in population studies, such as the National Health and Nutrition Survey [1, 3], the Women's Health Study [2] and the National Comorbidity Survey Replication [22]. However, it should be considered that, at variance from our study, in most of the aforementioned surveys information on migraine was self-reported, and misclassification due to underreporting could be possible. An additional strength of our study is that we classified patients according to BMI based on measured height and weight, while other studies relied on self-reported height and weight [7, 23, 24]. Finally, at variance from most studies, we defined and classified migraine cases according to diagnostic criteria of IHS [19].

Some limitations of our study merit discussion and consideration. First, given the retrospective nature of the study, generalizability of our results may be limited and we acknowledge that further prospective, randomized studies designed to comprehensively evaluate the effects of antimigraine drugs in obese subjects are needed. Notwithstanding this limitation, we must highlight that pooling together individual data from three identical randomized studies could have helped in achieving a sufficiently powered sample of subjects for the study purpose. Second, although it has been reported that preventative antimigraine drugs may cause weight gain, we were unable to evaluate such an effect because we did not track changes in body weight during the study [25]. However, it is unlikely that

**Table 1** Demographic and baseline clinical characteristics of the 220 normal-weight subjects and of the 109 overweight or obese subjects of the intention-to-treat population

| | Normal weight ($n = 220$) | Overweight or obese ($n = 109$) | $p$ value |
|---|---|---|---|
| Age (years, mean ± SD) | 38 ± 10 | 41 ± 9 | <0.05 |
| Females ($n$, %) | 189 (86) | 85 (78) | NS |
| Height (cm, mean ± SD) | 166 ± 8 | 166 ± 10 | NS |
| Weight (kg, mean ± SD) | 60 ± 9 | 83 ± 14 | <0.0001 |
| BMI (kg/m$^2$, mean ± SD) | 22 ± 2 | 30 ± 2 | <0.0001 |
| Age at onset of migraine (years, mean ± SD) | 18 ± 8 | 17 ± 9 | NS |
| Migraine attack duration >2 days ($n$, %) | 50 (23) | 29 (25) | NS |
| MIDAS score (mean ± SD) | 21 ± 15 | 26 ± 18 | <0.05 |
| No use of triptans in the previous 3 months ($n$, %) | 85 (39) | 47 (43) | NS |
| Migraine attacks with aura ($n$, %) | 22 (10) | 9 (8) | NS |

Data are shown as mean (±SD), or absolute ($n$) and relative frequency (%). $p$ value refers to the statistical significance of the between-group difference

*BMI* body mass index, *MIDAS* migraine disability assessment

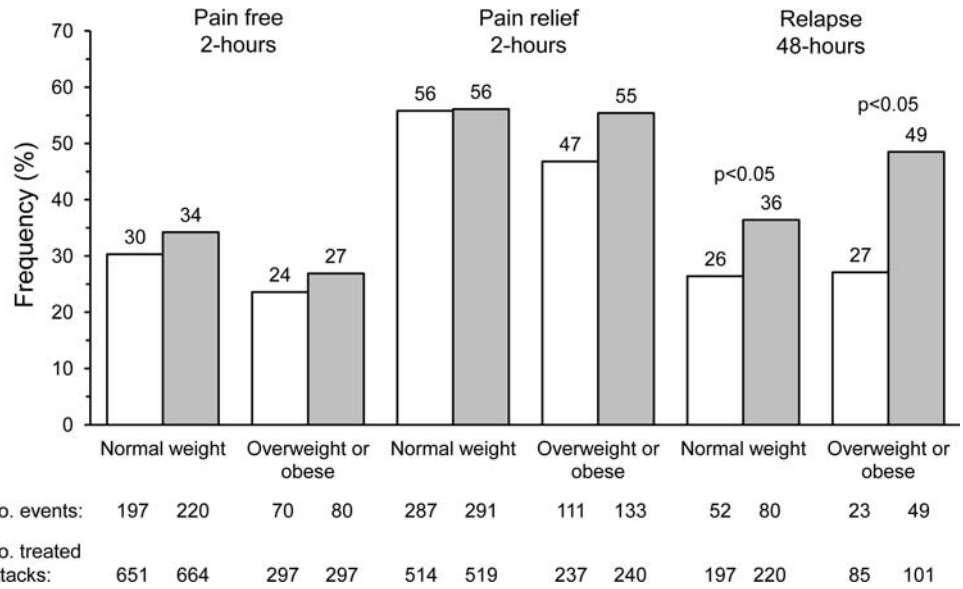


**Fig. 2** Main study endpoints (pain free at 2 h, pain relief at 2 h and relapses at 48 h) in the 220 normal weight subjects and in the 109 overweight or obese subjects of the intention-to-treat population. Data are separately shown for frovatriptan- (*white bars*) and comparator-treated patients (*gray bars*). The number (no.) of events and of treated attacks is reported at the bottom of each bar. $p$ value refers to the statistical significance of the between-treatment difference

triptans taken occasionally during the acute attack, as in our study, may have a negative effect on weight as shown for other medications used for headache prophylaxis [25]. Finally, we cannot exclude that our obese subjects were receiving inadequate doses of study medication and thus that the differences in pain free and relapse between lean and obese subjects could be related to under treatment of the latter group.

In conclusion, our systematic analysis of individual data of double-blind, cross-over trials, suggests that frovatriptan, in contrast to other triptans, retains a sustained antimigraine effect in both non-obese and obese subjects with acute migraine. It also demonstrates a more marked alleviation of migraine headaches in lean individuals. Our results encourage the planning of further randomized trials specifically assessing the impact of different headache medications in obese migraineurs.

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**Conflict of interest** All authors have occasionally served as scientific consultants for manufacturers of frovatriptan, rizatriptan, zolmitriptan or almotriptan. Deborha Pezzola and Dario Zava are employees of the manufacturer of frovatriptan.

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SESSION IV UNCONVENTIONAL TREATMENTS

# Biofeedback and behavioral treatments: filling some gaps

**Frank Andrasik · Licia Grazzi**



**Abstract** Biofeedback and related behavioral approaches have been employed for decades in the management of recurrent headache conditions, with ample evidence to support their clinical utility. Initially, these treatments were employed entirely in the office and required an extended number of face-to-face sessions. Researchers have entered a new era wherein they are focusing on ways to make these treatments less intensive on the part of therapists, less expensive on the part of patients, more widely available and accessible, and retain their level of effectiveness. Initial efforts have focused on PLOT, group, internet, and mass media delivery approaches. This article discusses further approaches being explored to continue to extend behavioral treatment options for patients, focusing on alternative approaches for managing headaches, discussing the value of exercise, addressing depression and sleep problems more directly, and incorporating techniques of motivational interviewing. The importance, role, and value of patient education are stressed throughout.

**Keywords** Biofeedback · Behavior therapy · Headaches · Sleep · Acceptance and commitment therapy · Motivational interviewing

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## Introduction

Biofeedback and related behavioral treatments (primarily progressive muscle relaxation training and its variants), as well as cognitive behavior therapy—also termed stress management or stress coping—have a long history within the field of headache management, dating as far back as the late 1960s–early 1970s. In the ensuing decades, these three primary treatment modalities have garnered a strong base of empirical support. One needs only to examine the report by the US Headache Consortium [1], which over a decade ago concluded that relaxation training, relaxation combined with thermal biofeedback training, electromyographic biofeedback, and cognitive-behavioral therapy "may be considered as treatment options for prevention of migraine." Accordingly, members of the Consortium assigned these treatments the Grade of "A" (defined as the presence of multiple well-designed randomized controlled trials that have revealed a consistent pattern of positive findings). Meta-analytic and other reviews examining the clinical utility of biofeedback and related behavioral treatments continue to reveal them to be efficacious, superior to various placebo comparisons, and comparable to findings obtained with prophylactic medications, both for migraine and tension-type headaches [2–10], with effects enduring absent a need for "booster" sessions [11] (although a minority of reviewers dissent in their appraisals [12, 13]). Evidence is accumulating for the value of augmenting pharmacological therapies with behavioral approaches to enhance overall outcomes, beginning with the seminal work of Holroyd et al. [14, 15] and continuing with further investigations from Holroyd to his colleagues [16–18]. Initial research supports the value of combining behavioral procedures with pharmacological agents for improving headache outcomes and minimizing patient

relapse over an extended time period for patients with chronic migraine that is complicated by analgesic overuse [19]. The predominant treatment for medication overuse headache nonetheless continues to focus chiefly on pharmacological approaches (e.g., withdraw offending medications and replace with more appropriate regimens), without adding behavioral adjuncts [20].

Despite this strong and generally consistent support, behavioral treatments are not widely used in clinical practice. Some of the reasons for this (e.g., effort and cost-intensive nature), as well as ways to enhance accessibility, were addressed in a past article [21]. Evidence continues to accrue that these biofeedback and behavioral procedures can be adapted for delivery models that make them more accessible/affordable without appreciable loss in effectiveness (e.g., administration in group formats; incorporation of the PLOT approach—prudent limited office treatment—wherein direct contact with the healthcare provider is reduced and much of the therapy is redesigned to be completed by the patient outside of the office; internet delivery; and mass media approaches). Thus, they do not need further attention here per se. This article seeks, rather, to fill a few gaps in the literature, by pointing out areas insufficiently addressed or not stressed sufficiently and therefore in need of further consideration, as well as other, more recent, interventional approaches that are more easily implemented and less demanding for patients. We begin with a brief discussion of patient education, adherence, and motivation, topics intricately intertwined, but often not given the attention warranted.

## The importance of education, adherence, and motivation

### Education

No matter what treatment is pursued, patients need specific, tailored, and understandable information in order to enhance "buy in." This is essential because patients are responsible for making the majority of therapeutic decisions about what to do and when to do so (whether it be taking a pill or engaging in pain coping strategies). Education alone can lead to clinical improvements in both primary (pain frequency, intensity, and duration) and secondary measures (functional status, quality of life, depressive symptoms, and service utilization) of pain [22–25]. In fact, Holroyd and Andrasik [26] describe a patient who essentially became headache free from the insight she gained through one session of education (admittedly this is rare). Brief patient education has been shown to enhance adherence to abortive medications, which in turn has led to improved outcomes [14], and presumably lessened the likelihood of medication overuse.

The following are among the most important areas to include in patient education:

- Provision of a basic understanding of headache pathology,
- Education about the typical course of the chronic nature of headache,
- Reassurance of the benign nature of headaches (once other causes have been ruled out),
- Instruction about the proper application of medication, if indicated,
- Point out the pivotal importance of patient involvement and exactly what is required for successfully applying behavioral techniques.

Patients who understand the mechanisms of their prescribed medications and how they fit with their treatment plan are twice as likely to fill the prescription [27]. Frank conversations with patients help set the occasion to discuss the potential for medication overuse headache, adverse effects of medications, and possible deleterious drug interactions, as well as the effects and interactions of any over-the-counter agents and herbal treatments they may be taking. Having patients maintain detailed daily headache records can aid them in learning the relationship between their thoughts, behaviors, emotional, and lifestyle choices [28].

The degree of patient understanding and agreement needs to be evaluated by requesting feedback and employing specific communication strategies. The "Ask–Tell–Ask" strategy has been used successfully in the American Migraine Communication Study II [29]. This strategy acknowledges that effective education requires assessing what the patient already knows and believes, then building upon this understanding and correcting misconceptions when necessary. The "Ask-Tell-Ask" technique relies upon open-ended questions, active listening, and "being fully present" with the patient.

Rains et al. [30] point out the following as being critical to effective education:

- Limit instructions to 3–4 major points during each discussion,
- Use simple, everyday language, especially when explaining diagnoses and treatment instructions (model or demonstrate, when possible),
- Supplement oral instructions with written materials,
- Involve the patient's family members or significant others,
- Ask patients to restate recommendations back to you ("I want to make sure I am being clear and you are

understanding what I am saying, so please say back to me in your own words what we just covered"),
- In conclusion, repeat and reinforce the concepts that were discussed.

### Adherence

Adherence, in contrast to compliance, refers to an active and collaborative involvement by the patient when implementing a therapeutic regimen [31, 32]. Non-adherence can adversely impact headache management in multiple ways [33–35]. It can

- Lead to misuse of medication (including unfilled, overused, underused, incorrectly used, and non-advised discontinuation of prescribed medications or treatments),
- Contribute to inconsistent appointment keeping (and maintenance of headache diary records),
- Promote an unwillingness or inability to follow clinical suggestions.

Improper medication use may not only limit effectiveness but may also aggravate the primary headache condition when taken to excess [31].

Rates of adherence for behavioral recommendations (e.g., alcohol or substance use, dietary modifications, weight loss, exercise, smoking cessation) are even lower than rates of adherence for prescribed medication regimens [36]. Socio-demographic factors play a role in predicting adherence, but even more important is a patient's perceived level of self-efficacy [37, 38].

### Patient motivation

Most models addressing health-related behaviors hypothesize that health-related behavior change and motivation are based upon the following basic components [39–41]: the patient's readiness for change, level of self-efficacy, and outcome efficacy. Skills and/or knowledge alone are not sufficient to ensure behavior change. The patient must want to change, believe that he or she can, and believe that the necessary actions will accomplish the desired goal(s).

Application of the transtheoretical model [42, 43] may be helpful in deciding the best initial course of action to pursue with a given patient. In this model, a patient's readiness and motivation for change can be categorized into one of five stages:

- Stage 1: Precontemplation (the patient does not recognize a problem exists and is not even thinking about changing behavior),
- Stage 2: Contemplation (the patient recognizes a problem and a need and begins to think about changing behavior; the patient may even be in the process of developing a plan, but has yet to take any action),
- Stage 3: Preparation (the patient has completed needed research, developed a plan, and may begin making minor changes or actions),
- Stage 4: Action (the patient is now actively engaged in behavior change or new actions),
- Stage 5: Maintenance (the patient is continuing behaviors necessary to maintain changes).

Therefore, therapists need to consider a patient's stage of readiness for change and tailor their interventions, clinical advice, and education accordingly. Rains et al. [31] provide several behavioral strategies to enhance patient adherence and maximize headache management that readers may found helpful. Finally, it is important to remember that patients do not always progress through these stages in an orderly manner and, at times, may loop back to lower stages before significant change or upward progress is made.

## Filling some gaps: a selective review

### A new slant on addressing headache triggers

Much has been written about headache antecedents, with the exhortation to avoid known triggers to the extent possible. Martin and colleagues [44–46] have presented a radically different approach, one that questions this "one size fits all" strategy. Rather than avoidance across the board, Martin recommends that patients be taught how to cope with many triggers.

His argument is based upon the following premises:

- As research has not clearly identified how triggers precipitate headache, theoretical support for widespread use of avoidance is lacking.
- The advice for widespread avoidance of triggers implies there is something inherent in triggers themselves.
- Routine avoidance of triggers may alter their potency by decreasing tolerance.
- As potential triggers are so ubiquitous, it becomes impossible to avoid all with any consistency. Attempts to do so would markedly restrict a person's lifestyle.
- Extensive research in the areas of chronic pain, stress, and anxiety, to name just a few, demonstrates better outcomes when individuals confront versus avoid the problems. In fact, one of the hallmark techniques for overcoming a host of anxiety disorders is prolonged exposure.
- Finally, drawing upon the above mentioned literatures, it is expected that avoidance may lead to a short-term

reduction in headache activity, but over the long term will paradoxically increase headache activity through a variety of mechanisms—sensitization, reduced tolerance, failure to habituate/adapt, absence of opportunities to acquire coping skills.

Martin does not suggest that exposure to help reduce the salience of triggers is the preferred strategy for addressing all suspected triggers. Rather he advocates a more careful analysis of potential triggers, avoiding or minimizing to the extent possible some types (e.g., automobile exhaust fumes, dehydration, hunger, sleep deprivation), but systematically addressing those that can be directly confronted (e.g., noise, light intensities, and related visual disturbances. Some preliminary research supports the latter approach as an alternative method for dealing with triggers, with one caveat. This approach requires considerable judgment, may take considerable time, and involves some amount of trial and error. It is not easily applied within a brief office format.

## Obesity, depression, and sleep

In a landmark paper, Bigal and Lipton [47] identified key risk factors for headaches progressing to more chronic and severe forms into those non-modifiable and those potentially modifiable. From their identified list of "modifiable" risk factors, several can be considered as suitable for behaviorally oriented approaches: stressful life events, overuse of acute medications and/or caffeine, obesity, depression, and sleep disorders. Much of the burgeoning literature referenced at the beginning of this article is designed to teach patients how to cope better with stress and some of it has focused on the value of augmenting pharmacological treatments by behavioral approaches, so these do not merit further comment in this article. Obesity, depression, and sleep are touched upon in brief in the next sections of this article as illustrations where additional research is clearly warranted.

### *Obesity*

A growing body of literature supports the association between obesity and increased headache activity, particularly so for migraine [48, 49]. This finding holds for the relation between exercise and headache as well [50], in that the absence of exercise is associated with an increased risk of headache (with few exceptions). Behavioral therapists typically address weight management by teaching patients strategies for increasing physical activity, decreasing caloric consumption, or the two in combination. A recent review of outcomes from dietary interventions alone was inconclusive, owing to negative findings and methodological flaws inherent in the available studies [48, 49]. Evidence supporting the augmenting value of exercise and activity was more positive in the most recent published reviews [49–51], where studies have shown significant reductions in multiple measures of headache activity (e.g., frequency, intensity, headache days, and disability). As reductions in weight typically co-occur when one increases activity, the mechanism for headache reductions is unclear. Also, exercise is typically combined with other treatment components, making it difficult to determine the unique contributions of exercise. Further, exercise can enhance mood, raising this as an additional potential mediator of treatment [52]. Future work needs to address the optimal type and "dose" of exercise best suited to each patient, as well as ways to minimize participant dropout.

### *Depression*

Headache clinicians and researchers well know the strong association between negative mood and headache, as regards its high co-occurrence and bidirectional nature, increased impact on quality of life and disability, diminished response to treatment, increased risk of suicidality, and increased chronicity and potential for medication overuse [53–55]. Although depression is rarely *directly* or *solely* targeted in biofeedback and behavioral treatments, these treatments often lead to measureable improvements in depressive symptoms. A recent investigation has explored the utility of directly targeting depression in migraine patients with a behavioral treatment, administered in a single-session, one-day, 5-h workshop-type format, with promising outcomes [56]. Migraine patients, all of whom had comorbid depression (as assessed on the Patient Health Questionnaire-8, wherein at least 5 of the 8 criteria were endorsed, with one of them being "depressed mood" or "loss of interest or pleasure"), were randomly assigned to treatment as usual (TAU) or acceptance and commitment training combined with education (ACT-ED). ACT focused on teaching patients new ways of managing bothersome thoughts, feelings, and pain sensations, how to recognize ineffective habits and behavioral patterns, and strategies for exploring and establishing life and health goals and ways to effectively implement actions to increase the likelihood of achieving these goals. In this approach, patients are taught to manage troublesome thoughts in a way that is a marked departure from what has typically been done in the literature. Rather than challenging and disputing thoughts giving rise to stress and subsequent pain, in ACT patients are taught procedures to "develop cognitive distance" from and learn how to "willingly face expectations that cannot be changed"; hence, the focus on acceptance of uncontrollable events. Patients assigned to ACT-ED were markedly improved with respect to multiple

measures of disability and depression when compared to TAU, as assessed at a 3-month follow-up. Of note is the finding that a significantly larger portion of patients receiving ACT-ED no longer met clinical criteria for depression. The brevity of this type of intervention is appealing; however, questions remain about the durability of the findings, as well as its impact upon pain measures (which were not collected).

*Sleep*

Researchers have long noted a significant relationship between problematic sleep and headaches (beginning with Wright [57] and continuing to the present [58, 59]), although the direction of this relationship is not fully clear. Calhoun and Ford [59] describe one of the few investigations to directly test the effectiveness of a behavioral program to target sleep difficulties, in this case insomnia, in headache patients. All patients were female and were experiencing what then was termed "transformed" migraine. Following a careful assessment, the patients were randomly assigned to a behaviorally oriented sleep hygiene program or a placebo/sham sleep program, which included a partial cross-over (sham patients were subsequently offered the active program).

The Behavioral Sleep Medicine (BSM) program consisted of the five following components (each taught in 20-min segments, for a total time in treatment of approximately 1.5 h):

- Adopt a routine/consistent bedtime that permitted 8 h in bed,
- Eliminate all non-sleep-related activities; no watching TV, reading, or listening to music,
- Employ guided imagery/visualization to reduce the latency to sleep,
- Complete the evening meal a minimum of 4 h before bedtime and limit fluid intake within 2 h of bedtime,
- Eliminate/discontinue daytime naps.

Patients assigned to the sham condition were instructed to adhere to the below five components:

- Schedule the evening meal at a consistent time, one that did not vary by more than 1 h each day,
- Self-administer acupressure as instructed for 2 min, twice per day,
- Monitor fluid intake for three consecutive days.
- Every morning complete 5 min of "gentle range of motion exercises",
- Consume 1 serving of protein at breakfast.

At the first follow-up, occurring at 6 weeks, patients receiving BSM reported significant reductions with respect to headache frequency and intensity (with no such change for the placebo condition). Also, approximately 1/3 of those receiving BSM reverted to episodic migraine, while no one in the sham condition did. In the second phase, those initially assigned to BSM continued this treatment; those given the sham treatment were crossed over to the BSM condition. At the final follow-up, 43 % of sham patients who had now been given BSM reverted to episodic migraine, while those continuing BSM revealed a near doubling of the reversion rate to episodic migraine (now 58 %). All patients received usual care throughout the study, which included encouragement to taper and/or discontinue overused medications. At the end of the trial, all patients who reverted discontinued their offending medications, while 60 % of those who improved but did not fully revert stopped overuse of medications. These encouraging initial findings await replication, with a more extended follow-up evaluation.

Motivational interviewing

A final behaviorally oriented approach, termed "Motivational Interviewing" (MI), needs mention, as this approach has been successfully applied to augment treatment for numerous health- and non-health-related conditions [41], as well as medication adherence [60]. MI can be defined as below:

> Motivational interviewing is a form of collaborative conversation for strengthening a person's own motivation and commitment to change. It is a person-centered counseling style for addressing the common problem of ambivalence about change by paying particular attention to the language of change. It is designed to strengthen an individual's motivation for and movement toward a specific goal by eliciting and exploring the person's own reasons for change within an atmosphere of acceptance and compassion. See more at: http://www.motivationalinterviewing.org/#sthash.3niAvb2a.dpuf.

Thus, it refrains from imposing change that may be viewed as "externally-driven" and strives to be consistent with the patient's own wishes, values, and beliefs. Readers may find a wealth of information about MI at the following website: http://www.motivationalinterview.org.

To date, we could find only 1 instance of it being applied with headache patients. Stevens et al. [61] tested the value of this approach, administered via telephone, with adolescents who were experiencing chronic forms of headache (migraine or tension-type) accompanied by medication overuse. Following an evaluation, the adolescents were randomly assigned to comprehensive standard care (education, medication, and behavioral health services) alone or the preceding combined with MI, administered by a registered nurse specially trained in MI. To control for amount

of contact, the nurse attempted to reach each adolescent four times over the 4-month study period. However, MI techniques were discussed only in the experimental condition. At the end of the trial, those receiving the addition of MI revealed greater reductions in headache frequency than those receiving standard care alone, but only for those adolescents whose headaches were relatively lower in frequency at baseline. No changes occurred with respect to headache severity or disability.

The authors acknowledged a number of limitations in this pilot investigation, among these being the absence of fidelity checks to ensure that MI was delivered as intended, a less than desired number of calls were completed (an unspecified number of adolescents did not participate in all four planned calls), insufficient power, and the absence of extended follow-up data collection. The latter, combined with the brevity of the intervention, may have been inadequate for effects to emerge.

## Brief conclusions

As can be seen, much research remains to be completed in order to more fully exploit the utility of behavioral procedures. We hope this selective review helps encourage continued research efforts in this regard.

**Conflict of interest** We certify that there is no actual or potential conflict of interest in relation to this article.

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SESSION IV UNCONVENTIONAL TREATMENTS

# Effects of the acupoints PC 6 *Neiguan* and LR 3 *Taichong* on cerebral blood flow in normal subjects and in migraine patients

**P. E. Quirico · G. Allais · M. Ferrando · C. de Lorenzo · C. Burzio · F. Bergandi · S. Rolando · P. Schiapparelli · C. Benedetto**



**Abstract** Acupuncture has been proven to be effective in the treatment of various cardiovascular disorders; it acts both on the peripheral flow and on the cerebral flow. Our study aimed to evaluate the effects of the insertion of PC 6 *Neiguan* and LR 3 *Taichong* acupoints on the cerebral blood flow (CBF) in the middle cerebral artery (MCA). These effects were measured in a group of patients suffering from migraine without aura (Group M) and in a healthy control group (Group C). In the study, we included 16 patients suffering from migraine without aura, classified according to the criteria of the International Headache Society, and 14 healthy subjects as a control group. The subjects took part in the study on two different days, and on each day, the effect of a single acupoint was evaluated. Transcranial Doppler was used to measure the blood flow velocity (BFV) in the MCA. Our study showed that the stimulation of PC 6 *Neiguan* in both groups results in a significant and longlasting reduction in the average BFV in the MCA. After pricking LR 3 *Taichong,* instead, the average BFV undergoes a very sudden and marked increase; subsequently, it decreases and tends to stabilize at a slightly higher level compared with the baseline, recorded before needle insertion. Our data seem to suggest that these two acupoints have very different effects on CBF. The insertion of PC 6 *Neiguan* probably triggers a vasodilation in MCA, while the pricking of LR 3 *Taichong* determines a rapid and marked vasoconstriction.

**Keywords** Acupoints · Acupuncture · Cerebral blood flow · Migraine · Transcranial Doppler

**Abbreviations**

| | |
|---|---|
| BFV | Blood flow velocity |
| CBF | Cerebral blood flow |
| MCA | Middle cerebral artery |
| TCD | Transcranial Doppler |

## Introduction

Acupuncture has been proven to be effective in the treatment of various cardiovascular disorders; it is effective both on the peripheral flow and on the cerebral flow. Among these disorders are included strokes, vertebrobasilar insufficiency, and migraine [1–6]. These data support the hypothesis that acupuncture may have a direct influence on the cerebral blood flow (CBF).

Numerous neuroimaging studies, that have been carried out recently, demonstrate how the needle insertion can influence the cerebral blood flow [7–9].

Several authors have also evaluated the effects of electroacupuncture on ischemia caused by occluding the middle cerebral artery in animal brain; these studies have proven that the stimulation of precise acupoints can improve the blood flow in the infarcted area [10–13].

Notwithstanding these data, the effects of needle insertion on the CBF are not yet thoroughly understood.

Some studies, carried out with Transcranial Doppler (TCD), demonstrated that the stimulation of certain

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acupoints causes specific effects on the MCA blood flow [2, 14, 15].

This study aimed to evaluate the effects of the insertion of the acupoints PC 6 *Neiguan* and LR 3 *Taichong* on the MCA blood flow. These effects were measured in a group of patients suffering from migraine without aura and in a healthy control group.

## Patients and methods

A total of 30 subjects were included in the study. They were divided into two groups: a group of 14 healthy control subjects (Group C) and a group of 16 patients suffering from headache (Group M), classified as migraine without aura according to the criteria provided by the classification of the International Headache Society [16].

All subjects gave their informed consent to the participation in the study.

To take part in the evaluation, the patients had not to take any prophylactic therapy for migraine nor any kind of symptomatic medication during the previous 72 h.

The control group, instead, was made up of healthy subjects, which in particular had never suffered from headache and that did not take any medication.

The patients took part in the study on two different days, a week apart from each other, and on each day, the effect of a single acupoint was evaluated. Which of the two acupoints had to be treated firstly in the single subject was decided randomly, according to a computer-generated randomization list.

## Acupoint selection

The choice of the acupoints we stimulated was made considering their clinical characteristics, widely documented both by empirical data of Traditional Chinese Medicine and by recent scientific experiments.

Below, we illustrate a description of the localization, anatomical characteristics, stimulation techniques, and clinical indications for the two chosen acupoints (Fig. 1).

### PC 6 *Neiguan*

*Location*: two transverse inches above the skin crease of the wrist, between the tendons of the flexor radialis carpi and palmaris longus muscles.

*Posture*: with the palm facing up.

*Needling method:* perpendicular.

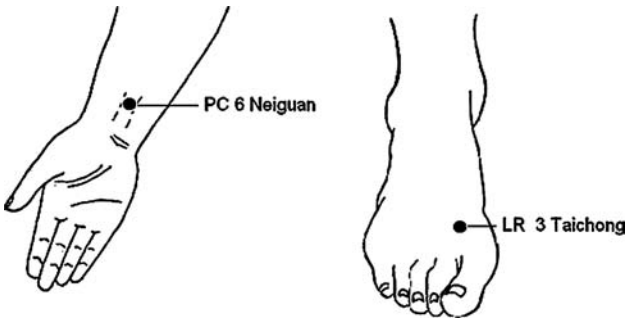


**Fig. 1** Location of the acupoints PC 6 *Neiguan* and LR 3 *Taichong*

*Needle sensation:* numbness and/or light electric sensation radiating to the hand and more specifically to the middle finger.

*Anatomy:* the needle crosses the skin; the subcutaneous tissue —passing between the flexor carpi radialis and palmaris longus muscles— crosses the superficial and deep flexor digitorum muscles and may reach the pronator quadratus muscle. In the superficial layer, there are branches of the medial and lateral antebrachial cutaneous nerves ($C_7$). Between the flexores muscles, there are the median nerve and vessels. In the deeper layer, there are the palmar interosseous nerve and vessels.

*Traditional clinical indication:* heart diseases, chest pain, and oppression. Gastric pain, nausea, vomiting. Anxiety, irritability, depression, insomnia, palpitations. Breast tension, dysmenorrhea. Hand and wrist pain. Abdominal surgical analgesia.

*Experimental data*: some studies show the effects of PC 6 *Neiguan* on increasing cutaneous blood flow [18] and also the brain flow [11]. Moreover, PC 6 *Neiguan* can decrease heart rate and blood pressure, reduce the afterload in the left ventricule [19], and can regulate coronary diameter in a different way, depending on the type of angina pectoris [20], not only quickly relieving the symptoms of acute angina pectoris, but also improving nitroglycerine's therapeutic effects [21].

### LR 3 *Taichong*

*Location*: on the dorsum of the foot, at the midpoint of the depression located 1 inch distally to the joint, and between the heads of the first and second metatarsal bones.

*Posture*: seated or supine.

*Needling method:* perpendicular

*Needle sensation*: local soreness and distension, sometimes radiating to the fingers.

*Anatomy:* the needle crosses the skin, the subcutaneous tissue, and running lateral to the extensor brevis muscle of the big toe, penetrates the first dorsal interosseous muscle. In the superficial layer, there are the dorsal venous arch of the foot and the cutaneous branches of the deep and superficial peroneal nerves ($L_5$). In the deeper layer, there are the first dorsal metatarsal artery and the deep peroneal nerve.

*Traditional clinical indication:* headache, dizziness, tremor, epilepsy, premenstrual syndrome, dysmenorrhea, amenorrhea, and difficult labor. Eyesight disorders and eye diseases. Depression, irritability, insomnia. Urogenital pain and infections. Foot pain. Hypochondrial pain.

*Experimental data:* LR 3 *Taichong* is the distal point of the foot most commonly used in clinical trials for migraine [5, 22, 23] and also has long-term antihypertensive effect, improving effectively day–night rhythm variation in young patients with hypertension [24].

The experimental procedure consisted of two sessions lasting 30 min each. During the test, the subject was placed in a quiet room with a constant temperature of 23–24 Celsius degrees and was invited to lie down comfortably on the medical bed, in a supine position. Transcranial Doppler measurements were carried out by means of a commercially available device (Multidop X4, DWL, Germany) equipped with a 2-MHz pulsed-wave probe that was carefully positioned over the right MCA and, after obtaining the best signal from the artery, was fixed in position, so as to avoid the constant manual repositioning. In this way, the signal was constantly picked up during the whole time of the observation.

After fixing the probe, the subject was invited to relax, and for 10 min, the basal blood flow in MCA was monitored.

Subsequently, PC 6 *Neiguan* or LR 3 *Taichong* was punctured bilaterally by an experienced acupuncturist with 0.3-mm-diameter sterile disposable steel needles (length 52 mm) that were inserted to a depth of 10–20 mm and manipulated until the subject reported the characteristic irradiating sensation, said to indicate effective needling, that is commonly called *De Qi*. After obtaining *De Qi*, the needle was left in place until its extraction at the fifth minute.

Transcranial Doppler parameters were recorded: in basal conditions, immediately after needle insertion, at 1 and 3 min from needle insertion, immediately before needle extraction, and finally, further 5 min after the extraction. The same times of measurement were adopted for both groups and for both PC 6 *Neiguan* and LR 3 *Taichong* acupoints.

All the obtained data were statistically processed using an analysis of variance (ANOVA) for repeated measures.

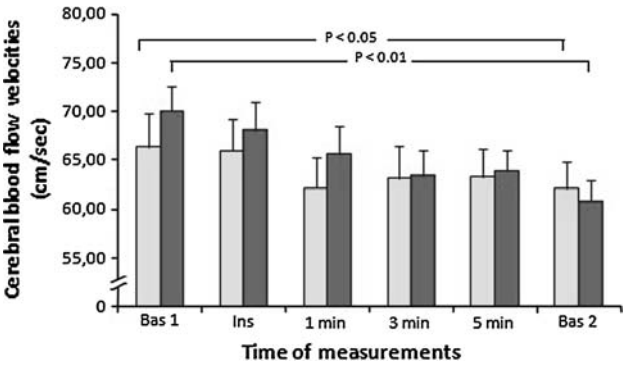


**Fig. 2** Mean values ($x \pm$ s.e.m.) of cerebral blood flow velocities (expressed in cm/s) in the MCA in migraine patients (*red columns*) and healthy control subjects (*yellow columns*) after *Neiguan* pricking. The measurements here considered were obtained in basal conditions before needle insertion (*Bas 1*), immediately after needle insertion (*Ins*), at 1 min and 3 min from needle insertion, immediately before needle extraction at 5 min and other 5 min after this (*Bas 2*) (color figure online)

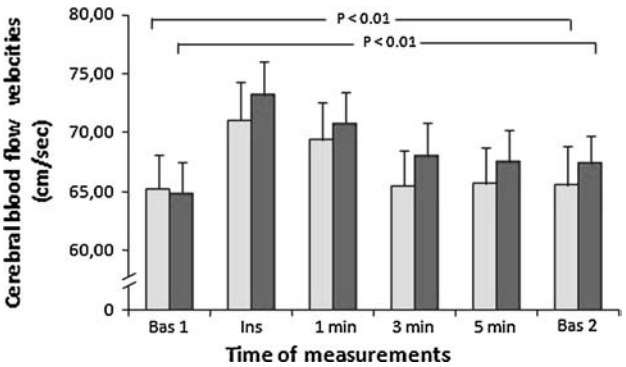


**Fig. 3** Mean values ($x \pm$ SEM) of cerebral blood flow velocities (expressed in cm/s) in the MCA in migraine patients (*red columns*) and healthy control subjects (*yellow columns*) after *Taichong* pricking. The measurements here considered were obtained in basal conditions before needle insertion (*Bas 1*), immediately after needle insertion (*Ins*), at 1 min and 3 min from needle insertion, immediately before needle extraction at 5 min and other 5 min after this (*Bas 2*) (color figure online)

The comparison between the averages obtained at each single time of measurement in the two groups was made using the Student's *t* test.

## Results

Our study demonstrated that the stimulation of PC 6 *Neiguan* causes in both groups a significant decrease on the average MCA BFV.

Figure 2 shows the trend of the BFV at the various observation times in the two studied populations. In Group M, the MCA BFV appears to diminish continuously with a highly significant trend ($p < 0.01$), and to a greater extent than in Group C. In Group C, the average BFV appears to be reduced in a statistically significant way too ($p < 0.05$),

but the trend is less constant because there are some fluctuations during the decrease. Nevertheless, no significant difference between Group C and Group M is present at each single time of measurement.

The pricking of LR 3 *Taichong* (Fig. 3), on the contrary, causes a very sudden and marked increase in the average MCA BFV that results statistically significant in both groups ($p < 0.01$). Subsequently, the BFV diminishes, and it tends to stabilize at a slightly higher level compared with the basal one recorded before needle insertion.

Migraine patients, also in this experimental situation, seem to be more reactive to the acupunctural stimulus, but no statistically significant difference between MCA BFVs in the two groups is detectable at any time of the study.

## Discussion

Our results seem to suggest that acupoints PC 6 *Neiguan* and LR 3 *Taichong* cause very different effects on cerebral circulation.

PC 6 *Neiguan* seems to trigger a vasodilating effect on the MCA; this vascular response appears to be less rapid and intense compared with the one, of opposite sign, that occurs after the stimulation of LR 3 *Taichong*.

This datum could be explained by the fact that insertion in PC 6 *Neiguan* (as suggested by both traditional clinical indication and current scientific research) [19–21] acts in greater measure on cardiovascular function than on cerebral circulation.

Another observable fact is that the decrease in BFV in the MCA after pricking PC 6 *Neiguan* is maintained longer in time compared with what happens after pricking LR 3 *Taichong*; this suggests that the effect of PC 6 *Neiguan* might be mediated by the release of vasodilating substances into the circulation.

The insertion at LR 3 *Taichong*, instead, causes a very sudden and marked increase in the BFV, as a probable expression of vasoconstriction in the MCA, and a subsequent reduction in the BFV, which then tends to stabilize, even if, at a higher level than the basal one.

The action of LR 3 *Taichong* on CBF appears to be more pronounced, at least in the short term, compared with that of PC 6 *Neiguan*; this observation suggests that LR 3 *Taichong* probably acts more specifically on cerebral circulation, fact that is not unlikely, as this acupoint is the most used distal point in the treatment of migraine. The extreme rapidity with which the BFV accelerates seems to suggest that, in this case, the effect of the stimulation of the acupoint might depend on a direct nervous stimulation rather than slower, secretory mechanisms.

However, preliminary data of this study need experimental confirmation on a broader population of migraine patients and healthy subjects before drawing definitive conclusions.

**Conflict of interest** All the authors certify that there is no actual or potential conflict of interest in relation to this article.

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# Herbal therapy in migraine

**G. D'Andrea · S. Cevoli · D. Cologno**



**Abstract** The use of herbal therapies is ancient and increasing worldwide. There is a growing body of evidence supporting the efficacy of various "complementary" and alternative medicine approaches in the management of headache disorders. Promising tools to treat migraine patients are herbal products. In particular constituents of Petasites hybridus, *Tanacetum Parthenium* and Ginkgo Biloba have shown antimigraine action in clinical studies. A miscellaneous of recreational drugs and other herbal remedies have been supposed to have a role in headache treatment but quality of clinical studies in this field is low and inconclusive. Further research is warranted in this area.

**Keywords** Complementary and alternative medicine · Migraine · Feverfew · Petasites · Ginkgolide B

## Introduction

Migraine therapy is based on drugs that reduce the excitability of the CNS (antiepileptics, calcium antagonists, etc.) or others that antagonize the inflammatory phase of the migraine attacks (FANS). All these therapies have, often, an insufficient efficacy and are accompanied with a numerous side effects. For these reasons many of these treatments are not indicated to cure in particular pediatric headache patients [1]. Promising tools to treat migraine patients (adults and children) are herbal products. In particular constituents of Ginkgo Biloba (ginkgolide b) that modulates glutamate, inhibits PAF action and exerts mitochondrial protection [2], Petasites hybridus that antagonizes the inflammatory soup formation [3], *Tanacetum Parthenium* that inhibits prostaglandins [4] have shown antimigraine action in clinical studies. In this brief review, those herbal products are described that, with their pharmacological properties, have or may have a useful impact in the cure of migraine patients.

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## Feverfew

Feverfew (*Tanacetum parthenium L.*) belonging to the family Asteraceae has a long history of use. Traditionally, the herb has been used as an antipyretic, analgesic and antiinflammatory, it was also used for allergies, nausea and vomiting [4]. The most important active principles are the sesquiterpene lactones, among which are parthenolide, flavonoids and volatile oils. Feverfew effects as herbal remedy for migraine involve a wide variety of physiologic pathways. Parthenolide has an antiinflammatory activity mediated by inhibition of prostaglandin synthesis. Feverfew has effects on vascular smooth muscle and it is a potent inhibitor of serotonin release from platelets to polymorphonuclear leukocyte granules. Inhibition of histamine release is another mechanism demonstrated [4]. Parthenolide significantly reduced nitroglycerin-induced Fos expression in the nucleus trigeminalis caudalis [5] and inhibited nitric oxide synthesis [6]. Recently, a study

reported that parthenolide inhibits nociception and neurogenic vasodilatation in the trigeminovascular system by targeting TRPA1 channel [7]. In the last decades, several clinical trials have tested the effectiveness of feverfew extracts for the prophylaxis of migraine with controversial findings. A first systematic review and its update included six double-blind, placebo-controlled trials (RCT): four studies reported positive results favoring feverfew and two trials, one of which was of good quality, reported negative results [8, 9]. Patients medicated with feverfew for several years before enrolling in a study were randomized to placebo or to continue feverfew therapy. Incidence of headache increased significantly in patients who switched to placebo. Moreover, the feverfew withdrawal caused a "post-feverfew syndrome" characterized by severe headache, insomnia, nervousness and joint pain [10]. In 2004, a Cochrane Collaboration systematic review included only five trials involving 343 patients: results from these trials were mixed and did not convincingly establish that feverfew was more effective than placebo for preventing migraine [11]. After this review other trials were published. Negative results were reported in a RCT of a compound providing a combination of riboflavin (400 mg/die), magnesium (300 mg/die) and feverfew (100 mg/die) [12]. Taking conflicting results into account, the efficacy and tolerability of a $CO_2$ extract of feverfew (Mig-99, 6.25 mg t.i.d), for migraine prevention was preliminarily investigated in a dose-finding study [13] and then in a phase III study [14]. Hundred and seventy patients completed the study protocol. The migraine frequency decreased from 4.76 by 1.9 attacks per months in the verum group and by 1.3 attacks in the placebo group ($p = 0.045$). Logistic regression of responder rates showed an odds ratio of 3.4 (CI = 1.4–7.8) in favor of Mig-99. After this study, Quality Standards Subcommittee of the American Academy of Neurology stated that Mig-99 is probably effective for migraine prevention (Level B) [15]. Feverfew was evaluated also for acute migraine treatment. A recent randomized, double-blind, pilot study compared the efficacy of a lipid-based formulation of a sublingual homeopathic product of feverfew and ginger (LipiGesic$^{TM}$ M) versus a matching placebo as treatment for acute migraine attack at onset, during the mild headache phase [16]. 163 attacks were treated with feverfew/ginger and only 58 with placebo. At 2 h, 32 % of subjects in the active group and 16 % of subjects in the placebo group were pain free ($p = 0.02$); 63 and 39 %, respectively, reported pain relief ($p = 0.02$). However, this pilot study presents some limitations and there is no clear explanation about the mechanism of action of the homeopathic intervention [16]. Generally, feverfew resulted well tolerated with only mild and transient adverse effects, probably due to a contact phenomenon, the most serious being mouth ulceration for powdered products and gastrointestinal disturbances [4]. Uncertainty as regards the component responsible for its biological activity in the extracts, and qualitative or quantitative variability of components contained in the different preparations (capsules, tablets, ethanolic extracts, supercritical $CO_2$ extracts) should be addressed in future studies.

## Petasites

In recent years, *Petasites hybridus* root extract, also known commonly as "butterbur", has been touted as a promising new treatment for migraine prevention. The butterbur plant is a perennial shrub found throughout Europe and parts of Asia. It was used for many centuries as a remedy for fever, spasms, wound healing and more recently for pain, such as migraine. Although mechanism of action of Petasites is not fully understood, it likely acts through calcium channel regulation and inhibition of peptide leukotriene biosynthesis, thus influencing the inflammatory cascade associated with migraine [17]. The pharmacologically active compounds in butterbur are sesquiterpenes such as petasin and isopetasin. They exert a highly potent antiinflammatory effect through inhibition of leukotriene synthesis and COX-2-mediated prostaglandin E2 release [18]. While the butterbur plant also contains pyrrolizidine alkaloids, which are hepatotoxic, carcinogenic, lung toxic and prothrombotic; these substances are removed in the commercially available preparations, such as Petadolex® Petaforce, Petadolor H, Tesalin, and Tussilago) [3, 19]. Nonetheless, patients should be advised to use only butterbur products that are certified and labeled "PA-free". The efficacy of *Petasites hybridus* in migraine prevention has been evaluated in several studies [20–22]. German authors [20] carried out the first randomized, group-parallel, placebo-controlled, double-blind clinical study with Petadolex in 60 migraine with and without aura patients. They received either Petadolex or placebo at a dosage of two capsules (each capsule contains 25 mg) twice daily over 12 weeks. The frequency of migraine attacks decreased by a maximum of 60 % compared to the baseline with a statistically significant difference from placebo. Petasites was exceptionally well tolerated with no adverse events reported. An independent reanalysis of its efficacy criteria was subsequently performed [21] because of flawed statistical analyses in the original study, and confirmed the superiority of the butterbur extract over placebo for all primary variables of efficacy. Later, a three-arm, parallel-group randomized controlled trial of 245 patients [22] showed that Petasites extract 75 mg twice daily was more effective than placebo in decreasing the number of monthly migraine attacks (58 vs. 28 %). The most frequently reported adverse reactions

were mild gastrointestinal events, especially eructation (burping). Until now four cases of a reversible cholestatic hepatitis have been probably associated with long-term administration of butterbur (incidence of 1:175,000). It is unknown which components of butterbur are responsible for the long-term hepatotoxicity [23]. Given its global safety and tolerability, Petadolex® may be a good option in the treatment of pediatric migraine. Unfortunately, few pediatric studies have been done and even fewer have been of high quality or based on a large sample [24–26]. In all these studies nearly 80 % of all patients treated with Petadolex® reported a reduction in migraine frequency of at least 50 % with no significant differences from placebo during follow-up. Pediatric butterbur dosing ranged from 50 to 150 mg total daily dose (TDD) is divided two times per day within these pediatric studies [26]. Safety has not been established for butterbur use in pregnant or lactating females or children less than 6 years of age and it is therefore not advised in these patients. Petadolex guarantees that it contains at least 15 % petasin and is PA-free; it is difficult to extrapolate the effects of the studies to other forms of butterbur; therefore, the use of non-Petadolex butterbur is not recommended. Finally, patients should notify their providers if they are on or plan to take any anticholinergic medications as butterbur may interact with them. Butterbur is not available in Italy but it is a prescribed medication in Germany and Switzerland, thereby subject to regulation and standards of preparation [23]. However, butterbur is considered a food in the United States and as such is not subject to FDA approval or standardization of preparation [23]. Petasites is established as effective for migraine prevention (2 Class I studies) and there is a level A recommendation for its use from the recent evidence-based guidelines on treatments for episodic migraine prevention in adults [15].

## Ginkgolide B

Ginkgolide B, a diterpene, is an herbal constituent extract from *Ginkgo biloba* tree leaves [27]. Ginkgolide B has a theoretical basis for migraine prophylaxis. Mechanisms of action supposed to be involved in migraine treatment include modulation of the glutamatergic transmission in the CNS [28] and antagonism of platelet-activating factor (PAF) receptor. PAF is a potent proinflammatory and nociceptive agent released during inflammation process [29]. In addition, PAF has been shown to induce more serotonin secretion from platelets in migraine patients than controls [30]. Moreover, PAF released during the first phase of migraine attack may sensitize the trigeminal-vascular endings and induce pain [31]. Ginkgolide B was tested for migraine prophylaxis only in open-label studies. A combination of 60 mg of ginkgo biloba terpenes phytosome, 11 mg coenzyme $Q_{10}$ and 8.7 mg vitamin B2 resulted effective in reducing migraine with aura frequency in 50 adults patients: a decrement from $3.7 \pm 2.2$ to $2.0 \pm 1.9$ ($p < 0.05$) was detected. In a very small and preliminary study, the same combination had a role as a possible acute treatment of migraine aura [32]. A combination of ginkgo biloba terpenes phytosome 80 mg, coenzyme $Q_{10}$ 20 mg, vitamin B2 1.6 mg and magnesium 300 mg was evaluated in different studies involving 330 children with promising results: significant reduction in migraine without aura frequency was reported [33–35]. Greater reduction in the ginkgo biloba terpenes phytosome group compared with *Griffonia simplicifolia* extracts was reported in a open-label, non-randomized study. Both preparations reduced all outcome measures after 6 months of treatment [35]. All the evidence in favor of ginkgo biloba terpenes phytosome is derived from trials where it was combined with other nutraceuticals known to have a possible effect in reducing migraine frequency [36]. However, vitamin B2 and coenzyme Q10 were present in low concentrations. Ginkgolide B (ginkgo biloba terpenes phytosome) resulted well tolerated in all the previous studies, only minor transient gastrointestinal upset was described in a small percentage of patients. A powered double-blind, randomized, placebo-controlled study is necessary before considering Ginkgolide B in migraine guidelines.

## Recreational "herbal" drugs

Although controversial, the evidence for the use of recreational drugs such as marijuana, lysergic acid diethylamide (LSD) and psilocybin is worth mentioning for the insight it provides regarding the pathophysiology of migraine and cluster headache [37, 38]. While only few reports on cluster headache describing intriguing results using LSD and psilocybin are available, cannabinoids in particular have a long history of use in the abortive and prophylactic treatment of migraine. Hence, in USA cannabinoids cannot be prescribed by physicians; they are used by patients for relief of headache, helped by the growing number of American states that have legalized medical marijuana.

Tetrahydrocannabinol (delta-9-THC; the psychoactive component of cannabis), cannabidiol and dimethyl heptylpentyl cannabidiol (the non-psychomimetic components of marijuana derivatives) have been demonstrated to inhibit the 14C-labeled serotonin release from normal platelets [39] only during a migraine attack. Delta-9-THC exerts all of its known central effects through the CB-1 and CB-2 cannabinoid receptors, which were discovered by studying the effects of an endogenous cannabinoid, named anandamide. It demonstrates a predilection for areas involved in

nociception, exerting an inhibitory effect on serotonin type 3 (5-HT3) receptors [40], thus supporting antiemetic effect and suggesting analgesic effect. Anandamide, also, was able to inhibit neurogenic dural vasodilatation via-CGRP and NO-induced dural vessel dilation in the intravital microscopy model and it was able to activate the vanilloid type 1 (TRPV1) receptor causing vasodilation via the release CGRP [41, 42]. These data seem to suggest that CB receptors may have therapeutic potential in headache. More recently [43], it has been observed a novel interaction between serotonergic and endocannabinoid systems in the processing of somatosensory nociceptive information, suggesting that some of the therapeutic action of triptans may be via endocannabinoid containing neurons in the ventrolateral periaqueductal gray. In the same research setting, cannabinoids such as Delta-9-THC and CB1 receptor agonist showed a dose-dependent suppression effect on cortical spreading depression in rat brain suggesting a potential therapeutic effect also in migraine with aura [44]. Further research on the effects of these substances may result in a greater understanding of the mechanisms of migraine.

## Miscellaneous

Isolated reports are available in literature on different herbal remedies and spices for migraine pain (Table 1). In the majority, they could show efficacy in migraine attacks probably inhibiting platelet activity, with an antiinflammatory and analgesic effect. Spices, other than herbs, such as chilis, turmeric, cayenne pepper, ginger, garlic and onions, could have beneficial effect on migraine attacks. Two of them in particular, such as chilis and turmeric, deserve citations in this review because their components are available in Italy in medication compounds. An intriguing isolated report of unexpected relief of migraine in a young female migraineur after intake of one-and-a-half teaspoonfuls of chili sauce [45], a spice long known to trigger migrainous attacks, highlights the pain-killing action of capsaicin, an active component in chili and other peppers that makes them hot. From recent findings obtained in experimental animals [46, 47], it is known that capsaicin could modulate the function of the trigeminovascular pathway by depleting substance P, with a strong inhibitor effect on platelet aggregation and desensitization of TRP channels, in particular the TRPV1 channel, expressed by nociceptive neurons. Unfortunately, capsaicin has a poor oral bioavailability, so it is very difficult to reach high concentrations in plasma of migraineurs after oral ingestion. Curcumin (diferuloylmethane), an orange-yellow component of turmeric or curry powder, is a polyphenol natural product isolated from the rhizome of the plant Curcuma longa, used for centuries in some medicinal preparation or as a food-coloring agent. In recent years, extensive in vitro and in vivo studies suggested curcumin has antioxidant and antiinflammatory properties mediated by numerous molecular targets of cellular signaling molecules, including cyclooxygenases, protein kinase C, protein tyrosine kinases and endonucleases. It was found that curcumin is rapidly emerging as a potent agent with significant antinociceptive properties [48]. Although no clinical studies on migraine have been yet reported on headaches and migraines, this substance seems very interesting for the hypothesized mechanisms of its antihyperalgesic effects, some of them likely implicated in migraine, such as mitigation of the capsaicin induced TRVP1 pain hypersensitivity [49] and dose-dependent attenuating effect on the release of nitric oxide, which further decreases the strength of the nociceptive stimuli [50]. In every published clinical trial, curcumin appears to be extremely safe, even at doses up to 8 g daily, with no adverse events. Further large-scale studies are needed in humans and in particular in migraine patients to fully elaborate and harness the pain-mitigating effects of curcumin.

**Table 1** Herbs that "could" relieve migraine pain

| Name | Hypothetical mechanism of action in migraine |
|---|---|
| Griffonia simplicifolia | Suppress platelet aggregation |
| Lippia alba | Antiinflammatory and analgesic effects |
| Tou Feng Yu pill (TFY) | Decrease plasma levels of CGRP, serum NO, and content of brain dopamine, antagonize vasospasm, and increase cerebral blood flow |
| Goshuyuto | Suppress platelet aggregation |
| Lavender essential oil | Direct analgesic effect for inhalation |
| Harpagophytum procumbens or "Devil's Claw" | Antiinflammatory and analgesic effects |
| Pinus radiata bark extract | Antioxidant effect |
| Isoflavones | Antiinflammatory, analgesic and antioxidant effects |

## Conclusion

There is a growing body of evidence supporting the efficacy of various "complementary" and alternative medicine approaches in the management of headache disorders. Alternative or complementary modes of treatment often lack scientific proof of efficacy. Given the side effects of traditional prescription medications, there is an increasing demand for "natural" treatment of headaches. Many of

these complementary modes are inexpensive, harmless, and possibly effective. These treatment modalities include "herbal therapy". Therefore, it is important that headache clinicians and researchers treating adult and pediatric migraines explore therapies that are safe, effective and affordable, using them as alternative monotherapy option or as "add on" preventive therapy. As for mechanisms behind botanical treatments, the lack of funding for studying these agents will continue to retard progress in this area as well, but hopefully the future will bring more concentrated efforts.

**Conflict of interest** S. Cevoli and D. Cologno do not have actual or potential conflict of interest in relation to this article. G. D'Andrea is president and sole administrator of Pharmaval®.

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# Riboflavin and migraine: the bridge over troubled mitochondria

**Bruno Colombo · Lorenzo Saraceno · Giancarlo Comi**



**Abstract** Brain energy metabolism has been found to be disturbed in migraine. A mitochondrial defect may reduce the threshold for migraine attacks both increasing neuronal excitability and leading migrainous brain to a hyper-responsiveness to triggering stimuli. Riboflavin, a major co-factor in oxidative metabolism, may overcome this impairment. RCT studies in adult confirmed that riboflavin is safe and probably effective in migraine prophylaxis, based on level B evidence. Improving brain energy metabolism may reduce the susceptibility to migraine when brain energy demand increases due to both physiological and biopsychological factors.

**Keywords** Migraine · Mitochondria · Riboflavin

## Introduction

Although pathophysiology of migraine is still uncertain, brain energy metabolism in migraine has been found to be disturbed. There are evidences that in migraine, neuronal dysfunction is present and that brain of migraineurs is hyperexcitable. These data are suggestive for a possible abnormal brain energy activity, both during and between migraine attacks [1].

This fascinating theory is supported by a large line of evidence (Table 1).

In example, migraine patients show a lack of habituation (unchanged or increased response to repetitive stimulation), possibly due to an increased cortical excitability or a reduced intracortical inhibition [2].

It is conceivable that the continuous interaction between excitatory and inhibitory neurons determines the "cortex excitability threshold" leading to a sort of oscillation between the two excitability poles [3]. This mechanism is possibly related to mitochondrial activity. Mitochondria are bacterium-size organelles found in all mammalian cell, functioning both to produce adenosine tri-phosphate (ATP) via the electron transport chain and reactive oxygen species (ROS). They also regulate calcium homeostasis and apoptosis [4]. In case of brain mitochondrial dysfunction, impaired oxidative metabolism could lead to a diminished energy production, leading to a disturbance in cortex excitability [5]. In fact, brain is highly dependent on oxidative metabolism. This altered mitochondrial metabolism could affect migraine susceptibility lowering the threshold for propagation of migraine attack (i.e., cortical spreading depression) (Table 2). This could be explained by mitochondrial activity disregulation leading to impaired cellular ion homeostasis (particularly of calcium), membrane instability with raising neuronal transmembrane potential and more easily depolarizable neurons in case of adequate triggering stimuli. Several mechanisms may be involved (Table 3).

## Mitochondria and migraine: an intriguing evidence

A great number of biochemical and phosphorus magnetic resonance spectroscopy studies have shown that functionality of mitochondria in migraine patients is impaired with specific patterns of metabolic abnormalities. The biochemical evidence of impairment in NADH dehydrogenase and cytochrome-*c* oxidase in patients affected by migraine

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**Table 1** Brain hyperexcitability in migraine

| |
|---|
| Interictal brain abnormal information processing |
| $CO_2$ hyper-reactivity |
| Enhanced photic driving and enhanced visual stimulation |
| Lower threshold for generation of phosphenes on Transcranial Magnetic Stimulation (TMS) |
| Abnormal habituation on auditory evoked potentials |

**Table 2** The link between impaired mitochondrial activity and migraine

| |
|---|
| Mitochondrial dysfunction (abnormality of oxidative metabolism) → decreased ATP production and energy metabolism → imbalance in calcium ions → increase of neuronal excitability → disturbance of neuronal information processing → decreased migraine threshold → triggering of cortical spreading depression |

**Table 3** How can a primary brain mitochondrial defect possibly reduce the threshold for migraine?

| |
|---|
| Reduction of mitochondrial energy reserve may lead to a local rise in lactate concentration. This mechanism may be enhanced by the coexistence of habituation defect in sensory processing. The imbalance of brain metabolic homeostasis might trigger the trigeminovascular system |
| The sensitivity of meningeal blood vessels to exogenous stimuli (dietary or nitric oxide) may be due to mitochondrial abnormalities in the wall of meningeal blood vessels |
| A functional mitochondrial defect (primary or secondary) confined in several brain areas (heteroplasmic defect) may enhance neuronal excitability if restricted in brainstem structures or trigeminal nerve nucleus |

was detected, as well as the lower platelet levels of superoxide dismutase in patients affected by migraine with aura [6, 7]. These data are suggestive for a vulnerability to oxidative stress. In other studies, energy failure was associated to decarboxylase enzymes shift and increasing levels of neuromodulators tyramine, octopamine and synephrine [8]. With phosphorus magnetic resonance spectroscopy (a technique used to evaluate brain energy metabolism in vivo) it is possible to detect the intracellular concentration of phosphocreatine (PCr), adenosine diphosphate (ADP) and inorganic phosphate (Pi). In migraine patients, low PCr–Pi ratios (a measurement of intracellular energy status and mitochondrial functionality) and high levels of ADP (showing a lower energy reserve in neurons) were demonstrated, confirming a low availability of free energy and an unstable metabolic state in the brain of migraineurs [9, 10]. This could lead to a diminished ability to cope with increased energy demand. The intriguing question whether these abnormalities are an effect of brain hyperexcitability or are consequences of primary mitochondrial disregulation is still unsolved. In other words, the cause of impaired energy metabolism is debatable: is it primary or secondary to causative factors such as ion channel disorders or reduced magnesium concentration? Anyway, the predilection of maternal inheritance of migraine makes a mitochondrial etiology particularly reliable. Genetic studies on full mitochondrial DNA are suggested to detect a possible role of mitochondrial-related gene in migraine.

## Riboflavin: the possible connection

Riboflavin, or Vitamin B2, is a water-soluble precursor to coenzymes, flavin mononucleotide (FMN) and flavin–adenosine–dinucleotide (FAD), both of which are of pivotal importance for electron transport in mitochondrial complex I and II. These so-called "yellow enzymes" have the role to transport hydrogen and are fundamental not only in the degradation of a great number of substrates such as amino acids, fatty acids and purines but also particularly in the oxido-reduction reactions of the mitochondrial respiratory chain. Riboflavin is considered a vital component of mitochondrial energy production. It is particularly important to normal production of ATP, leading to membrane stability and sustaining adequate energy-related cellular functions. The evidence that riboflavin is able to improve both biochemical and clinical abnormalities and reduce the frequency of migraine attacks in a subgroup of patient with MELAS, and other mitochondrial diseases provided a theoretical basis to utilize Vitamin B2 as a compound able to replete mitochondrial energy stores in migraineurs, enhancing mitochondrial function and efficiency [11, 12]. In fact, riboflavin directly influences the activity of mitochondria respiratory chain flavin-dependent respiratory enzymes affecting mitochondrial phosphorylation.

The maximal dose of riboflavin absorbable from a single dose is 27 mg with saturation of absorption reached at 30–50 mg. Half-life of riboflavin is about 1 h [13].

First report (open-label study) concerning the successful use of riboflavin in migraine prophylaxis was published in 1946 [14]. Years later, in 1994, another open-label study confirmed the improvement of migraine severity in 68.2 % of patients treated with riboflavin 400 mg daily both alone and in association with Aspirin 75 mg [15]. This result was replicated in another open-label study [16]. Most recently, in a third open-label trial, 62.5 % of a sample of adult patients affected by migraine were responsive to riboflavin (400 mg daily for 4 months), particularly if not carrying mitochondrial DNA H haplotype (an haplogroup particularly found in the European population). The presence of aura was not associated with riboflavin effectiveness.

These results suggested that response to riboflavin might be influenced by mitochondrial DNA haplogroups [17].

Two small RCTs in adult patients have valuated the efficacy of riboflavin for the prophylaxis of migraine. First well-designed RCT compared placebo to riboflavin (duration 4 months), showing the superiority of riboflavin in reducing the frequency of attacks (50 % reduction in 59 % of patients compared to 15 % for placebo, number needed to treat of 2.8). Minor adverse events (polyuria and diarrhea) were reported in the treatment group. A common side effect is a bright yellow discolouration of the urine [18]. In the second study, a combination of riboflavin (400 mg), magnesium and feverfew was compared with low-dose riboflavin (25 mg daily). Results showed no difference between groups in the outcomes measures [19].

Based on these literature data (although classified of low quality), the American Academy of Neurology Guideline concludes that riboflavin is probably effective in the prophylaxis of migraine in adults, based on level B evidence [20]. The Canadian Headache Society strongly recommends the use of riboflavin in adults affected by migraine based on very low side effects profile and promising clinical results [21].

An RCT study in pediatric patients affected by migraine (4 months of treatment) compared high-dose riboflavin (at least 200 mg/day) to placebo in migraine prevention. Results showed no statistically significant difference in the responder rates, although the placebo rate was particularly high (66.6 %) [22]. This negative result could be explained by methodological issues. Admittedly, this study was not powered to detect a small or moderate statistical difference between active and placebo groups (possible bias in sample size calculations). An open-label study in pediatric patients (in this group severely affected patients were represented) suggested that high-dose riboflavin (200 or 400 mg on a daily basis for 3–6 months) may be effective in migraine, particularly in boys. The results showed that 68.4 % of the included patients had a reduction of 50 % or more in the frequency of attacks with same response rates of two dosages [23]. A subsequent RCT cross-over study addressed the effectiveness of a 50 mg/day dose of riboflavin (4 months of treatment) in the prevention of migraine in a small group (42 subjects) of pediatric patients (age 6–13 years) [24]. The results were not statistically significant (no difference in migraine duration, frequency and severity between the two groups), possibly due to the suboptimal low dose of riboflavin if compared with other studies.

Based on these study results, riboflavin is not recommended for the prophylaxis of pediatric migraine. To understand this failure in pediatric population, we have to consider that the once daily dosing used in the literature could be possibly not sufficient to achieve and maintain adequate steady-state levels of riboflavin (the half-life is about one hour) in order to sustain a definite preventive activity for migraine. Further studies with multiple daily dosing and correct administration (the absorption of riboflavin is diminished if taken on an empty stomach) are to be planned to investigate why the effect of riboflavin is defined in adults, but not achieved in pediatric population.

## Conclusion

Migraine attacks may be sustained by an impaired oxidative metabolism, leading to the "threshold character" of migraine pathology. Mitochondria have a pivotal role in this energetic imbalance, by influencing neuronal processing and excitability, making the migrainous brain hyper-responsive to several different stimuli. High-dose riboflavin might be helpful in reducing this impairment, overcoming the mitochondrial disturbance. Results in RCT studies are encouraging in adults affected by migraine, suggesting this well-tolerated treatment as a favorable option. More studies with adequate methodologies are needed to investigate the efficacy of riboflavin in children affected by migraine. Approaching independent mechanisms of migraine pathophysiology with a rational polytherapy addressing the multiple aspects of the disease might be a successful option. Riboflavin could be considered for future combination in migraine treatments, so-called pharmacological synergy, considering the abundant scientific evidence supporting the theory of a mitochondrial disturbance enhancing migraine disorder.

**Conflict of interest** I certify that there is no actual or potential conflict of interest in relation to this article.

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SESSION IV UNCONVENTIONAL TREATMENTS

# Complementary and alternative medicine (CAM) use in an Italian cohort of pediatric headache patients: the tip of the iceberg

**D. Dalla Libera · B. Colombo · G. Pavan · G. Comi**



**Abstract** The use of complementary alternative medicine (CAM) in paediatric populations is considerably increased, especially for pain and chronic conditions, as demonstrated by epidemiological surveys both in Europe and in the USA. In our study, CAM was used in 76 % patients of a cohort of 124 children affected by headache (age 4–16 years; 67 % female; 70 % migraine without aura, 12 % migraine with aura, 18 % tensive headache according to IHS criteria) consecutively recruited at a Pediatric Headache University Center. CAM was used as preventive treatment in 80 % cases. The main reasons for seeking CAM were: the wish of avoiding chronic use of drugs with their related side effects, the desire of an integrated approach, the reported inefficacy of conventional medicine, and a more suitable children disposition to CAM than to pharmacological compound. Female gender, younger age, migraine without aura, parents' higher educational status, maternal use of CAM and other associated chronic conditions, correlated with CAM use ($p < 0.05$). 73 % patients chose CAM also to treat other diseases (i.e. allergies, colitis, asthma, insomnia, muscle-scheletric disorders and dysmenorrhoea). The most assumed CAM were: herbal remedies (64 %) such as Valeriana, Ginkgo biloba, Boswellia serrata, Vitex agnus-castus, passion flower, Linden tree; vitamins/minerals supplements (40 %) with magnesium, 5-Hydroxytryptophan, vitamin B6 or B12, Multivitamin compounds; Homeopathy (47 %) with Silicea, Ignatia Amara, Pulsatilla, Aconitum, Nux Vomica, Calcarea phosphorica; physical treatment (45 %) such as Ayurvedic massage, shiatsu, osteopathy; yoga (33 %); acupuncture (11 %). CAM—often integrated with conventional care—was auto-prescribed in 30 % of the cases, suggested by non-physician in 22 %, by the General Practitioner in 24 % and by paediatrician in 24 %. Both general practitioners and neurologists were mostly unaware of their patients' CAM use. In conclusion, neurologists should inquire for CAM use and be prepared to learn about CAM therapies or to directly interact with CAM trained experts, in order to coordinate an integrative approach to health, as especially required in paediatric headache patients and their parents. Further studies are required to investigate safety and efficacy of CAM in pediatric headache, as a possible side-medicine to conventional pharmacological approach.

**Keywords** Migraine · Complementary and alternative therapy (CAM) · Pediatric · Headache · Integrative medicine

## Introduction

The National Institutes of Health defines complementary and alternative medicine (CAM) as "a group of diverse medical and health care systems, practices, and products that are not generally considered conventional medicine". In the general population, chronic pain is among the main reasons for CAM use [1–5]. A survey of CAM providers in the UK revealed headaches as the second most frequently quoted condition believed to benefit from CAM [6]. In

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recent years, CAM use has increased considerably also in pediatric populations, especially for chronic conditions such as pain, headache, attention deficit hyperactivity disorder, asthma, colic and emotional distress. A recent USA cross-sectional survey data pointed out that youth aged 10–17 years old who experience headache have a 2.1 times greater likelihood of using CAM compared with youth who do not experience headache [7–9].

As neurologists concerned with treating pediatric headache know, parents often request behavioral treatment either in addition or as an alternative to pharmacologic treatment for their children, including recommendations on lifestyle, diet, sleep habits, and stress management strategies [10].

Several strategies different from the merely pharmacological ones have been proved with good results, such as the use of cognitive behavioral therapy which, in combination with amitriptyline, was demonstrated to reduce days with headache and migraine-related disability than the drug alone [11, 12].

Many young headache patients suffer significant functional disability, with a worse school, physical and psychosocial and emotional quality of life, especially if their headache is associated to other chronic conditions, and they are seeking for alternative options to pharmacological treatment [10, 13].

A variety of herbs and other supplements (such as Ginkgo biloba, magnesium, Tanacetum parthenium, Petasites hybridus root, Boswellia serrata) have already been largely studied for headache treatment [14–17]. In parallel, alternative medical systems, body-work therapies and mind-body therapies (yoga, relaxation, meditation, cognitive-behavioral treatment) have shown to provide benefit in both adults and youth, probably by affecting emotional and neural substrates and balancing hyperexcitability [18].

In literature, few surveys focused on patterns of use of CAM in children and adolescents affected by migraine. The aim of our study was to investigate the prevalence, the pattern, the reasons for and the predictors of CAM use in pediatric headache setting.

## Materials and methods

### Patients collection

One hundred twenty-four children, aged 4–16 years (median age 12 years), mostly female (67 %) were consecutively recruited at the Paediatric Headache Centre of San Raffaele Hospital in Milan Italy, in 1 year. They all came from a metropolitan area around Milano, 90 % were white Caucasian, 5 % Asian and 5 % Africans.

Children were evaluated by expert neurologists and their headache was classified according to the International Classification of Headache Disorders (IHS) as follows: 70 % migraine without aura, 12 % migraine with aura, 18 % tensive headache (ICHD-II).

The young patients, together with their parents, underwent a semi-structured interview, during their first admission to San Raffaele Headache Centre, regarding type, modality, reasons for, perceived benefit, lifetime experience and attitudes with CAM.

### Statistical analysis

A descriptive statistics was performed concerning prevalence of features associated with headache. All data were reported as median and interquartile range (IR) because non-gaussian distributed. Mann–Whitney *U* test and Kruskall–Wallis test with Dunn's multiple comparison test were used as appropriate. Spearman's rank test was used to test correlations between variables. GraphPad Prism 4, GraphPad Instat 3 and SPSS (Statistical Product and Services Solutions, version 11.5; SPSS Inc., Chicago, IL, USA) software were used for analysis. A probability value $<0.05$ was considered significant.

## Results

Findings from the survey showed that CAM was used by 76 % of young patients and 43 % of them chose more than one CAM modality in order to improve their headache.

The most commonly used CAM were: herbal remedies (64 %) such as Valeriana, Ginkgo biloba, Boswellia serrata, Vitex agnus-castus, passion flower, Linden tree, Helichrysum; vitamins/minerals supplements (40 %) with magnesium, 5-hydroxytryptophan, vitamin B6 or B12, multivitamin compounds; Homeopathy (47 %) with Silicea, Ignatia Amara, Pulsatilla, Aconitum, Nux-vomica, Calcarea phosphorica; physical treatment (45 %) such as Ayurvedic massage, shiatsu, osteopathy; Yoga-Therapy (33 %); Bach Flowers (16 %), Aromatherapy (14 %) with Ginger essential oil, lavender, sandalwood, eucalyptus, peppermint, rosemary; acupuncture (11 %).

Most patients experience CAM as preventive treatment (80 % patients; median time of use: 12 months), 5 % for acute "on demand" therapy and 15 % for both. Interestingly, CAM were often used not directly as a remedy for headache, but for a better management of stress, which is considered as one of the most relevant precipitating factors of migraine by patients themselves.

A multi-combined approach of CAM with standard care was present for 58 % patients.

Reasons for CAM adhesion were: the wish of avoiding chronic use of drugs with their related side effects (70 % patients), the desire of an integrated approach (52 %), the

reported dissatisfaction with current conventional medicine (32 % patients), or a more suitable youth disposition (20 %).

The following headache features correlated with CAM use: pain defined as mild-to-moderate, attacks frequency minor than 4 and higher than 15 attacks per month, other associated chronic conditions (asthma, sickle cell disease, arthritis). Furthermore, patients with the higher number of medical examinations per year were more easily prone to CAM use, in comparison to those who rarely visit doctors.

The main CAM users were patients affected by migraine without aura (53 %), followed by those with tensive headache (38 %). Female gender, younger age, parents' higher educational status correlated with CAM use ($p < 0.05$), while no differences for parents occupation were evident. Religious aspects have not been investigated—such as in other papers on CAM—since most of the patients declare themselves religious (especially catholic). A higher prevalence of CAM was also related to a familiar healthy preventive lifestyle (sports, no smoking or alcohol intakes, attention to nutrition). Furthermore, 80 % patients using CAM had a familiar history of headache: in 65 % there was also a history of familiar (mostly maternal) CAM usage. A correlation with prior use of CAM for other medical reasons and current CAM administration for headache was evident ($p < 0.001$). In fact, 73 % of the patients used CAM also to treat other diseases (55 % for anxiety, 52 % for allergies, 31 % for colitis, 39 % for respiratory disorders, 23 % for insomnia, 20 % for muscle-scheletric disorders and 18 % for dysmenorrhoea).

Exploring the referral source of CAM, it resulted that CAM was auto-prescribed in 30 % of the cases and bought in pharmacies (40 %), supermarket (20 %) or online (40 %); suggested by non-physician in 22 %, by the General Practioner in 24 % and by paediatrician in 24 %. Surprisingly, only 25 % of the patients were assessed by physicians certified as CAM experts.

Of note, most of the patients did not spontaneously declare of assuming CAM if not precisely inquired by the clinician. They also admitted to be positively impressed if their neurologists were acknowledged about CAM and could providing any specific suggestion, considering it a reason to come back for follow-up.

Even if it was out of the aim of the study to evaluate evidence for efficacy of CAM approaches, we can report a self-reported perceived benefit on headache in 57 % of the cases. No adverse events or side effects were described except for two cases (transient diarrhoea with magnesium, excessive sedation with Valeriana).

## Discussion

The attitude towards CAM of young patients suffering from headache and their parents is mainly positive. The use of CAM is widespread and the more chronic is the headache, the more likely CAM will be a treatment option. CAM is not usually taken instead of conventional care, but in addition to it. Exploring parents' perspectives toward complementary and alternative medicine, we discovered that CAM usage is particularly motivated by fear of side effects and dissatisfaction with conventional therapies. Moreover, parents regarded CAM as an headache preventive treatment. Prevention in the pediatric setting is an issue by far more developed than in adults medicine, both for the necessity of avoiding a possible later chronicization of the disease and for the existing fear of pharmacological side effects of over-the-counter medications and of long-term pharmacological treatment. Thus, CAM is used for coping with putative headache triggers such as emotional distress, infections and insomnia. It is known that acute and chronic pain in children is frequently complicated by the complex psychological components of pain perception, according to the "neurolimbic pain networks" theory and CAM may be useful for modulating emotion and the balance of the interoceptive system, and consequently functional connectivity [18].

Interestingly enough, even if CAM is not covered by national insurance systems, users pay almost all costs out of pocket, suggesting their belief that CAM therapies have benefits may outweigh their costs. This fits well to user profile, as found by a majority of authors, who discovered that being female, of younger age, coming from a higher parental levels of education, interested in healthy preventive lifestyle, were facts predictive of CAM use.

Patients are very prepared to CAM, despite the lack of scientific studies confirming efficacy or possible side effects, and they are prone to use it even if it is not proposed by a physician. According to a previous work, more than 50 % of adults with migraines/severe headaches did not discuss CAM use with their health care provider [4]. This findings may compel neurologists concerned with headache to inquire and learn about CAM therapies or to directly interact with CAM trained experts, in order to coordinate an integrative approach to health and promote well-being.

Admittedly, this pilot study has a limited sample size, reducing its specific power: patients attending a tertiary university center may be a special subset of headache sufferers. We are taking into account just the tip of the iceberg, since we are not considering patients who preferentially use CAM and do not come to headache clinic for consultation and patients who prefer not declaring CAM usage, afraid of being negatively judged from conventional physicians. According to our data, two wide national surveys survey from United Stated examining CAM use among representative samples of youth outside an headache clinic, who experience headache found that 29.6 %

used CAM (mostly biologically based products and mind-body therapies), rising to 41 % for the headache sufferers who also experienced difficulties with emotions, concentration, behaviour, school attendance, or daily activities and rising even more for patients with other chronic conditions [7].

CAM therapies are estimated helpful by most patients, who would appreciate to have more information and prescriptions of CAM. Neurologists should pay attention to the possible interactions between CAM and conventional medical treatments for headache and their possible adverse events. However, the great diversity of methods, therapies, dogmas on CAM, and the concept of a personalized treatment make studies design difficult. Further additional studies are needed on CAM in children, in order to identify who exactly will benefit from it.

## Conclusion

CAM is attracting more and more attention within health care, especially among people with headache and migraine, even if neurologists are often unaware and underestimated their use. The identification of a user profile showed that being female, of younger age and with a higher parents' educational levels are predictive of CAM use. Thus, continuing education is important to ensure that neurologists, paediatricians and general practitioners acquire a good knowledge on CAM therapies, so that they will be ready to face proper individualized counseling of children and their parents on CAM. Further studies are required to investigate safety and efficacy of CAM in pediatric headache, as a possible side-medicine to conventional pharmacological approach.

**Conflict of interest** I certify that there is no actual or potential conflict of interest in relation to this article.

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# Higher burden of migraine compared to other neurological conditions: results from a cross-sectional study

**Matilde Leonardi**



**Abstract** Headache disorders are prevalent, burdensome and costly. However, it is difficult to get an idea of how much of a burden do they cause if they are not compared with other conditions. Using data from PARADISE project, we compared 80 migraineurs and 80 patients similar for age, gender and work condition. Our results showed that the amount of psycho-social difficulties was higher among patients with migraine than among patients with epilepsy, stroke, multiple sclerosis or Parkinson's disease.

**Keywords** Disability · Migraine · Burden of disease · Psycho-social difficulties

## Introduction

Headache disorders are prevalent: most adults have suffered from one or more types during the last year and the global burden of headache is large [1]. The most common types are tension-type headache (TTH), migraine and medication-overuse headache (MOH), that are associated to different disease cost [2]. The Global Burden of Disease Survey 2010 confirmed that headache disorders are among the top 10 causes of disability worldwide [3], a finding that was also described by Stovner and colleagues earlier [4]. It is, paradoxically, a widely ignored burden as stated by the World Health Organization (WHO) in the Atlas of Headache Disorders and Resources in the World 2011 [5, 6].

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Published evidence indicates that migraine is the most costly neurological disease for European society [2, 7, 8], although there are large variations in the cost estimates across the countries where data are available [9]. These are probably due mainly to differences in methodology and periods of time over which estimates have been made. For example, most investigators have used a 'top-down' approach, which carries the risk of underestimating or omitting cost items that are not fully captured in national statistics. Moreover, most studies were conducted before the impact of triptans on both direct and indirect costs [10]. The general opinion is that available estimates of the cost of migraine in Europe are likely to be underestimated [2, 4].

Given their high prevalence, it has been suggested that non-migrainous headache disorders are at least as costly as migraine [7]: yet, the economic impact of TTH and MOH in Europe has been largely unknown, and these disorders have been omitted from estimates of the cost of brain, and only recently addressed by the Eurolight project [2]. Therefore, the actual total cost of headache in Europe is unknown, and in light of headaches disorders magnitude and of the burden that they cause, this constitutes a major paradox.

Disability attributed to headache is also difficult to quantify completely. Common proxies are lost time and reduced productivity, for which well-validated instruments exist [11, 12]. In a recent article, Steiner and colleagues [13] presented the development of HARDSHIP, a questionnaire aimed to study the burden of headache in multiple countries. Different parts of the questionnaire investigated different issues relevant to describe the burden. The evaluation of the burden in an intermittent diseases such as headaches and migraine, in particular, poses the issue of reliability of recall for the patients. In the HARDSHIP questionnaire burden questions have commonly been

limited to a 3-month timeframe as a compromise between the limits of recall and the purpose of enquiry. When the latter is the assessment of an individual patient for therapeutic reasons, the period must be long enough to be representative of that individual. In large-group studies, this is quite unnecessary: different considerations apply, because population—rather than individual—representativeness is sought. The authors support the idea that burden arises also in interictal periods and they focus also on questions able to evaluate the burden between attacks. In fact interictal burden arises because headache attacks are unpleasant, and those who experience them frequently are likely to worry about when the next may occur, and attempt to eliminate possible triggers through lifestyle compromise. Interictal burden, which is continuous, is likely to affect subjective well-being and may be sufficient to impair quality of life. Steiner and colleagues conclude that the cumulative burden due to headaches, accruing over a lifetime, cannot be fully assessed until late in a lifetime. Furthermore, attribution may be uncertain. Nevertheless, a consequence of recurring inability to work may be decreased probability of promotion, and a consequence of lost school-time may be reduced career opportunities [13].

To have an idea of the importance of the burden of headaches it is also useful to compare it towards other neurological disorders that are a public health problem too. What are the psycho-social difficulties of migraine? How much do these difficulties cause an impact on the person or on the society? To better understand these issues it is important to compare with the approach of Horizontal epidemiology how heavy is a disease when compared to others with similar public health final impact.

## Methods

The study was carried out in the context of PARADISE Project (Psychosocial fActors Relevant to BrAin DISorders in Europe), funded under by the European Commission and designed to develop a strategy and a protocol for documenting and analyzing information about the epidemiology of psycho-social difficulties in a broad and heterogeneous range of neurological diseases. Subjects participating in PARADISE study were enrolled if they had a diagnosis corresponding to migraine (with or without aura), epilepsy, stroke, multiple sclerosis or Parkinson's disease. For each condition, 80 patients were enrolled.

The protocol included a list of 64 PSDs addressing impairments in mental and neurological system-related functions, as well as activities referring to mobility, communication, self-care work and household duties. For each item a 1–5 response scale from no problem/difficulty to extreme problem/difficulty is available.

**Table 1** Main demographic and clinical variables

| | Migraine sample | Non-migraine sample |
|---|---|---|
| Gender (F/M) | 69/11 | 69/11 |
| | Chi square: 0.00 | |
| Employment (work/non-work) | 57/23 | 57/23 |
| | Chi square: 0.00 | |
| Age (mean ± SD) | 44.5 ± 12.1 | 44.2 ± 5.8 |
| | *t*: 0.21 ($P = .835$) | |
| Migraine (with aura/without aura) | 13/67 | – |
| Epilepsy | – | 22 |
| Multiple sclerosis | – | 33 |
| Stroke | – | 18 |
| Parkinson's disease | – | 7 |
| Disease duration | 21.2 ± 14.6 | 9.7 ± 10.9 |
| | *t*: 5.62 ($P < .001$) | |

### Data analysis

A post hoc selection of patients similar for age, gender and work condition was made: independent sample *t* test and Chi square were used to verify the match between migraineurs and non-migraineurs. Demographic and clinical variables are presented as frequencies or percentages, and using mean ± SD for continuous variables.

The most frequent PSD (i.e. those reported by more than 50 % of the patients) were analysed: Chi square was used to assess the relationship between having migraine vs. other neurological conditions and having vs. not having impairments or difficulties in the selected PSD.

## Results

Main demographic and clinical variables are reported in Table 1, together with *t* test and Chi square used to assess similarity of the two groups: the only difference was with average disease duration.

Seventeen PSD were reported as a problem in more than 50 % of patients. Figure 1 reports the two most commonly reported PSD together with Chi square analysis showing difference between migraineurs and patients with the other neurological conditions. With the exceptions of mood swings and sensation being a different person to the disease, migraineurs always reported an higher prevalence of PSD and the difference was particularly important for the following: sensation of not being rested; sensation of being unable to find the words to say what the respondent is thinking; sensory disturbances, e.g. hypersensitivity to light or noise blurred or double vision; bodily ache ($P < .01$);

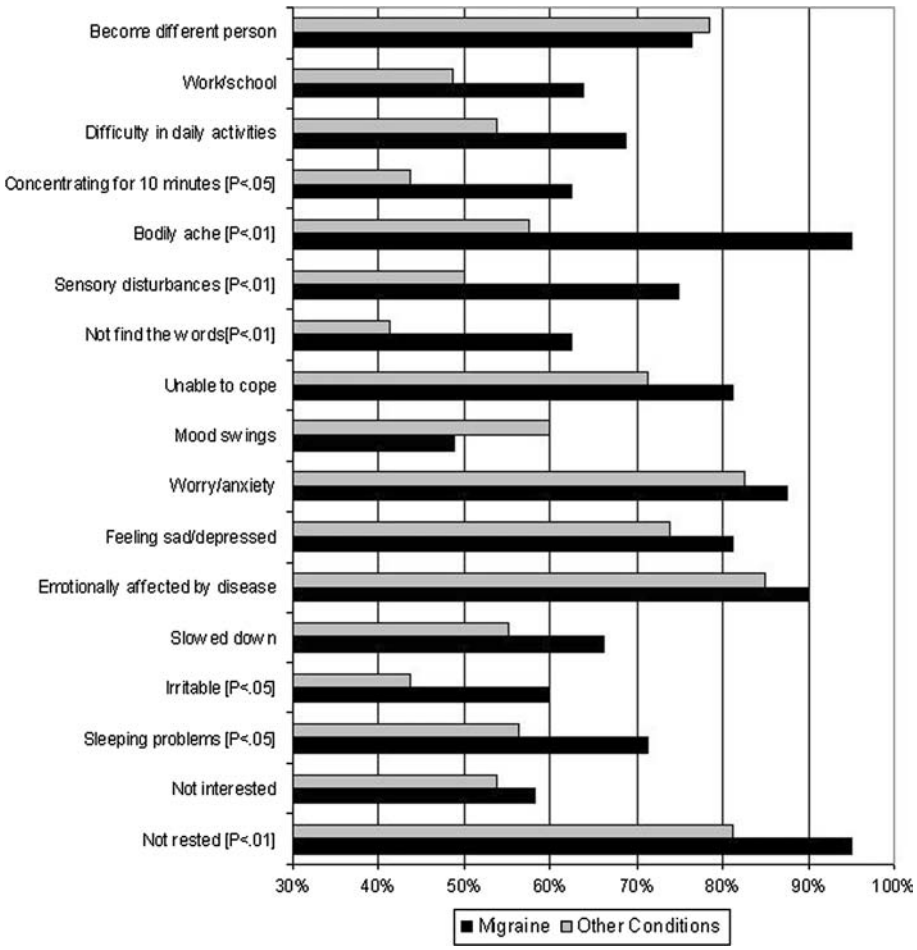


**Fig. 1** Difference between migraineurs and patients with other condition for the most prevalent PSDs

sleeping problems; irritability; difficulties in concentrating for ten minutes ($P < .05$).

## Discussion

This study showed that, in a group of migraineurs matched patients with other neurological conditions for age, gender and employment, the amount of PSDs was higher among patients with migraine.

The burden and the public health impact of headaches are then a combination of multiple factors. Public health is defined as the science and practice of protecting and improving the health of the population through prevention, promotion, health education, and management of diseases including neurological disorders. In other words, public health is viewed as a comprehensive approach concerned with the health of the community as a whole rather than with medical health care that deals primarily with treatment of individuals. In this perspective it is important to evaluate the burden of the disease; thus its impact and its societal costs, considering the bio-psychosocial model of health and disability that defines disability as an interaction of a person's disease and his/her environmental factors. PARADISE gave the opportunity to test the hypothesis of commonalities, both in PSDs and their determinants. This hypothesis was called 'horizontal epidemiology'to highlight the difference from the standard, brain disorder-specific, silo-like, or vertical approach. This kind of epidemiology allows to make comparison between the elements that are between the main causes of burden in several diseases. What these data add to the known burden of migraine and headache disorders is the comparison of PSD in migraineurs and in a selected group of patients with other neurological disorders: this comparison clearly show that for several PSDs, prevalence among migraineurs is higher.

Limitations to this study include the limited sample size and the non-homogeneity across conditions: therefore, caution should be used before generalising these data.

In conclusion, we compared PSDs as measure of disease burden among migraineurs and patients with other neurological conditions: our preliminary data show that the lived experience of disease burden is higher among migraineurs.

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# Post-traumatic headaches: a clinical overview

**A. Russo · F. D'Onofrio · F. Conte · V. Petretta · G. Tedeschi · A. Tessitore**



**Abstract** Headache attributed to head and/or neck trauma or injury, the so-called post-traumatic headache (PTH), is the most common secondary headache disorder and one of the most controversial clinical entities in the headache field, due to its unclear pathophysiological mechanisms and the unsolved role of associated psychological and medico-legal aspects. PTH, as a significant cause of morbidity after traumatic brain injury, may occur as an isolated symptom or as one of a constellation of symptoms known as post-concussive syndrome. However, in many cases, PTH might also represent an accentuation of non-disabling, remote or infrequent pre-existing primary headaches rather than a new onset headache strictly related to the trauma. Recently, the International Classification of Headache Disorders attempted to classify PTH; however, many unsolved issues are still to be clarified. In this brief review, we will focus on PTH clinical aspects and diagnostic criteria.

**Keywords** Post-traumatic headache · PTH · Clinical aspects · Whiplash injury · Trauma

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## Clinical aspects

Headache attributed to trauma or injury to the head and/or neck [1], so-called post-traumatic headache (PTH), is one of the most controversial clinical entities in the headache field due to its unclear pathophysiological mechanisms and the unsolved role of associated psychological and medico-legal aspects [2, 3]. Its pathophysiology may be related to acute increases in excitatory neurotransmitters after a traumatic brain injury (TBI) due to direct or indirect forces to the head, causing a critical mismatch between the energy supply and the demand [4, 5]. Nevertheless, immune-excitotoxicity processes may also be playing a central role in PTH. Indeed, the interaction between brain immune receptors and excitatory glutamate receptors could cause dendritic retraction, synaptic injury, damage to microtubules and mitochondrial suppression [6]. Furthermore, several structures, in addition to brain, could be damaged by trauma or injury to the head and/or neck such as vertebrae, facet joints and nerves. For example, whiplash-associated headache (WAH) is caused by a cervical injury due to significant acceleration-deceleration movements [2, 3]. Finally, although neglected, meningeal irritation due to craniotomy represents an important cause of PTH [7]. Each structural injury may lead to a different phenotype of headache. For example, myofascial injury is likely to produce "tension-type like" headache, whereas nerves involvement, such as the occipital nerve damage, may result in neuralgic pain. However, PTH phenotype is not well established and shares clinical characteristics with different primary headaches [8, 9] albeit migraine-like and tension-type headaches are considered predominant [10–14]. Rarely, PTH could be phenotypically similar to hemicrania continua, chronic paroxysmal hemicrania and SUNCT syndrome.

PTH is often secondary to motor vehicle collisions followed by falls, occupational, sports and recreational accidents, and assaults [15], although different risk factors have been suggested for onset, increased duration and slower recovery, such as female gender, lower socioeconomic status, unstable pre-injury work history and pre-existing psychopathology or pre-morbid personality [10–14].

PTH, as a significant cause of morbidity after TBI, may occur as an isolated symptom or as one of a constellation of symptoms falling into four distinct clusters (somatic, sleep, cognitive, and emotional) known as post-concussive syndrome (PCS) [16]. PTH as a symptom of PCS is likely to have the most negative impact on function and participation in work and social activities [17–20]. Interestingly, the relationship between TBI intensity and resulting degree of functional impairment due to PTH severity has never been conclusively established, and several studies demonstrated a poor or inverse correlation between TBI severity and persisting PTH, but the reasons of this phenomenon are still unclear [21, 22]. Similarly, the role of an expectation or a litigation for PTH in promoting headache development and persistence is under debate. Several authors have highlighted an higher PTH incidence in countries characterized by medico-legal compensation systems and a lower PTH incidence in countries without insurance systems that remunerate patients for injury [15]. In many cases, PTH may represent an accentuation of non-disabling, remote or infrequent pre-existing primary headaches rather than a new onset headache strictly related to TBI [2, 3, 7]. Quite different is the case of post-traumatic cluster headache (CH). Indeed, CH patients seem to be characterized by a risk-taking lifestyle that, likely, may predispose to TBI [23–25].

In PTH secondary to mild TBI, conventional neuroimaging studies such as computed tomography or magnetic resonance imaging (MRI) did not show identifiable abnormalities [26]. However, a recent diffusion tensor imaging study demonstrated that mild TBI may alter the diffusion of water molecules in white matter pathways, specifically in fronto-striatal and fronto-limbic circuits. Furthermore, fiber-tracking and tract-specific analyses demonstrated a midbrain and brainstem involvement [27]. Although functional MRI approaches have not been systematically applied to PTH, according to previous studies in subjects with TBI, whole-brain functional connectivity abnormalities in default mode network, fronto-parietal network or in migraine related structures have been demonstrated [28, 29].

Overall, PTH should be considered a serious medical and socioeconomic problem that must be adequately addressed. Indeed, there are different pitfalls in the PTH management, such as the risk of medication overuse, the presence of significant co-morbidity and the co-existence of legal procedures related to TBI. The risk of development in chronic headache should be early identified in PTH patients to prevent "pain-killers" overuse that could contribute to pain persistence due to medication overuse [13, 14, 20]. The presence of co-morbidity may represent an obstacle to PTH therapy, because PCS symptoms (such as post-traumatic sleep disturbances, mood disturbances and psychosocial stressors) could, in turn, influence headache development and perpetuation. Finally, legal procedures may make difficult PTH long-term management and so the expectation of a medico-legal compensation in PTH patients should be closely examined, although headache resolution does not typically occur following legal settlements and the malingering could be a factor in only a small minority of patients [17–20].

Only few studies have examined PTH response to preventive and rescue treatment and no strong evidence from clinical trials is available, suggesting PTH management based on likeness of primary headache [30, 31]. Non-pharmacological treatments, including physical and psychological therapy, are often recommended [13, 20].

## ICHD-3 beta version classification

Recently, the Headache Classification Committee of the International Headache Society (IHS) [1] have classified three types of PTH subdivided into acute (5.1 acute headache attributed to traumatic injury to the head; 5.3 acute headache attributed to whiplash; 5.5 acute headache attributed to craniotomy) and persistent (5.2 persistent headache attributed to traumatic injury to the head; 5.4 persistent headache attributed to whiplash; 5.6 persistent headache attributed to craniotomy). Acute and persistent headache attributed to traumatic injury to the head have been further subdivided in two subtypes: "attributed to moderate or severe traumatic injury to the head" (coded as 5.1.1 and 5.2.1) or "attributed to mild traumatic injury to the head" (coded as 5.1.2 and 5.2.2). The first one should be considered when injury to the head is associated with at least one of: loss of consciousness for >30 min; Glasgow Coma Scale (GCS) score <13; post-traumatic amnesia lasting >24 h; alteration in level of awareness for >24 h; imaging evidence of a traumatic head injury such as intracranial haemorrhage and/or brain contusion. Previous ICHD-II category "headache attributed to traumatic intracranial haematoma" (concerning PTH secondary to subdural or epidural hematomas and subarachnoid haemorrhages) [32] has been included in the item "imaging evidence of a traumatic head injury". Conversely, previous acute or chronic "headache attributed to other head and/or neck trauma" [32] has not been contemplated in ICHD-III (beta version) criteria.

Based on ICHD-3 (beta version) classification, PTH starts within 7 days after trauma, whiplash, craniotomy or regaining of consciousness following the head injury and lasts, when it is classified as acute, for less than 3 months. For persistent PTH, the ICHD-3 (beta version) criteria require that the headache developed within 7 days after trauma, whiplash, craniotomy or regaining of consciousness following the head injury, should persist for more than 3 months. This time period is consistent with ICHD-II diagnostic criteria [32], although the term "persistent" has been adopted in place of "chronic". Nevertheless, despite the efforts by the IHS to classify and clarify PTH, many unsolved issues are still to be elucidated. While it is true that, for acute PTH diagnosis, a 7-day interval may provide an higher specificity supporting a stronger evidence of cause and effect relationship, diagnostic criteria provide a correlative loss of sensitivity. Indeed, the requirement that PTH must be reported to have developed within 7 days from trauma or injury is somewhat arbitrary and a longer latency between trauma or injury and PTH is indeed frequent. To overcome these limitations, alternative criteria have been suggested, in ICHD-3 (beta version) appendix, such as "delayed-onset acute headache attributed to moderate or severe traumatic injury to the head" and "delayed-onset acute headache attributed to mild traumatic injury to the head" if the interval between trauma or injury and PTH onset is greater than 7 days. Similarly, the distinction between acute and persistent PTH, in some authors' opinion, lacks sufficient pathophysiological reasoning [34]. The temporal definition of 3 months to distinguish between acute and persistent headache appears unusually short in PTH [35, 36] and a clear-cut period of more than 6 or 12 months would be more useful [37]. Finally, it would be useful to underline that ICHD-3 (beta version) diagnostic criteria suggest TBI severity subdivision in only two great categories including "mild traumatic injury to the head" and "moderate or severe traumatic injury to the head". In order to achieve a more accurate diagnosis, additional categories, such as very mild or very severe traumatic head injury should be critically considered [1].

## Conclusion

PTH is an important public health issue due to both its frequency and high burden of disability. Fortunately, the outcome for the majority of patients is that PTH spontaneously dissipates over a period of few days, weeks or months. Nevertheless, the lack of well-defined phenotype makes PTH recognition difficult to achieve by means of current diagnostic criteria and, similarly, clinical uncertainty and the presence of comorbid psychiatric disorders and litigation have contributed to lack of progress in biological understanding of PTH [26]. Future clinical studies will be needed (a) to evaluate, a clear-cut time point in which a change in headache features could clearly differentiate acute from persistent PTH, and (b) to well establish frequency and clinical features of PTH attacks, because, in a very heterogeneous disorder, the risk is that PTH definition may be extended to include a variety of different clinical entities. Furthermore, integrative epidemiological, biological, neuropsychological and imaging studies could be very useful in identifying pathophysiological mechanisms and diagnostic biomarkers of PTH morbidity and severity and, finally, to compare the relative efficacy of different pharmacological and non-pharmacological approaches.

**Conflict of interest** The authors certify that there is no actual or potential conflict of interest in relation to this article.

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ORAL COMMUNICATIONS

# Headache in a population of hospital workers

**G. Viticchi · L. Falsetti · P. Pettinari · L. Provinciali · M. Silvestrini · M. Bartolini**



**Abstract** Headache prevalence is very high, especially during working life. Hospital workers are expected to be particularly careful with health problems. Few data are available about the dimension of the headache-related problems among hospital workers, including disease awareness and diagnostic delay. 502 subjects employed in our hospital (doctors, nurses, technicians, administrative employees) were enrolled over a 3-month period and submitted to a questionnaire about the presence of headache, its characteristics and time spent from disease onset to diagnosis. We used the ID-migraine test, a validated tool, to obtain a correct migraine diagnosis based on a three-question test. Age and education were collected as continuous variables while the other variables (sex, presence of headache, presence of migraine, diagnosis put by the general practitioners) were encoded as binary. The difference of the distribution of the analyzed variables in tables was evaluated with $\chi^2$ test. The data were analyzed with SPSS 13.0 for Windows systems. In the analyzed population (mean age $40.15 \pm 11.0$ years; males 60.7 %), 216 patients complained of headache (43.1 %) and 77 (15.4 %) were diagnosed as migraineous at the in-hospital evaluation. Among the 216 cephalalgic patients, the majority (59.7 %, $p < 0.0001$ at $\chi^2$ test) did not refer to their general practitioner. Of the 77 patients affected by migraine, 55.8 % referred to their general practitioner, but only 27 (35.1 %) received a definite migraine diagnosis. Fifty subjects (64.9 %) were still undiagnosed and unevaluated at the moment of our survey ($p < 0.0001$ at $\chi^2$ test). Headache prevalence was very high in this population of hospital workers. Diagnostic errors and delays were frequent. Unexpectedly, self-awareness of the headache was very low. Headache, particularly migraine, is a relevant cause of loss of working days and low productivity. Our findings suggest the necessity to program initiatives aimed to raise the awareness of headache in order to improve diagnostic and therapeutic possibilities.

**Keywords** Migraine · Headache · Hospital workers · Self-awareness

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## Introduction

Headache is a high prevalent condition, especially during working lifetime. Several studies have shown that in Europe headache is among the most frequent cause of reduced productivity and absenteeism [1], with a mean annual cost of €1222 per person. Preliminary reports suggested that very often patients lack self-awareness of their headache, and they do not refer to their general practitioner or to a neurologist.

Hospital workers, even with different qualifications, are expected to be particularly careful with health problems. Few data are available about the dimension of headache-related problems in a hospital workers population including disease awareness and diagnostic delay.

## Methods

We consecutively enrolled subjects of both sexes employed in our hospital (University Hospital of Ancona) with different qualifications: doctors, nurses, technicians, administrative

employees and sanitary operators. We submitted them to a written questionnaire regarding the presence of headache and its characteristics; further, we investigated if subjects went to their general practitioners for their symptoms and the time spent from disease onset to diagnosis. We adopted the ID-migraine test, a validated tool to formulate a migraine diagnosis in primary care setting based on a three-question test [2]. Age and education were collected as continuous variables while the other variables (sex, presence of headache, presence of migraine, diagnosis put by the general practitioners) were encoded as binary. The difference of the distribution of the analyzed variables in tables was evaluated with $\chi^2$ test. The data were analyzed with SPSS 13.0 for Windows systems.

## Results

During a 3-month period, we enrolled 502 subjects employed in our hospital who filled in the questionnaire. The analyzed population presented a mean age of $40.15 \pm 11.0$ years; males represented 60.7 % of the population. Of the analyzed sample, 216 subjects presented a history of headache (43.1 %). According to ID-migraine test, 77 workers (15.4 %) were diagnosed as migraineous at the in-hospital evaluation. Among the 216 cephalalgic patients, only 87 (40.3 %) referred to their general practitioner, while the majority (129 patients, 59.7 % of the sample) did not refer to their doctor ($p < 0.0001$ at $\chi^2$ test). Of the 77 patients affected by migraine without aura, only 43 (55.8 %) referred to their general practitioner. Only 27 (35.1 %) had a definite migraine diagnosis, while 50 (64.9 %) subjects were still undiagnosed and unevaluated at the moment of our survey ($p < 0.0001$ at $\chi^2$ test).

## Discussion

Our data show that the prevalence of headache in a population of hospital workers is high. This fact reflects the normal epidemiology of migraine, that is especially present among 20–40-year-old people. However, few people referred to their doctor for headache, and this is an unexpected finding. A large Italian study showed that 62.4 % of migraine patients visited their general practitioner in the last year and only the 38.2 % were evaluated by a specialist for headache [3]. Several different studies of our group showed that migraine patients often spend many years to obtain a correct diagnosis, performing several useless instrumental examinations and specialistic visits [4, 5]. In the present study, only the 40.3 % of the patient referred to their general practitioner. This finding suggests that hospital workers are not more sensitized regarding the headache problematic than general population. Also, only few patients received a correct diagnosis by their general practitioner. This element confirmed our previous data about the difficulties to apply IHS diagnostic criteria for migraine [6]. IHS criteria are theoretically simple and easy to apply in a clinical contest, without the need for hospitalization or instrumental exams, yet many general practitioner did not use them and it seems that they tend to confound migraine with other pathologies as sinusitis or cervical arthrosis.

Our findings show that hospital workers generally have a low self-awareness about headache presence and tend to avoid evaluation by their general practitioner. On the other hand, when they referred to the general practitioner, a correct diagnosis was put only in a minority of cases. Our data suggest the opportunity, and the usefulness to promote events to raise the awareness on cephalalgic disorders in order to improve diagnostic and therapeutic pathways.

**Conflict of interest** The authors certify that there is no actual or potential conflict of interest in relation to this article.

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ORAL COMMUNICATIONS

# Relationship between primary headache and nutrition: a questionnaire about dietary habits of patients with headache

**M. G. Saracco · G. Calabrese · M. Cavallini · V. Montano · B. Rinaldi · W. Valfrè · M. Aguggia**



**Abstract** The role of food associated with the headache has been the subject of scientific research since 1900, especially for migraine patients. A substantial proportion of patients (ranging from 12 to 60 %) report that their migraine attacks may be precipitated by dietary elements, certain eating habits (fasting) and abuse (caffeine and alcoholic beverages abuse and withdrawal). The biological mechanism by means of triggers in general and food in particular precipitate migraine attacks remains obscure. Based on the data in the literature, we performed an osservational study searching for possible correlations between nutrition and primary headaches. We enrolled 50 consecutive patients from the Headache Center of the Neurology Department of Hospital "Cardinal Massaia" of Asti and submitted them a 14-item questionnaire for the assessment of relationship between primary headache and food. Our preliminary data, although the follow up is still in progress, show that there are strong associations between the onset of the headache and dietary habits. It will be necessary to analyze a larger sample in order to draw more precise conclusions on this topic.

**Keywords** Migraine · Tension type headache · Nutrition

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## Introduction

The role of food associated with the headache has been the subject of scientific research since 1900, especially for migraine patients. A substantial proportion of patients (ranging from 12 to 60 %) report that their migraine attacks may be precipitated by dietary elements: fasting, alcohol, chocolate and cheese are the most frequently reported dietary factors precipitating headache [1].

There is not a correlation not only with food, but also with certain eating habits.

A regular diet is so uncommon in industrialized countries than in less developed countries. Particularly exposed to this risk are also followers of some religions, such as Muslims during Ramadan (they abstain from eating and drinking from sunrise to sunset completely for 30 days) and the Jews on Yom Kippur (when they must totally abstain from drinking and eating for over 24 h, i.e., a few moments before sunset to the next sunset, to the appearance of the first stars). Even the suspension of caffeine intake (in high consumers of coffee) has its own importance. In addition, fasting also includes the suspension of the drink, with the consequent relative dehydration.

Nutrition plays a central role in headaches of children. They are accustomed to a hasty breakfast, often with insufficient caloric intake in relation to the needs of the morning; hence the ease with which the headache begins in the late morning or early afternoon in the young and in the very young [2, 4].

A last but not less important is that correlation exists between headache and abuse, for example caffeine and alcoholic beverages abuse and withdrawal.

The finding that diet-sensitive migraineurs are usually sensitive to several and different foods leads to the hypothesis of antigenic similarities between these disparate

foods or common chemical constituents, but a clear scientific explanation of the mechanisms implicated in the development of migraine attacks supposedly precipitated by food is still lacking. The possibility that the elimination diets based on the hypothesis of food hypersensivity IgE or IgG-mediated improve migraine has been explored in different studies but the results are inconclusive. Fasting as trigger for migraine is frequently reported. Some migraineurs show reactive hypoglycaemia due to diet-induced hyperinsulinism. In conclusion, identification of environmental factors (including dietary factors) that consistently trigger migraine in some subjects may be helpful to reduce attacks frequency. The biological mechanism by means of which triggers in general and food in particular precipitate migraine attacks remains obscure [3].

## Materials and methods

Based on the data in the literature, we performed an observational study searching for possible correlations between nutrition and primary headaches. In particular, we investigated not only patients suffering from migraine, as previously reported in the majority of studies, but also tension type headache. Furthermore, we investigated whether there were correlations between headaches and some details and still poorly investigated dietary habits (i.e., high-protein diets).

We enrolled 50 consecutive patients from the Headache Center of the Neurology Department of Hospital "Cardinal Massaia" of Asti.

All the patients fullfill diagnostic criteria for migraine without aura, migraine with aura or tension type headache (both chronic and episodic form) based on ICHD II critheria.

We performed a 14-item questionnaire for the assessment of relationship between primary headache and food, which was submitted by a nurse to each patient before the clinical evaluation and after providing an informed consent. The patient was then followed up at 3 and 12 months.

## Results

About 20 % of the patients suffered from migraine with aura, 55 % from migraine without aura, 20 % tension type headache, and 5 % from chronic migraine I.

About 40 % of patients with migraine without aura associated the headache to lifestyle or dietary habits (Fig. 1), while only the 1 % of patients with migraine with aura reported this association (Fig. 2).

Among the patient with tension type headache, a 20 % referred their headache to dietary habits (Fig. 3).

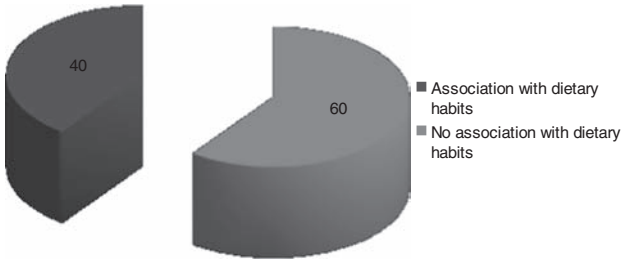


**Fig. 1** Among patients with migraine without aura 40 % associated with its status or lifestyle or the foods eaten

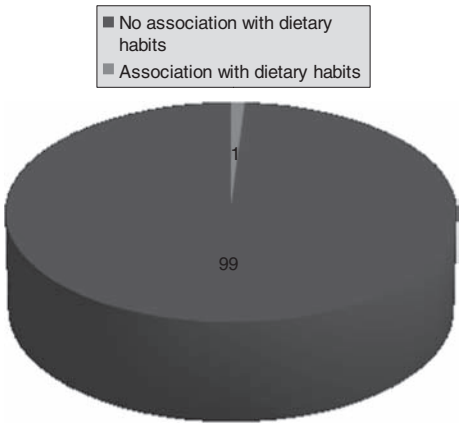


**Fig. 2** Among patients with migraine with aura only 1 % has been associated with their migraine food

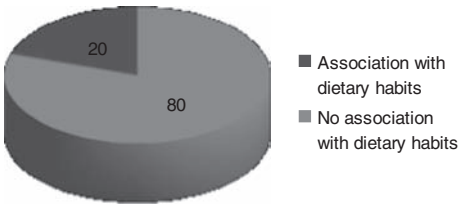


**Fig. 3** Among patients with tension-type headache, only 20 % have associated their discomfort food

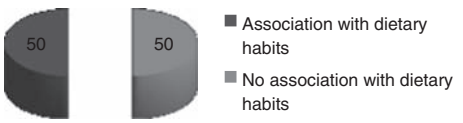


**Fig. 4** Among patients with chronic migraine 50 % have associated with their lifestyle and nutrition to their disease

About 50 % of patients suffered from chronic migraine associated the headache to the lifestyle or dietary habits (Fig. 4).

## Conclusions

The follow up is still in progress for all the patients.

Our preliminary data, althought, show that there are strong associations between the onset of the headache and dietary habits.

However, in addition to the end of the follow up, it will be necessary to analyze a larger sample in order to draw more precise conclusions on this topic.

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ORAL COMMUNICATIONS

# The increased distensibility of the wall of cerebral arterial network may play a role in the pathogenic mechanism of migraine headache

**S. Viola · P. Viola · M. P. Buongarzone · L. Fiorelli · P. Litterio**



**Abstract** The aim was to evaluate whether patients with episodic migraine with (MA+) and without aura (MA−), during the interictal period of migraine would have an altered distensibility of the wall of cerebral arterial network and whether it would play a role in migraine headache. To evaluate the distensibility of the wall of cerebral arterial network, we measured the time-delay in milliseconds (ms) between the R-wave of an electrocardiogram and the arterial pulse wave of cerebral microcirculation (R-APWCMtd) on the frontal cortex detected by near-infrared spectroscopy (NIRS) in 10 patients with MA+ (age 39.5 ± 12.2 years), in 10 with MA− (age 40.3 ± 10.2 years), according to ICHD-3 criteria 2012, during the interictal period of migraine, and in 15 age-, sex- and height-matched healthy control subjects. The patients with migraine had a significantly longer R-APWCMtd than the control subjects $F = 13.4$, $p < 0.001$: MA+:+38.3 ms; MA−:+34.7 ms indicating an increased distensibility of the wall of cerebral arterial network. In multiple regression analysis, R-APWCMtd was significantly associated with migraine ($R^2 = 0.50$, $p < 0.0001$) but not with age, gender, height, migraine attack frequency and disease duration. The increased distensibility leads to an increased flow pulsatility into intracranial dural meningeal vessels that may lead to a mechanical stimulation of the nociceptors that innervate the dural vasculature. This condition may play a role in promoting the sensitization of trigeminovascular afferents and sterile inflammation within the dura mater that are fundamental to the pathogenesis of migraine headache.

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**Keywords** NIRS · R-APWCMtd · Flow pulsatility · Mechanical nociceptors · Migraine headache · PWV

## Introduction

It is now well accepted that migraine headache is mediated by the increased sensitivity and ensuing activation of trigeminovascular nociceptive afferents that innervate the dura mater and their related blood vessels. One of the fundamental questions is to determine which processes actually play a role in promoting such condition [1].

A work has found that trigeminal pain-sensing neurons (nociceptors) innervating the dura are sensitive to mechanical stimulation [2]. A recent study has shown that this mechanosensitive nociceptor may be the ion channel transient receptor-potential vanilloid 4 (TRPV4) [2]. Many studies indicate the existence of a systemic vascular involvement in migraine [3]. A recent study suggests that an altered distensibility of the aortic wall may lead to an increased flow pulsatility or pulsatile energy into cerebral microcirculation [4]. The purpose of the present study was to evaluate whether patients with episodic migraine with (MA+) and without aura (MA−), during the interictal period of migraine, would have an altered distensibility of the wall of cerebral arterial network and whether it would play a role in migraine headache.

## Methods

The patients with episodic migraine were consecutively recruited at the outpatient Headache Center of the

Neuroscience Department of our hospital. The study was approved by the local ethics committee. All the patients and control subjects gave their informed consent prior to inclusion in the study. We studied 10 patients with MA+ (age 39.5 ± 12.2 years) and 10 with MA− (age 40.3 ± 10.2 years), according to ICHD-3 beta criteria 2012, during the interictal period of migraine and 15 age-, sex- and height-matched healthy control subjects. We excluded secondary headaches by appropriate laboratory and imaging diagnostic tests. The cases and controls were free from overt cardiovascular events (CVE) including angina pectoris and myocardial infarction, transient ischemic attack (TIA), ischemic stroke, major cardiovascular risk factors (diabetes, hypertension, and hypercholesterolemia) and migraine prophylactic medications. Subjects were asked not to use any inflammatory or analgesic drugs for 3 days before examination. At rest in all the participants, the time delay in millisecond (ms) between the R-wave of an electrocardiogram and the foot of arterial pulse wave of cerebral microcirculation (R-APWCMtd), detected by transcranial NIRS (T-NIRS EVO II, CW system) a safe and noninvasive technology [5] on the frontal cortex of both sides (position F1, F2 of the international 10–20 EEG system), was determined to measure the distensibility of the wall of cerebral arterial network according to Bramwell and Hill equation [6, 7]:

$$\mathrm{PWV} = \frac{1}{\sqrt{\rho \times \text{distensibility}}} \quad (1)$$

and according to the pulse wave velocity (PWV) equation [6, 7]:

$$\mathrm{PWV} = \frac{D}{T} \quad (2)$$

PWV is pulse wave velocity, $D$ is the distance traveled by the wave, $T$ is the time for the wave to travel that distance and $\rho$ is the density of blood.

## R-APWCMtd

Every heartbeat causes a pulsatile pressure gradient that propagates through the cerebral arterial network [6] (aorta, carotid artery, mean cerebral artery, cerebral microcirculation that includes arterioles and capillaries), and causes local changes in blood flow and volume. The local changes in blood volume are due to the elastic wall of the cerebral arterial network. In the microcirculation of cerebral cortex, small local changes in blood volume are still present and are revealed by means of NIRS that we call arterial pulse waves of cerebral microcirculation (APWCM) [5]. Pulse wave velocity is the speed at which the forward pressure wave is transmitted from the aorta through the vascular tree. It is calculated by the time period taken for the arterial waveform to pass between two points or by the time period between the contraction of ventricles and arrival of this wave to the peripheral artery measurement site (for example, the finger; in our study the frontal cortex) [6]. Contraction of the ventricles is detected using R peak of the ECG signal and arrival of the pressure pulse is detected at the foot of APWCM signal [6]. Pulse wave velocity provides information on the distensibility of the arterial vessel being studied [7]. Distensibility is inversely related to arterial stiffness [7].

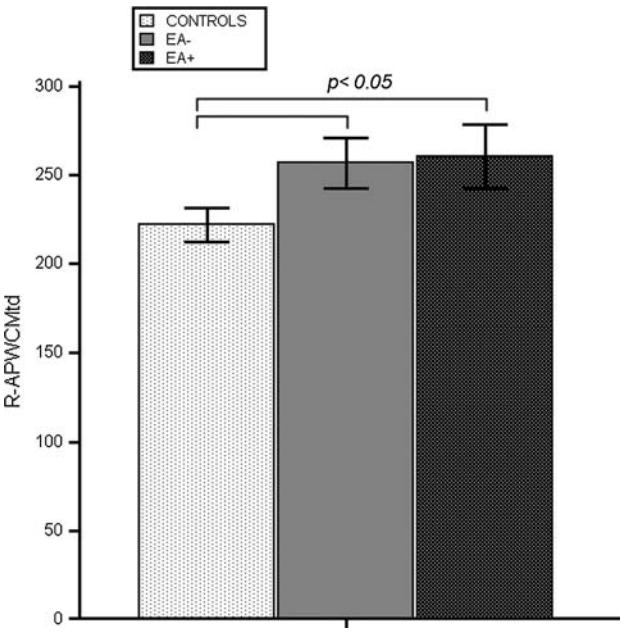


**Fig. 1** Time delay in milliseconds between the R-wave of an electrocardiogram and the foot of arterial pulse wave of cerebral microcirculation (R-APWCMtd) in 10 migraine patients with and 10 migraine patients without aura and in 15 age-, sex- and height-matched control subjects. One-way ANOVA is used in combination with Student–Newman–Keuls post hoc test to identify differences among groups. For each group, the R-APWCMtd values are plotted. Values are mean ± SD

## Statistical analysis

We used Med. Calc. statistical software, version 12.5.0.0. Age, sex and height differences between the migraine patients and healthy controls were tested using the unpaired $t$ test. The association of migraine with MA+ and MA− with the R-APWCMtd values was assessed using one-way ANOVA. When group comparisons showed significant differences, the Student–Newman–Keuls post hoc test was applied to identify differences among groups.

Linear regression analysis was used to estimate prediction of R-APWCMtd by including simultaneously in the model the following variables: age, sex, body height, migraine attack frequency, disease duration and migraine status.

## Results

The patients with migraine had a significantly longer R-APWCMtd than the control subjects $F = 13.4$, $p < 0.001$: MA+:+38.3 ms; MA−:+34.7 ms (Fig. 1). In the multiple regression analysis, the R-APWCMtd was significantly associated with migraine (coefficient of determination $R^2 = 0.50$, multiple correlation coefficient 0.71, $p < 0.0001$) but not with age, gender, height, migraine attack frequency and disease duration. The two groups were matched (no significant difference) for age, sex and height. There was no significant difference between the right and left R-APWCMtd of frontal cortex in the migraine patients $p = 0.77$ and controls $p = 0.70$.

## Discussion

In our study, we excluded all subjects with major vascular risk factors, CVE, TIA or ischemic stroke, migraine prophylactic medications and to the subjects were asked not to use any inflammatory or analgesic drugs for 3 days before examination. In addition, the patients and controls were matched by age, sex and height (distance traveled by the wave) and we assume that intracranial pressure is within the normal range in the patients and controls. These confounding factors may chance the distensibility of cerebral arterial network and therefore R-APWCMtd. This longer R-APWCMtd suggests an increased arterial distensibility (or reduced arterial stiffness) of cerebral arterial network, because the pulsatile pressure gradient propagates more slowly in presence of increased arterial distensibility (according to Bramwell & Hill and PWV equation) [7]. In our recent work we have proposed some possible explanations for the increased arterial distensibility in our migraine patients [8]. The multivariate regression analysis shows that R-APWCMtd is independently associated with migraine. In addition, in the migraine patients there was no significant correlation between the R-APWCMtd and migraine attack frequency and disease duration and, therefore, the R-APWCMtd does not indicate disease severity. These findings provide evidence that a longer R-APWCMtd may be the earliest stage of disease and may play a role in migraine pathogenesis.

### The increased distensibility may play a role in migraine headache?

In young, healthy adults, the aorta has a high distensibility and first-generation arteries are relatively stiff. This abrupt transition from the aortic distensibility (low impedance) to the stiff (high impedance) branch vessels represents an impedance mismatch [4]. When a traveling wave encounters such a discontinuity, a portion of the pulsatile energy stored in that wave is reflected back and, therefore, is not transmitted into the distal vasculature [4]. This wave reflection represents a protective mechanism that limits the transmission of excessive flow pulsatility into the microcirculation [4]. Wave speed and characteristic impedance are linked by water hummer equation [9].

$$Z = \frac{\rho \times c}{A} \tag{3}$$

$Z$ is the vascular impedance, $A$ is the cross sectional area, $c$ is the wave velocity and $\rho$ is the density of blood.

Because the aorta is a little part of the cerebral arterial network and, in addition, recent works [3] have shown an increased wave velocity (decreased time period of progression wave) on the aortic wall in migraine patients compared with healthy control, it is possible assume that the longer R-APWCMtd in our migraine patients is due to the increased distensibility of the carotid artery, mean cerebral artery and cerebral microcirculation; the longer R-APWCMtd leading to a decreased PWV or $c$, leads to a reduction of $Z$ of this second part of the cerebral arterial network. In brief, this condition may lead to reduction of the impedance mismatch and thereby may facilitate the transmission of excessive pulsatile energy or flow pulsatility into the cerebral microcirculation. However, the increased transmission of pulsatile energy or flow pulsatility may induce an adaptive mechanism by which the cerebral vascular bed protects itself from pulsatile barotrauma by elevating the local vascular resistance (peripheral vasoconstriction) [4, 10]. This finding is in agreement with previous studies [3] and, in addition, may explain the generalized peripheral vasoconstriction that has been observed during in the interictal period of migraine that might represent a determinant of the vasospastic disorders observed in migraine patients, including variant angina [3]. It is important to note that the adaptive mechanism, increasing the blood flow velocity, increases the shear stress that a recent study has implicated in the genesis of migraine [11]. The principal blood supply of the dura is via the middle meningeal artery, one of the terminal branches of the maxillary division of the external carotid artery and, therefore, it is possible to assume an increased transmission of pulsatile energy or flow pulsatility into this artery. A recent review suggests that the increased amplitude pulsations in the occipital and superficial temporal branches of the external carotid arteries may play a role in migraine headache [12]. A study suggests a mechanism where multiple triggers act on different cerebral structures to activate parasympathetic fibers innervating the meningeal vessels and produce their initial vasodilatation [13, 14]. The initial vasodilatation may lead to excessive flow pulsatility into the meningeal vessel, in migraine patients but

not in healthy control. Additionally in migraine, we speculate an increased distensibility of the meningeal vessel wall that may contribute to the excessive flow pulsatility. The excessive flow pulsatility may sensitize the mechanosensitive nociceptor TRPV4 of the trigeminovascular system [2]. This may explain the worsening of migraine headache by coughing, breath-holding or sudden head movement and, additionally, the throbbing pain of migraine that has been proposed to come from pulsatile flow of blood [2]. The meningeal arteries lie mainly in the outer, or endosteal layer of the dura, which in humans is a tough membrane that is rigid, resistant to stretching and is tightly attached to the cranial bones. We suppose that this condition may facilitate the mechanical stimulation of this pain-sensing neuron (nociceptor) innervating the dura and their related blood vessels. The firing of the trigeminovascular fibers presumably causes the release of neuropeptides from their peripheral endings, thereby initiating the inflammatory process underlying the migraine pain and perpetuating the vasodilation [14]. In migraine, stimulation of the trigeminal nerve causes neurogenic inflammation via release of neuropeptides including Substance P, nitric oxide, vasoactive intestinal polypeptide, serotonina (5-HT), Neurokinin A and calcitonin gene related peptide (CGRP) leading to a sterile neurogenic inflammation [14]. In addition, the definitive proof that the pain of migraine is caused solely by an inflammatory process is lacking [14]. This supports our hypothesis. At present the "migraine cannot be understood without a clear understanding of the dynamic role of the blood vessel in its pathogenesis" [15].

In conclusion, in our migraine patients, a longer R-APWCMtd is independently associated with migraine and indicates an increased distensibility of the wall of cerebral arterial network. The increased distensibility leads to an increased flow pulsatility into intracranial dural meningeal vessels that may lead to a mechanical stimulation of the nociceptors that innervate the dural vasculature. This condition may play a role in promoting the sensitization of trigeminovascular afferents and a sterile inflammation within the dura mater that are fundamental to the pathogenesis of migraine headache.

**Conflict of interest** The authors certify that there is no actual or potential conflict of interest in relation to this article.

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ORAL COMMUNICATIONS

# Is the brain of migraineurs "different" even in dreams?

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**Abstract** Migraineurs brain is hyper-excitable and hypometabolic. Dreaming is a mental state characterized by hallucinatory features in which imagery, emotion, motor skills and memory are created de novo. To evaluate dreams in different kinds of headache. We included 219 controls; 148 migraineurs (66 with aura–MA, 82 without aura–MO); 45 tension type headache (TTH) patients. ICHD-II diagnostic criteria were used. Ad hoc questionnaire was used to evaluate oneiric activity. The Generalized Anxiety Disorder Questionnaire, and the Patient Health Questionnaire were administered to evaluate anxiety and mood. The prevalence of dreamers was similar in different groups. Frequency of visual and auditory dreams was not different between groups. Migraineurs, particularly MA, had an increased frequency of taste dreams (present in 19.6 % of controls, 40.9 % of MA, 23.2 % of MO, 11.1 % of TTH, $p < 0.01$), and of olfactory dreams (present in 20 % of controls, 36 % of MA, 35 % of MO and 20 % of TTH, $p < 0.01$). Anxiety and mood did not influence these results. The increased frequency of taste and olfactory dreams among migraineurs seems to be specific, possibly reflecting a particular sensitivity of gustative and olfactory brain structures, as suggested by osmofobia and nausea, typical of migraine. This may suggest the role of some cerebral structures, such as amygdala and hypothalamus, which are known to be involved in migraine mechanisms as well in the biology of sleep and dreaming.

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**Keywords** Migraine · Dreams · Behavior · Mood · Anxiety

## Background

Migraineurs brain is hyper-excitable and hypo-metabolic [1]. These peculiarities may account for some clinical manifestations of migraine (M): increased tendency to anxiety and depressive mood [2], even at a non-pathologic level, and frequent obsessive trait of personality. Migraine is also associated with sleep disorders [3] and sleep behavior with a bidirectional relationship [4].

Dreaming is a universal mental state characterized by hallucinatory features in which imagery, emotion, motor skills, and memory are created de novo. All these aspects can simulate waking experiences, but they are generated by different neurobiological processes. Only a few studies investigated the oneiric activity in migraineurs [5], and frequently only from a psychological point of view.

## Aim of the study

To investigate some dream aspects in primary headache patients, and particularly in those with M, based on the hypothesis of the pivotal role of the limbic system in the interconnection between M mechanisms, sleep, dream, mood, and anxiety.

## Materials and methods

We enrolled a group of primary headache outpatients consecutively evaluated in the headache center of the

L. Sacco Hospital, Milan, Italy, between June 2012 and December 2013. These were 193 patients (50 males and 143 females; mean age 37.9 ± 15.1). Headache diagnoses were made according to ICHD-II criteria. A group of 219 non-cephalgic age-matched subjects recruited from university and hospital staff (107 males and 112 females; mean age 38.4 ± 18.8) was used as control group.

A semi-structured retrospective self-reported ad hoc questionnaire was administered to all the studied subjects to evaluate oneiric activity, with particular regard to sensory experiences (presence of visual, acoustic, olfactory, and taste sensations). The Generalized Anxiety Disorder Questionnaire (GAD-7) and the Patient Health Questionnaire (PHQ-9) was administered to all the studied subjects to evaluate the possible effects of anxiety and depression on dreams.

## Results

A total of 412 subjects were included, as the questionnaires distributed were filled-in and sent back by all the enrolled subjects: 219 controls; 148 migraineurs, 66 with M with aura (MA), 16 males and 50 females, mean age 38.4 ± 15.5; 82 with M without aura (MO), 19 males and 63 females, mean age 37.4 ± 14.6; 45 patients with tension type headache (TTH), 15 males and 30 females, mean age 37.9 ± 15.4.

The percentages of subjects able to re-evocate dreams at awakening was similar in all the groups, ranging from 86 to 91 %: dreamers were 189 out of 219 controls, 59 out 66 MA patients, 73 out of 82 MO patients, and 41 out of 45 TTH patients ($\chi^2$ = ns).

No differences between migraineurs and other groups in term of visual and auditory sensations: visual dreams in 75 % of controls; 64 % of MA; 78 % of MO; 82 % of TTH patients ($\chi^2$ = ns); auditory dreams in 62 % of ctrl, 69 % of MA, 69 % of MO and 64 % of TTH patients ($\chi^2$ = ns). Migraineurs, especially MA patients, showed an increased frequency of gustative dreams: taste perceptions were reported by 43 out of 219 controls (19.6 %); 27 out of 66 MA patients (40.9 %); 19 out of 82 MO patients (23.2 %); 5 out of 45 TTH patients ($p = 0.0007$ at $\chi^2$). In the whole group of migraineurs, gustative dreams were reported in a higher frequency if compared with ctrl (31.1 vs 19.6 %, $p = 0.009$ at $\chi^2$ test). In the MA group, taste sensations were reported in a higher proportion of subjects with respect to controls (41 vs 19.6 %, $p = 0.0003$ at $\chi^2$ test), while no differences were found between MO and ctrl (23 vs 19.6 %, $p$ = NS at $\chi^2$ test). Taste dreams were more frequent among MA patients than MO (41 vs 23 %, $p = 0.02$ at $\chi^2$ test). No differences between TTH and ctrl. In addition, olfactory dreams were more frequent among migraineurs than in the other groups: olfactory sensations were present in 43 out of 219 controls (20 %); in 24 out of 66 MA (36); in 29 out of 82 MO (35 %); in 9 out 45 TTH (20 %); $p = 0.006$ at $\chi^2$ test. Olfactory sensations during dreams were more frequent among migraineurs with respect to controls (35.8 vs 19.6 %, $p = 0.0005$ at $\chi^2$). This higher prevalence of olfactory dreams was present in both MA and MO with respect to controls: MA vs ctrl, 36.4 vs 19.6 % ($p = 0.002$ at $\chi^2$ test); MO vs ctrl, 35.4 vs 19.6 % ($p = 0.006$ at $\chi^2$ test). No differences emerged comparing MO with MA patients. No differences were found also between TTH and controls.

These findings were not influenced by anxiety and depression scores ($p$ = ns at $t$ test, by the comparison of PHQ-9 and GAD-7 levels between subjects with and without gustative and olfactory dreams), neither by sleep behavioral aspects (latency of sleep onset and frequency of awakenings, data not reported).

## Discussion

We investigated some aspects of oneiric activity in primary headache patients, and particularly in those with M. The first observation was that the percentage of subjects able to recall dreams at awakening was similar in headache patients and in controls, even if migraineurs may complain of an increased amount of nocturnal awakenings and a delayed sleep onset, as shown by a previous study [6]. On the other hand, qualitative diversities characterizing M patients emerged from our analyses. In fact, the brain of migraineurs seems to dream differently, with an increased frequency of taste and olfactory sensations during the

| Diagnostic groups | Visual dreams | B/W dreams | In color dreams | In color and B/W dreams | Auditory dreams | Gustative dreams* | Olfactory dreams§ |
|---|---|---|---|---|---|---|---|
| ctrl (219) | 164 (75 %) | 25 (11.4 %) | 139 (63.5 %) | 0 (0 %) | 136 (62 %) | 43 (19.6 %) | 43 (20 %) |
| MA (66) | 49 (64 %) | 7 (10.6 %) | 44 (66.6 %) | 2 (3 %) | 48 (69 %) | 27 (40.9 %) | 24 (36 %) |
| MO (82) | 64 (78 %) | 5 (6 %) | 63 (76.8 %) | 4 (4.9 %) | 57 (69 %) | 19 (23.2 %) | 29 (35 %) |
| TTH (45) | 37 (82 %) | 8 (17.7 %) | 30 (66.6 %) | 1 (82.2 %) | 29 (64 %) | 5 (11.1 %) | 9 (20 %) |

* $p = 0.0007$, § $p < 0.006$

oneiric activity, which are generally less frequent than the visual and auditory dreams [7]. These elements suggest that in the brain of migraineurs some cerebral structures, such as piriform and entorhinal cortices, nucleus ambiguous, amygdala and hypothalamus, may show some peculiar abnormalities, although it is not possible to infer if they are part of the dysfunctional state of M, or are caused by M course. We note that some of these areas, especially amygdale and hypothalamus are considered as being involved in migraine mechanisms, and that a part of the pathways connecting the above-listed areas form an archaic system involved in the in the biology of sleep and dreaming, both in terms of content, recalling and of emotional elements. The observation that mood and anxiety do not influence this increased prevalence of gustative and olfactory dreams in migraineurs underlines the peculiarity of this relationship that seems to be specific of migraine. Our results may offer a new point of view on the peculiarity of migraine brain as far as the relevance of these archaic brain structures, which can regarded as the substrate linking several functions; namely, primary needs (such as sleep and food), mood, as well as omeostatic and allostatic reactions.

**Conflict of interest** We certify that there is no actual or potential conflict of interest in relation to this article.

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ORAL COMMUNICATIONS

# Evaluation of immune parameters in chronic migraine with medication overuse

**L. Grazzi · E. Corsini · E. Ciusani · S. Usai · C. Vasco · G. Bussone**



**Abstract** It has been postulated that chronic pain and chronic migraine in particular, can be connected to immunologic disturbances. Moreover the psychiatric comorbidity is often responsible of migraine chronification, but also of developing of particular immune function alterations. The role of the immune system in migraine precipitation is still under debate also if speculations about the evidence of infections in migraine patients has been performed, but not always corroborated by clinical and scientific explanations. In this report we present an evaluation of specific immune parameters in patients suffering from different forms of migraine respect to controls in order to determine possible alterations in immune function: speculations about the evidenced abnormalities are attempted.

**Keywords** Chronic migraine · Episodic migraine · CTRL subjects · Immunologic parameters

## Introduction

The involvement of Immune System (IS) and the evidence of abnormal function of IS in chronic pain condition has been largely debated [1] without achieving definite conclusions. In particular Chronic Migraine (CM), as a condition of prolonged pain, has been studied from this point of view [2]. Preceding reports have demonstrated as in migraine, a dysfunction of IS can be evidenced: eczema or asthma can be comorbid with migraine in a significant subgroup of migraine patients [3].

Some years ago, a meta-analytic report [4] evidenced that investigations of the literature have been conducted to show a selective expression changes of mediators of inflammation during migraine in order to obtain information about physiological evidences of abnormal functioning of IS in migraine. Unfortunately, up to now, there is no clear evidence in the literature of a clear-cut well defined immunological disorder in migraine patients and available results were obtained with limited groups of patients.

On the other side, researchers have confirmed a decreased leukocyte phagocytotic ability and increased plasma levels of TNF-alfa and it is well documented that stress, often induced by chronic pain condition, and glucocorticoids suppress the functioning of IS and cause increased vulnerability to infections [5, 6].

One more aspect concern the debated association between CM condition and psychiatric comorbidity: also, from the literature, it has been noted how psychiatric conditions are often responsible of altered IS functioning [7–9].

On the basis of the preceding observations, we present in this study an evaluation of some specific immunological parameters in three different groups of subjects in order to define if alterations in immunological function can be evidenced in patients suffering from a chronic pain condition as CM: first group (Group A), patients suffering from chronic migraine with medication overuse (CM) before a withdrawal procedure; second group (Group B), healthy control subjects (HC) of same age and general characteristics; third group (Group C), patients suffering from episodic migraine without aura (EM). Blood samples were collected from all these groups.

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## Methods

Blood samples from 29 patients suffering from chronic migraine with medication overuse (CM) (diagnosis was made according with HIS criteria 2004) [10] (Group A, 24F, 5 M, mean age 45.7 ± 11.0), 27 healthy controls (HC, Group B, 25F, 2 M, mean age 40.9 ± 8.4) and 26 patients with episodic migraine without aura (EM) (diagnosis was made according with HIS criteria 2004) [10] (Group C, 25F, 1 M, mean age 36.8 ± 9.4) were collected.

Patients and controls were similar for age and general characteristics.

Samples were collected in the morning, and the following analysis were performed: complete white blood cells count (WBC) by an haematology analyzer (Advia 2120, Siemens), evaluation of the peripheral blood lymphocyte subsets CD3, CD4, CD8, CD19 by flow cytometry (FACS Vantage, Becton–Dickinson) and quantitation of Beta endorphins plasma levels by a commercially available ELISA kit (USCN).

Patients with medication overuse were studied before an intervention of withdrawal in a day hospital setting and before that any preventive medication for migraine was given. EM patients used triptans or NSAIDS occasionally (3–4 per month) to manage their migraine attack.

## Results

The analysis of samples evidenced the following results: no differences were observed between HC and EM patients in all studied parameters, while WBC and Lymphocytes were significantly higher in CM patients (respectively, 9,386 ± 2,258 and 2,563 ± 796) as compared to HC (6,174 ± 1,429, $p < 0.0000001$ and 1,790 ± 349, $p < 0.0000225$) and EM patients (5,953 ± 2,715, $p < 0.000044$ and 1,680 ± 677, $p < 0.0000522$).

CD3, CD4, CD8 and CD19 (expressed as absolute number/μL) were significantly higher in CM patients than in EM patients and HC (CD3: 1,935 ± 657.23 vs 1,262.19 ± 528.08 vs 1,334.69 ± 248.99: $p < 0.0001$; $p < 0.0001$; $p$ ns HC vs EM; CD4: 1,110.75 ± 500.94 vs 815.73 ± 286.2 vs 770.44 ± 180.12: $p < 0.002$; $p < 0.012$; $p$ ns HC vs EM, CD8: 748.92 ± 263.92 vs 506.48 ± 265.31 vs 518.83 ± 173.18: $p < 0.002$; $p < 0.0006$; $p$ ns HC vs EM; CD19: 383.14 ± 182,72 vs 202.18 ± 119.81 vs 194.54 ± 68.55: $p < 0.001$; $p < 0.00001$; $p$ ns HC vs EM).

Beta endorphins levels (expressed in pg/mL) were significantly lower in CM patients as compared to HC (14.7 ± 5.4 vs 20.14 ± 5.81, $p < 0.001$), while EM patients displayed intermediate values (16.12 ± 7.75).

## Discussion

Abnormal parameters of IS functioning have been identified in some chronic pain conditions [1] also if they were not well determined in migraine.

Some authors evidenced systemic changes of specific immune parameters used for establishing a possible immune dysfunction in patients suffering from episodic migraine [2].

Specific aspects involved in migraine pathogenesis, show that a local inflammatory response is elicited during migraine attack as well as the clinical efficacy of NSAIDs or involvement in spreading depression process [4].

The alterations we found in chronic migraine patients concern principally WBC, lymphocytes and some lymphocyte subsets as CD4, CD19, CD8, CD3.

These alterations, may indicate an inflammatory state in patients suffering from chronic forms of migraine with medication overuse, compare to controls and patients with episodic form, similar to those showed from preceding literature [4–9].

The increase in specific lymphocyte subsets can be due to the significant increase in WBC and total lymphocytes population and it can be induced by the chronic migraine condition itself, also if it can not be excluded that in patients with medication overuse, the frequent use of different kinds of medication, NSAIDs in particular, can influence the immune system function.

Moreover it has to be mentioned that in preceding literature, chronic pain has been considered responsible of some modifications in immunological and haematological parameters [1].

It can be speculated that stress response, evidenced in chronic pain condition, implies an increase of glucocorticoids and consequently an alterations in immune function and immune parameters.

Finally, lower levels of beta endorphins in CM patients respect to the EM patients and HC, can suggest how chronic pain condition can influence levels of endorphins by lowering them significantly [8].

Data concerning CM patients confirm the results obtained by Leone et al. [11] where a significant reduction in beta-endorphin levels were observed in patients suffering from migraine with and without aura; this is probably induced by an altered transmitter modulation to peripheral blood mononuclear cells, which also could be part of a diffuse opioid system derangement in migraine subjects, more evident in CM patients.

In conclusion, patients with EM patients are similar to HC for leucocytes and lymphocyte subsets; on the other side, they are different from CM patients. It could be speculated that CM patients show permanent abnormalities and that Medication Overuse can contribute to the observed

abnormalities; on the other hand, patients suffering from Episodic Migraine show some fluctuations of the examined parameters which can be related to the pain attack itself.

More studies will be necessary to confirm these preliminary results and to explain the clinical implications of these abnormalities.

**Conflict of interest** I certify that there is no actual or potential conflict of interest in relation to this article.

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ORAL COMMUNICATIONS

# Onabotulinumtoxin A for prophylaxis in chronic migraine: preliminary data from headache regional centre of aosta valley

**C. Lia · P. Tosi · G. Giardini · L. Caligiana · E. Bottacchi**



**Abstract** Chronic migraine (CM) is a complex neurological disorder associated with substantial disability that affects approximately 2 % of general population. Onabotulinumtoxin A is employed for patients suffering from CM refractory to common therapeutic prophylaxis. Since May 2013, we have selected 22 patients referring to our headache centre with a history of CM which meets the diagnostic criteria of ICHD-3 beta (2013). The patients have been treated with onabotulinumtoxin A injection in 31 sites according to the protocol of the PREEMPT study at the total dosage of 155 U/treatment every 3 months. So far, eight patients have been subjected to three treatment sessions, five patients to two treatments and nine patients to one treatment. Three patients dropped for low compliance, but there were no serious adverse events. The frequency of headache days, the intensity of headache and the headache disability have been measured using headache diary, migraine disability assessment (MIDAS) questionnaire and headache impact test (HIT)-6 score. Data concerning the 13 patients who have been submitted to at least two treatment sessions have already shown a decrease of headache days of 20.64 % after the first treatment; MIDAS and HIT-6 scores have been significantly improved with a reduction of the scores, respectively, of 38.45 % for MIDAS and of 6.95 % for HIT-6. These are preliminary results because the observation time, the number of treatment sessions and the number of patients treated are still few.

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**Keywords** Onabotulinumtoxin A · Chronic migraine · Prophylaxis

## Introduction

Chronic migraine (CM) is a complex, progressive neurological disorder with a prevalence ranging 1–3 % of the general population and an incidence estimated to be 2.5 % per year [1]. CM produces much more disability, decreased productivity and disruption of quality of life than episodic migraine. CM is characterized by headache on ≥15 days per month for ≥3 months, of which ≥8 days meet criteria for migraine or respond to migraine-specific treatment [2].

Given the high disability associated with CM, the patients affected need adequate preventive treatments; on the contrary, CM is an undertreated neurological disorder.

Neurotoxins obtained from *Clostridium botulinum* are potent inhibitors of neurotransmission between neurons and muscles. Of the seven botulinum neurotoxin serotypes, botulinum neurotoxin type A, onabotulinumtoxin A, has been the most investigated in clinical studies. Onabotulinumtoxin A has been reported to relieve pain associated with a variety of conditions, including migraine, and it has become the first headache prophylactic therapy specifically approved for CM [3].

We use onabotulinumtoxin A to treat patients referring to our headache centre and suffering from CM refractory to common therapeutic prophylaxis.

## Methods

Since May 2013 we have selected 22 patients, 18 females and 4 males, aged 24–64 years, with a history of migraine

meeting the diagnostic criteria for CM listed in the third edition of the International Classification of Headache Disorders (ICHD-3 beta, 2013) [2]. All patients were previously treated by available medical therapies, but they had failed to respond to headache prophylactic medications that they found to be ineffective and/or intolerable.

According to the protocol of the PREEMPT study [4, 5], onabotulinumtoxin A has been administered as 31 fixed-site, fixed-dose (5 U), i.m. injections across seven specific head/neck muscle areas at the total dosage of 155 U/treatment; every session of local injections has been repeated every 3 months. So far, eight patients have been subjected to three treatment sessions, five patients to two treatments and nine patients to one treatment.

Number of days of headache per month and the intensity of headache have been recorded by an headache daily diary. The headache disability have been measured using migraine disability assessment (MIDAS) questionnaire [6] and headache impact test (HIT)-6 score [7].

## Results

Our patients are representative of the typical patient with CM: they have been highly disabled and experienced a mean of 67 headache days in the 3-month observation just before the first treatment session.

We have assessed the 13 patients who have been submitted to at least two treatment sessions: at baseline only 2 patients had a moderate disability with MIDAS total scores of 18 and 20, being part of grade III category; the other 11 patients had a very severe disability within the category of grade IV-B [8] with MIDAS total scores of 70–205. All patients had a severe HIT-6 score >60.

After the first treatment the group of 13 patients have already shown a decrease of headache days of 20.64 % ($p = 0.0093$); MIDAS total scores and HIT-6 scores have been significantly improved with a reduction of the scores, respectively, of 38.45 % ($p = 0.0026$) for MIDAS and of 6.95 % ($p = 0.0377$) for HIT-6. There was no significant reduction of headache intensity ($p = 0.2424$).

The subgroup of eight patients that have been submitted to the third session of injections have shown during the 3 months after the second treatment a decrease of headache days of 21.50 % ($p = 0.0352$) and an improvement of MIDAS total scores of 36.5 % ($p = 0.0212$); the HIT-6 scores and the intensity of headache have not been significantly reduced.

Three patients dropped for low compliance, two of them after the first treatment and one patient after the second session. There were no serious adverse events, but two patients reported mild/moderate neck pain.

## Conclusions

These are preliminary results because the observation time, the number of treatment sessions and the number of patients treated are still few. In spite of these limits, our data are stimulating to continue the assessment of new patients, especially of those refractory to preventive medications, or those intolerant or not compliant to it.

Moreover, we would emphasize the safety and the tolerability of onabotulinumtoxin A other than its long duration of action (3 months) that makes it attractive even in patients with medication overuse which should stop the drug addiction.

Finally, the clinical observation will help us to decide treatment duration even if recent findings seem to demonstrate the continued need and cumulative benefit over time with continued prophylaxis [9].

**Conflict of interest** I certify that there is no actual or potential conflict of interest in relation to this article.

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ORAL COMMUNICATIONS

# Intracranial idiopathic hypertension: 1-year follow-up study

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**Abstract** Standard guidelines for ongoing management, as well as definitive data about the long-term course of idiopathic intracranial hypertension (IIH) are not available. The aim of this study was to compare several clinical and instrumental variables as assessed at the time of diagnosis and then after 1 year in a sample of IIH patients. A total of 21 patients were studied. Our results confirmed that headache and TVO are the most frequent symptoms in IIH patients, and that overweight is a very common feature. A trend towards a favorable outcome in patients followed for 1 year and treated by usual medical therapy was found: intracranial pressure was lower at follow-up; improvement of headache and transient visual obscurations, as well as of papilledema, was reported in most patients. On the other hand, neuroradiological findings (such as empty sella, perioptic subarachnoid space distension, narrowing of the transverse sinuses) were substantially stable at follow. These findings may be relevant for future research as far as understanding the role of different clinical and instrumental findings as diagnostic items as well as predictors of outcome in IIH.

**Keywords** Idiopathic intracranial hypertension (IIH) · 1-year follow-up · Intracranial pressure (ICP) · Headache · Transient visual obscurations (TVO) · Papilledema · Neuroimaging

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## Introduction

Idiopathic intracranial hypertension (IIH) is the syndrome of elevated intracranial pressure in the absence of demonstrated brain lesions and other causal disorders [1–3]. Etiology is still unknown, and clinical presentation may be heterogeneous, with symptoms including headache, visual alterations, tinnitus, etc. Neurophthalmologic examination is of crucial importance in the diagnostic evaluation, and recent reports have described several peculiar neuroimaging aspects in IIH patients [4–6]. Standard guidelines for the treatment and for the ongoing management, as well as definitive data about the long-term course IIH are not available.

The aim of this study was compare data deriving from the assessment of several clinical and instrumental variables, which were evaluated at the time of diagnosis and then after 1 year in a sample of IIH patients, to have an insight on the course of the disease as well as on the possible correlations among different outcome variables.

## Methods

For the purpose of this study, we included in our analyses all patients with a diagnosis of IIH admitted to our Neurology Unit from January 2012 to December 2012, and who had a complete re-assessment during a second admission after 1 year. Diagnosis of IIH was made on the basis of an intracranial pressure (ICP) of 200 mm $H_2O$ or more at lumbar puncture performed in the recumbent position, according to the International Headache Society diagnostic criteria included in the ICHD-II (2004) [1].

Possible causes of intracranial hypertension were excluded through accurate clinical interview and

examination, and by brain MRI as well as by MR arteriography and MR venography. Besides these neuroradiological evaluations, other relevant variables were recorded: presence of headache, transient visual loss, and tinnitus; BMI; presence of papilledema; ICP values.

At discharge from the first admission, acetazolamide 500–1,000 mg was prescribed. Patients were regularly followed during 1 year with neurological and ophthalmologic evaluations every 3–4 months, to manage therapy.

Treatment was gradually tapered down and interrupted during the 2 weeks preceding the second admission.

## Results

Among 48 consecutive IIH patients diagnosed during 2012, 21 presented the above inclusion and exclusion criteria. They were 15 women and 6 males, mean age was 41.3 (range 23–62) years.

Mean ICP value was 288 mm $H_2O$ (range 200–500) at the first observation, and 220 mm $H_2O$ (range 120–450) at follow-up; 15 patients (71 %) had normal ICP at follow-up.

Headache was present in 15 (71 %) at the first evaluation; improvement in pain frequency/intensity was observed at 1-year follow-up in 7 (46 %) patients with headache at the first evaluation. Transient visual obscurations (TVO) were present in 18 patients (86 %) at the first evaluation; improvement in their frequency was reported at the 1-year follow-up by 15 of them (83 %). Tinnitus was complained by 9 patients (43 %); 6 of them (67 %) reported regression and 1 (11 %) improvement at follow-up.

Papilledema was found in 11 patients (52 %) with 9 of them (82 %) showing improvement at the 1-year follow-up. Optic disk pallor was found in two patients (18 %), and it was stable at follow-up. In all those patients without optic disk alterations at the first observation, examination was normal also at follow-up.

Mean BMI was 28.2 (range 47–21) at the first observation, and 26.7 (range 46–21) at follow-up; 13 (62 %) had different degrees of overweight, and 5 of them (38 %) showed a decrease in BMI $\geq$3 kg at follow-up.

No significant abnormalities in cerebral hemispheres, cerebellum, brainstem and in ventricular size were noted at MRI. MRA was normal in all patients.

As regards other MRI findings: protrusion of the optic nerve papillae into the vitreous cavity was present in 5 patients (24 %); empty sella was present in 17 patients (81 %) at the first examination, and in 3 more patients at follow-up; perioptic subarachnoid space distension was observed in 16 patients (76 %) at the first examination, and in 3 more patients at the follow-up examination; optic nerve tortuosity was present at the first examination in 6 patients (28.5 %), and in 1 more patient at the follow-up examination; flattening of the posterior aspect of the globe was present in 9 cases (43 %) at the first examination, and in 1 more patient at the follow-up examination;

MRV at the first examination showed narrowing of one transverse sinus in 6 cases (28.5 %), agenesis of the left transverse sinus in 1 case and bilateral narrowing of the transverse sinuses in 14 cases (67 %). All these findings were present also at the follow-up examination.

Around a quarter (5 on 21) patients developed intolerance to acetazolamide, or relevant side effects (such as numbness and tingling in the fingers and toes, taste alterations, calcium phosphate kidney stones, and metabolic acidosis): in these cases, furosemide or topiramate were prescribed.

## Discussion

Our results confirmed that headache and TVO are the most frequent symptoms in IIH patients, and that overweight is a very common association [2, 7].

Comprehensive reports about clinical and instrumental findings in longitudinal evaluations are sparse, and generally encountered in review papers. Only a few studies have concentrated on some IIH features to understand their role as possible predictors of outcome [8–10].

Our findings suggest a trend towards a favorable outcome in patients followed for 1 year and treated by usual medical therapy: ICP was generally lower at follow-up, falling into the normal range in most patients at the 1-year follow-up; improvement in TVO ad headache was reported by around 80 % and around 50 %, respectively, of those who reported these symptoms at the first observation.

As regards the instrumental variables included in the study, our results were not homogeneous as far as changes at follow-up.

Signs of optic disk abnormalities were evident in most patients at the first evaluation, with a general trend towards a good outcome, with improvement or regression of papilledema at follow-up.

High rates of those neuroradiological findings, which have been described in IIH were present in our sample, particularly empty sella and perioptic subarachnoid space distension. The comparison between MRI and MRV examinations performed at the first and at the second examinations showed that they were substantially stable (in some cases with a trend to increase) at follow-up.

These findings may be relevant for future research as far as understanding the role of neuroimaging in IIH. In fact, neuroimaging is not evaluated as a major diagnostic item [1, 3], although recently published data indicate a high sensitivity and specificity of the above reported

abnormalities at MRI, particularly for perioptic subarachnoid space distension [6, 11]. Furthermore, venous abnormalities have been proposed as a crucial finding in IIH without papilledema, and as a putative crucial aspect in IIH mechanisms [12]. As suggested by Digre [12], future studies are warranted to explore the role of imaging findings to diagnose IIH, particularly in those patients without evidence of papilledema, as well as to evaluate the (possible) changes of specific imaging findings as predictors of outcome and/or their correlations with other clinical and instrumental variables.

**Conflict of interest** D. D'Amico certifies that there is no actual or potential conflict of interest in relation to this article.

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ORAL COMMUNICATIONS

# Recurrent epistaxis following stabbing headache responsive to acetazolamide

**A. Ranieri · A. Topa · M. Cavaliere · R. De Simone**



**Abstract** The co-occurrence of epistaxis and headache is not uncommon in migraine patients, although only few case reports have been published. A trigeminovascular activation may be causally involved although the exact mechanisms linking epistaxis and migraine remain unclear. Significant dural sinus stenosis may sustain or worsen an increased cerebral venous pressure and is considered a radiological predictor of idiopathic intracranial hypertension. We report a 49-year-old female patient with chronic migraine associated to stabbing headache-like attacks followed by epistaxis and by the resolution or the significant improvement of pain. As she also reported adjunctive symptoms suggestive of raised intracranial pressure and showed a bilateral narrowing of transverse sinuses at MR-venography, a possible intracranial hypertension was hypothesized despite the lack of papilledema. Acetazolamide 250 mg twice/day was added to therapy and the patient reported sudden reduction of headache severity and frequency and complete resolution of both the stabbing pain and the recurrent epistaxis, maintained for 5 months. At treatment discontinuation she complained the worsening of migraine headache and the reoccurrence of the superimposed stabbing pain followed by epistaxis. The mechanism linking the sequential occurrence of painful stabs, epistaxis and relief from pain with raised intracranial pressure in our patients remains unclear. We speculate that the sudden reopening of collapsed collateral veins of the anterior venous circle, possibly prompted by periodic waves of central venous hypertension coupled with intracranial hypertensive peaks, could explain the unusual strict time succession of painful stabs, epistaxis, and subsequent resolution of pain.

**Keywords** Migraine-induced epistaxis · Stabbing headache · Intracranial hypertension · Sinus stenosis · Chronic migraine

## Introduction

In 1967, Ikonomoff described the occurrence of frequent spontaneous epistaxis in patients with "cerebro-cardiac form of migraine" [1] and successively, studying 24 patients with nose-bleeding, noticed that more than half of them presented with migraine [2]. A more recent controlled study on a pediatric population revealed that children affected with migraine were fourfold more likely to have a history of recurrent epistaxis than controls [3]. Despite these observations, to date only three cases of epistaxis occurring during a migraine attack have been described [4–6]. A trigeminovascular activation may be pathogenetically involved although mechanisms linking epistaxis and migraine remain unclear.

Idiopathic intracranial hypertension (IIH) is characterized by signs and symptoms of elevated intracranial pressure (ICP) without evidence of intracranial pathology. The diagnosis is based on the presence of papilledema, although cases without papilledema (IIHWOP) have been described. Because of the absence of papilledema, IIHWOP and chronic migraine are often clinically indistinguishable and its identification in chronic headache series is reported [7–9]. To date, sinus stenosis is considered a reliable predictor of IIH [10] and it is now included in IIH/IIHWOP diagnostic criteria [11]. Notably, sinus stenosis at magnetic

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resonance venography (MRV) is much more prevalent than expected in both IIHWOP and CM [12, 13] as well as in primary stabbing headache [14].

## Case report

We report a 49-year-old female patient diagnosed with migraine without aura and an almost 15 years history of chronic migraine. The patient presented with a near daily mild pain with frequent and long lasting exacerbations. She also complained of primary stabbing headache-like attacks, lasting 1–5 s. She reported that painful stabs superimposed to ongoing migraine pain, usually felt in the right parietal area, were immediately followed by epistaxis that coincided with the reduction of migraine intensity or by the resolution of pain. Epistaxis had regularly occurred about 4–5 days per month since many years, up to three times a day. The nosebleeds never occurred without such a pain. At observation the patient was assuming topiramate at the maximum tolerated dose of 50 mg/day with poor response. She also reported symptoms suggestive of raised ICP such as sense ear fullness, dizziness, transient blurred vision and worsening of headache in the recumbent position, but no papilledema was observed. General physical and neurological examinations were normal. No engorged mucosa or nostrils varicose vessels were found at ORL examination. Brain MRI was normal while MRV showed a bilateral narrowing of the proximal segment of both transverse sinuses.

A possible intracranial hypertension without papilledema associated to sinus stenosis was hypothesized and acetazolamide 250 mg twice/day was added to therapy. The patient reported a sudden reduction of headache severity and frequency (less than 15 headache days/month) and the complete resolution of both the stabbing pain and epistaxis, maintained for 5 months. At treatment discontinuation she complained the relapse of a chronic headache pattern and the reoccurrence of the painful stabs regularly followed by epistaxis.

## Comments

According to a controlled study, epistaxis is more frequent than expected in migraine patients [3]. A trigeminovascular activation is considered the shared pathogenetic step that might explain such comorbidity. However, epistaxis was found to precede migraine onset by 3 years on average and a strict temporal association between nosebleeds and headache was found in less than one-third of cases [3]. Moreover, as suggested by Barros [6] the trigeminovascular hypotesis presents an epidemiological weakness as migraine is common while the co-occurrence of migraine and epistaxis is infrequent. Thus, a pathogenetic mechanism different from the trigeminovascular vasodilation could be involved.

In the past history of our patient, the onset of chronic migraine was associated with symptoms suggestive of raised ICP and superimposed stabbing headache with subsequent epistaxis. The condition dramatically responded to acetazolamide, a drug lacking any efficacy in migraine prevention [15] and promptly relapsed after its discontinuation. These observations strongly suggest that the whole clinical presentation was secondary to a fluctuating raised ICP associated to sinus stenosis.

Notably, as in cases previously described [4–6], also in our patient the epistaxis preceded headache relief or resolution. The mechanism linking the sequential recurrence of stabbing headache, epistaxis and relief from pain with raised ICP is unclear. Most IIH/IIHWOP patients show large intraday ICP fluctuations [12, 16]. Moreover, there is evidence that cerebral venous outflow in IIH is partly shifted to vertebral venous circle via collateral afferents [17]. We speculate that in our patient with an unknown predisposition to nasal bleeding, a sudden shift of cerebral venous outflow towards the anterior venous circle, possibly prompted by a coupled venous/ICP hypertensive peak, could simultaneously explain: the painful stabs possibly due to the abrupt stretching of collateral veins of the anterior circle in course of nociceptive sensitization; the epistaxis possibly due to the acute venous congestion of nasal mucosae in a nose-bleeding predisposed individual; and the relief or remission of pain possibly promoted by the normalization of venous pressure and in turn of the ICP after the partial shift of venous outflow towards collateral veins. Such a model could be involved in the pathogenesis of idiopathic stabbing headache, a condition whose frequent association to sinus stenosis has been recently reported [14].

**Conflict of interest** None.

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ORAL COMMUNICATIONS

# Prevalence and profile of obsessive–compulsive trait in patients with chronic migraine and medication overuse

**M. Curone · V. Tullo · C. Lovati · A. Proietti-Cecchini · D. D'Amico**



**Abstract** Patients with chronic migraine (CM) and medication overuse headache (MOH) have high frequency of psychiatric comorbidity or psychopathological traits, the presence of which can influence the clinical course. The presence of subclinical obsessive compulsive disorder (OCD) is underestimated in migraine patients. The aim of this study was to estimate the prevalence and profile of obsessive–compulsive (OBS) trait in a sample of CM patients with MOH using the OBS questionnaire of Spectrum Collaborative Project. According to the new international classification of headache disorders (ICHD-III beta) criteria, 106 patients (15 M, 91 F, mean age 47.3 years) were selected in a consecutive clinical series. Our results showed that 36 % of patients with CM and MOH were positive at OBS-questionnaire. As far as the profile of OBS trait, we performed an evaluation of prevalence of items separating the first part of the questionnaire (childhood/adolescence and doubts in lifetime) from the other five domains: 21 % of the patients showed prevalence of items in childhood/adolescence domain; 79 % in doubts in lifetime domain; as for other five domains, 10.5 % of patients had prevalence of pathological answers among hypercontrol, 5.2 % in spending time, 23.7 % in perfectionism, 29 % in repetition and automation, and 31.5 % in specific themes (obsessive thoughts). The presence of subclinical OCD in migraine patients, and the link between progression to CM, particularly through MO, and OBS trait is still not well defined. The use of specific tools to assess this possible comorbidity should be encouraged in clinical and research settings.

**Keywords** Chronic migraine (CM) · Obsessive–compulsive disorder (OCD) · Obsessive–compulsive trait · Medication overuse headache (MOH)

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## Introduction

Patients with chronic migraine (CM) and medication overuse headache (MOH) have high frequency of psychiatric comorbidity or psychopathological traits, the presence of which can influence the clinical presentation, both as far as for response to treatment and long-term prognosis, including the possible relapses and the direct and indirect costs [1–3]. The obsessive–compulsive disorder (OCD) is characterized by the presence of obsessions out of the patient's control which cause anxiety and distress, and compulsions which are repetitive behaviors to prevent or reduce this anxiety [4]. A subclinical OCD can be a comorbid condition in migraine patients although a specific diagnosis is often lacking with a consequent underestimation of this association [5]. A compulsive quality of the behavior seems to be a feature shared by migraineurs with MO—who may overuse of symptomatic compounds due to the fear of next headache—and patients with OCD.

The spectrum collaborative project was established to develop and test instruments for the assessment of the spectrum of clinical features in psychiatric disorders, and is a complementary way of describing and assessing psychopathology by exploring personality traits with structured clinical interviews and self-reports [4]. The OBS spectrum assessment with self-report (lifetime) considers the different clinical expressions of the OCD which in fact may be the

only manifestation of the disorder. The OBS questionnaire (self-report, lifetime) of spectrum collaborative project consists of 183 items coded as present or absent (yes/no) for one or more periods of at least 3–5 days through the subject's lifetime or over the past week or month. It includes seven domains of questions regarding: childhood/adolescence (feelings or experiences that patient may have had during this period), doubt in lifetime (feelings, experiences, doubts at any time during the whole life), hypercontrol, spending time, perfectionism, repetition and automation, specific themes (obsessive and intrusive thoughts, feeling preoccupied with, feeling compelled to). Each item is scored as "0" (NO), "1" (YES). The threshold for total score for OBS self-report, lifetime is: 59 [4, 6].

The aim of this study was to estimate the prevalence and the profile of OBS trait in a sample of migraine patients with MOH.

## Patients and methods

Patients admitted to our headache center for headache evaluation from July 2013 to December 2013 were screened and selected according to the new third edition of the International Classification of Headache Disorders (ICHD-III beta) [7]. All those patients who satisfied both the diagnostic criteria for CM and MOH were admitted for inpatient withdrawal program to stop MO, and were invited to fill the OBS questionnaire (self-report, lifetime) of spectrum collaborative project at admission. Data obtained from OBS-questionnaires were added in an ad hoc database and analyzed. Regarding the profile of OBS trait, we performed an evaluation of prevalence of items separating the first part of the questionnaire (childhood/adolescence and doubts in lifetime domains) from the other five domains (hypercontrol, spending time, perfectionism, repetition and automation, specific themes (obsessive thoughts). We also performed a total score evaluation using it as a severity index of the OBS trait.

## Results

Among 489 screened patients, 106 (15 M, 91 F), mean age 47.3 years (range 20–71) with CM and MOH were included in the study. The analysis of data from the OBS questionnaires showed that 38 patients 36 % (4 M, 34F, mean age 50.1 years, range 29–71 years) exceeded the score of 59 items; 8/38 (21 %) patients showed prevalence of items in childhood/adolescence domain and 30/38 (79 %) in doubts in lifetime domain; as for other five domains, 4/38 (10.5 %) patients had prevalence of pathological answers among hypercontrol, 2/38 (5.2 %) in spending time, 9/38 (23.7 %) in perfectionism, 11/38 (29 %) in repetition and automation, and 12/38 (31.5 %) in specific themes (obsessive thoughts). Moreover, 8/38 (21 %) patients wrote down in the questionnaire several personal comments a part from the questions, in order to further specify the meaning of some answers (which was not requested): we considered this aspect as an additional possible obsessive trait. As regarding total score, the average score resulted 76.5/183 items (range 60–129) and 21/38 (55.2 %) patients showed a total score over 75/183 items.

## Discussion

Obsessive compulsive trait as well as subclinical OCD may have prognostic significance in the clinical course of CM patients [8–10]. Although some studies have highlighted the presence of OCD in patients with CM and MOH, the link between CM, MOH and subclinical OCD or OBS trait is still not well defined [8–10]. In this survey we performed an analysis of the scores to subscales in order to have an insight into the profile of the (sub)clinical OBS components in each patient. The relevant percentage of patients with prevalence of items in perfectionism, repetition/automation and in specific themes (obsessive thoughts) domains suggest that obsessive feelings and compulsions can fill the life of patients with CM and MOH more than headache, and also that the obsessive fear of pain may contribute to MO maintenance. The lack of control on impulsivity in these patients can increase the symptomatic drug intake and thus enhance the risk for progression from episodic to CM. Spectrum OBS self-report, lifetime instrument can be scored in a variety of ways, depending on the needs of the user, so clinicians and researchers can decide how to use it [4]. Performing a total score evaluation using it as a severity index allowed us to show that more than a half of our patients had a total score over 75/183 items, which indicates a tendency to show more psychopathological signs and behaviors although with a subclinical threshold: this aspect can provide a useful characterization of the importance of the OBS trait in these patients, potentially leading to a OCD. Since the comorbidity of untreated OCD or subclinical OCD in patients with CM and MOH may explain the failure of standard migraine preventive treatments and early relapse of MO, the personality of these patients should be deeply studied in order to reach an individually tailored treatment strategy [5, 10]. We found that ideas, thoughts, intrusive feelings, and repetitive behaviors reported by the studied patients were in fact part of the clinical features of OCD, but they did not fit

completely with the strict diagnostic criteria of DSM-V: this leads to a lack of specific psychiatric diagnosis. We note that the spectrum instrument for assessment of OBS trait (self-report, lifetime) [4, 6] is an easy to score and understand tool, and thus it could be used in CM patients, particularly in those with MOH, to exclude or confirm a psychopathological trait before starting a new preventive treatment.

**Conflict of interest** The authors certify that there is no actual or potential conflict of interest in relation to this article.

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ORAL COMMUNICATIONS

# Ear acupuncture and fMRI: a pilot study for assessing the specificity of auricular points

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**Abstract** In recent years research explored different acupuncture stimulation techniques but interest has focused primarily on somatic acupuncture and on a limited number of acupoints. As regards ear Acupuncture (EA) there is still some criticism about the clinical specificity of auricular points/areas representing organs or structures of the body. The aim of this study was to verify through (Functional magnetic resonance imaging) fMRI the hypothesis of EA point specificity using two auricular points having different topographical locations and clinical significance. Six healthy volunteers underwent two experimental fMRI sessions: the first was dedicated to the stimulation of Thumb Auricular Acupoint (TAA) and the second to the stimulation of Brain Stem Auricular Acupoint (BSAA). The stimulation of the needle placed in the TAA of the left ear produced an increase in activation bilaterally in the parietal operculum, region of the secondary somatosensory area SII. Stimulation of the needle placed in the BSAA of the left ear showed a pattern that largely overlapped regions belonging to the pain matrix, as shown to be involved in previous somatic acupuncture studies but with local differences in the left amygdala, anterior cingulate cortex, and cerebellum. The differences in activation patterns between TAA and BSAA stimulation support the specificity of the two acupoints. Moreover, the peculiarity of the regions involved in BSAA stimulation compared to those involved in the pain matrix, is in accordance with the therapeutic indications of this acupoint that include head pain, dizziness and vertigo. Our results provide preliminary evidence on the specificity of two auricular acupoints; further research is warranted by means of fMRI both in healthy volunteers and in patients carrying neurological/psychiatric syndromes.

**Keywords** Auricular acupoints · Ear acupuncture · fMRI · Pain matrix · Somatotopic representation

**Abbreviations**

| | |
|---|---|
| EA | Ear acupuncture |
| SA | Somatic acupuncture |
| TAA | Thumb auricular acupoint |
| BSAA | Brain stem auricular acupoint |
| fMRI | Functional magnetic resonance imaging |

## Introduction

In recent years an increasing number of studies has been published investigating brain response to acupuncture stimulation. However, even if research explored different stimulation techniques, the interest was focused primarily

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on somatic acupuncture (SA) and on a limited number of acupoints (i.e. LI 4, ST 36, BL 60, [1]).

Advances in imaging techniques have made it possible to reach a certain consensus regarding the main brain networks involved in SA needle stimulation [2] and have shown the systematic involvement of brain areas such as the somatosensory and association cortices (SI and SII), insula, thalamus, amygdala, hippocampus and cingulate cortex. Taken together, these distributed brain areas belong to the network known as the "pain matrix" [3], but their responses can highlight the dissociation between the sensory-discriminatory aspect of pain and its affective component elicited by nociceptive stimuli [4]. Similarly, it has also been shown that the same regions are involved and modulated in pain anticipation [5], analgesia and placebo conditions [6, 7].

Since one of the main goals of acupuncture is to contribute to pain relief, the assessment of its specific therapeutic effects through the interaction with the pain matrix has a key role in evaluating brain imaging results.

As regards ear acupuncture (EA), despite its worldwide increasing application [8], there is still some criticism and a low level of evidence about the clinical specificity of auricular points/areas representing organs or structures of the body. In particular, scientific evidences of the somatotopic representation of the human body on the outer ear, a basilar concept on which EA is based, are scarce. Only one paper describes the consistent correlation between the stimulation of the auricular thumb area and the cortical activation of the correspondent S1 cortex [9].

The aim of this preliminary study was to highlight the brain correlates of EA and the specificity of two different auricular acupoints [Thumb Auricular Acupoint (TAA) and Brain Stem Auricular Acupoint (BSAA)] having different topographical location and clinical significance.

## Materials and methods

Six healthy volunteers (three male, three female; mean age 43.8 years) underwent two experimental fMRI sessions, spaced 24 h apart. All the participants provided written informed consent according to the Vaud Ethics Committee approval for MR pilot studies. The first session was dedicated to the stimulation of the TAA and the second to the stimulation of the BSAA for a total of four fMRI sessions per subject. We used titanium semi-permanent needles (ASP, Sedatelec, France) to stimulate the two acupoints. Each experiment was organized in a block- design fashion, with an alternation of four active and four rest blocks, each of them lasting 30 s. The first session consisted of three

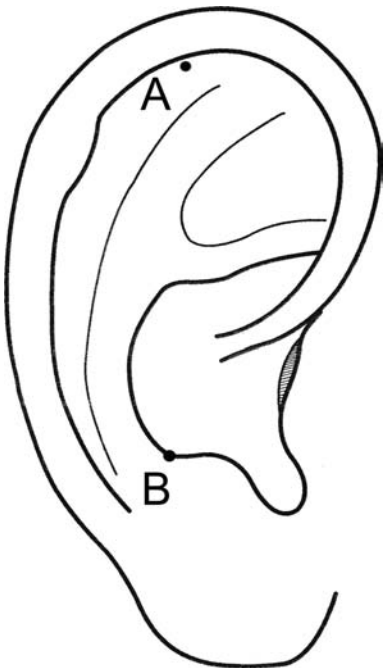


**Fig. 1** Location on the outer ear of thumb auricular acupoint (TAA, *A point*), and the Brain Stem Auricular Acupoint (BSAA, *B point*)

fMRI sessions. The active phase involved: flexion–extension of the left thumb, passive stimulation of the left thumb, and mechanical stimulation of the needle inserted in the TAA of the left ear. The TAA (Fig. 1, point A) was selected replicating the historic experiment performed by Paul Nogier and René Bourdiol [10]. We applied a nociceptive stimulation through a dynamometric clamp calibrated at 2 kg/cm$^2$ to the left thumb for 60 s. The pain evoked during stimulation had to be maintained in each volunteer on a threshold basis of 5 on a Numeric Rating Scale (NRS) of pain ranging from 0 = no pain to 10 = worst pain. One minute after the nociceptive stimulation was stopped, one point in the somatotopic area of the thumb in the ear became hyperalgesic at palpation using a pressure probe of maximal 250 gr pressure (Pain Pressure Test—PPT) [8]. This point corresponded to the TAA in which the needle was inserted.

The second session was dedicated to the stimulation of BSAA and involved one fMRI experiment. The active block consisted in the mechanical stimulation of the needle in the BSAA of the left ear. The brain stem point *naogan* of the Chinese standardized auricular map corresponds exactly to the landmark of the notch between the antitragus and the antihelix [11] (Fig. 1, point B). This point was therefore identified at inspection and marked with ink without performing any PPT.

In both, sessions participants were asked to rate the pain they were experiencing through the NRS in four occasions: right after needle insertion, at 120 and 180 s after insertion,

and after the fMRI to evaluate the pain felt during the mechanical stimulation of the ASP.

Image acquisition and processing

MRI protocol was performed on a Siemens 3T Tim Trio scanner and included a sagittal T1-weighted gradient-echo sequence (MPRAGE, 160 contiguous slices, 1 mm isotropic voxel, TR = 2300 ms, TE = 2.98 ms, FoV 256 mm) and the fMRI acquisition. Functional scans were acquired with an EPI sequence (TR = 3,000 ms, TE = 30 ms, flip angle = 90°, FoV 256 mm). The 28 axial slices (matrix size 128*128 with 4 mm slice thickness) were aligned with the anterior commissure–posterior commissure line. During each experiment, we collected 10 volumes for each block, for a total of 80 images. Magnetic resonance imaging data were pre-processed and analyzed using Statistical Parametric Mapping (SPM8, Wellcome Department of Imaging Neuroscience, London, England; http://www.fil.ion.ucl.ac.uk). Functional images were corrected for motion along the experiment by the mean of rigid-body transformations and then co-registered to the high-resolution T1w acquisitions. The anatomical images were then normalized to the MNI T1 template and the normalization parameters were applied to the functional images, which were finally smoothed with a 6 mm Gaussian kernel. All the pre-processing steps mentioned minimized the non-task-related variability, and thus the source of error within the acquired fMRI time series. Single-subject statistics were performed according to the General Linear Model and group analyses were performed modelling within-subject variability as fixed-effects. Contrasts of interest were thresholded for peak height at $p = 0.05$ (family-wise error (FWE) corrected), with an extent threshold ($k$) of 50 voxels. The limitation of modelling intra-subject variability as fixed effect implies that the results described should be considered descriptive thus providing valid inference only about the specific sample used [12].

## Results

Numeric Rating Scale pain scores decreased from a mean value of 4.6 ± 2.4 and of 5.1 ± 2.5, for TAA and BSAA, respectively, immediately after needle insertion, to 0.8 ± 1.1 and to 0.8 ± 0.7 after 120 s, and to 0 for both needles after 180 s. The mean value reported by subjects during the fMRI session was 3.6 ± 3.9 for TAA and 0.3 ± 0.5 for BSAA.

Functional MRI of voluntary movement of the left thumb revealed extensive activation of the right motor, right primary and secondary somatosensory (M1, SI and SII) cortices with a maximal activity in the precentral gyrus. Gentle touch showed a similar pattern in SI and SII cortices.

These first two experiments served as the basis for defining the volumes of interest for the detection of the effects of TAA stimulation. The applied mask included all sensory motor areas of the thumb (bilateral primary and secondary somatosensory cortices, primary motor cortex, supplementary motor area, and the cerebellum). The mask was created by thresholding the group result of the motor and touch paradigms ($p < 0.05$ FWE corrected) and by adding the same region mirrored to the other hemisphere. By applying the mask thus defined, activations of the TAA stimulation could be easily compared to the brain regions involved in either the voluntary movement or in gentle touch in both hemispheres.

As depicted in Fig. 2, the stimulation of the needle placed in the TAA of the left ear produced a focal increase in activation bilaterally in the parietal operculum, region of the secondary somatosensory area SII (clusters' centre of gravity: $x, y, z = -53, -26, -24$ and $62, -18, 18$ in MNI coordinates).

Stimulation of the needle placed in the BSAA of the left ear showed a significant and extensive pattern of increase and decrease activation compared to rest (Fig. 3, top row). Maximum intensity increase was reached in the left anterior insula (center of gravity of the cluster in the MNI 345 space $x, y, z = -40, 8, -2$) although the involvement of this region was bilateral ($x, y, z = 38, 13, -2$, Fig. 3,

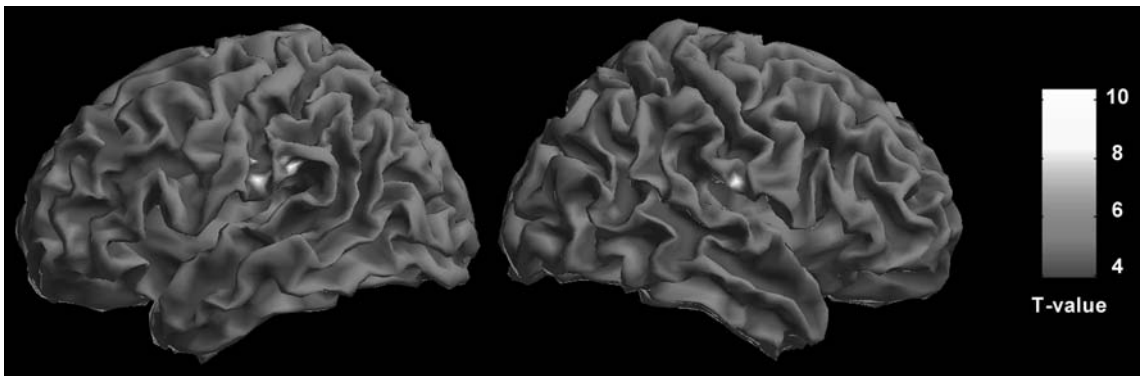


**Fig. 2** fMRI results of TAA stimulation represented on a 3D surface ($p < 0.05$ FWE corrected). *Colorbar* represents *T* values (color figure online)

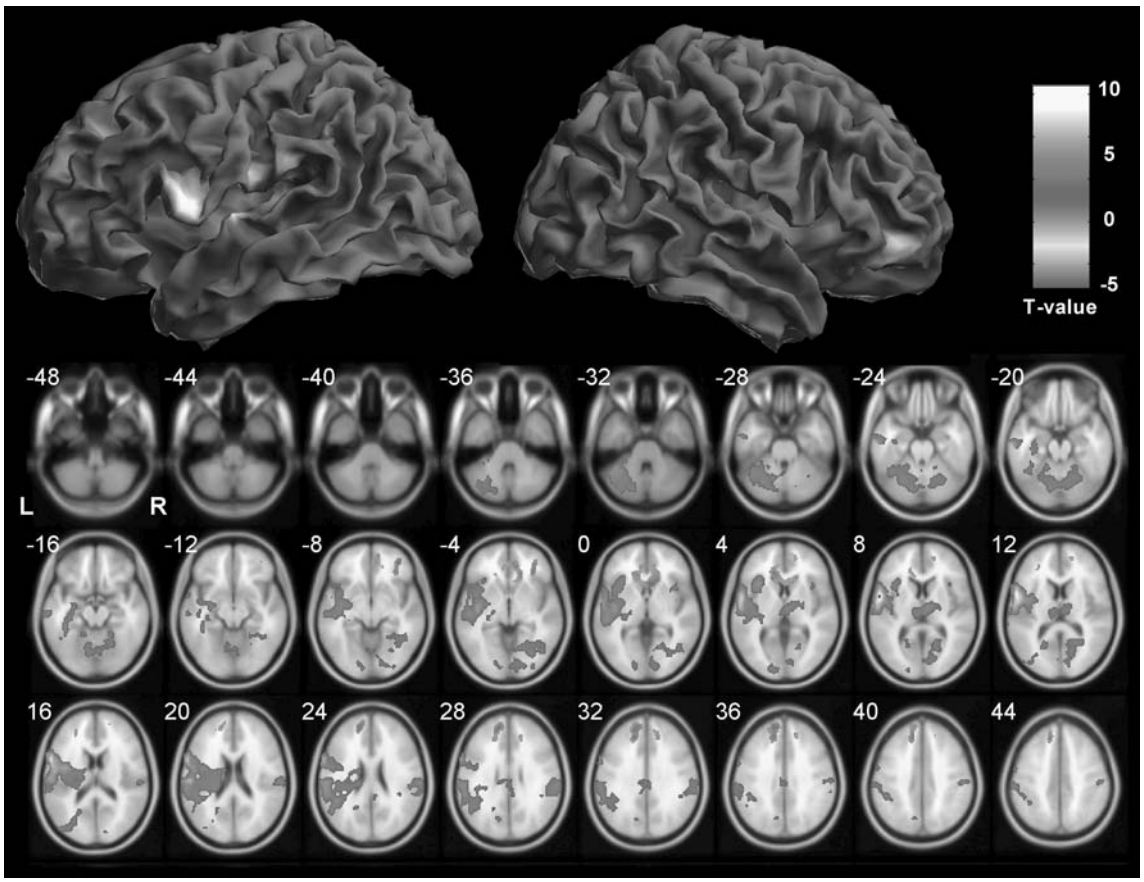


**Fig. 3** fMRI results of BSAA stimulation represented on a 3D surface (*top row*). Axial slices show deep activations ($p < 0.05$ FWE corrected). *Colorbar* represents *T* values (color figure online)

bottom part). A larger cluster included the left posterior insula ($x, y, z = -36,-18,-2$), extending to the precentral and inferior frontal gyri ($x, y, z = -57, 0, 7$). The bilateral involvement of postcentral ($x, y, z = -58, 19, 17$) and supramarginal gyri ($x, y, z = -57, 29, 24$) showed predominance in the left hemisphere. Moreover, we evidenced a bilateral increase of the BOLD signal in the thalamus ($x, y, z = 8,-12,7$ and $-8, -19, 7$), in the left amygdala ($x, y, z = -26, -6, -18$), and in the cerebellum (Lobule 4 and 5 bilaterally and lobule 6 with a left predominance).

Decreased activity compared to rest was found in the medial frontal gyrus ($x, y, z = 8, 48, -6$) extending to the subgenual anterior cingulate cortex ($x, y, z = 9, 34, 0$), in the caudate ($x, y, z = -5, 17, 0$ and $6, 15, 0$), in the superior frontal gyrus bilaterally ($x, y, z = -14, 44, 32$ and $13, 35, 31$) and in the right orbitofrontal cortex ($x, y, z = 35, 48, -9$).

It should be mentioned that activation of the brain due to the touching of the ear was removed from these results by excluding the region commonly activated in both experiments, and that the pattern of deep activations found during BSAA stimulation was absent in TAA activation (without the mask restriction).

Linear correlation analysis between the BOLD signal and NRS score of each subject at needle insertion did not show any statistically significant relations.

## Discussion

Our preliminary study achieved two main results, giving new evidence of the specificity of EA. We studied two acupoints located on distant parts of the ear and having different clinical significance. First, we showed that stimulation of the TAA selectively activates the secondary somatosensory area bilaterally. Instead, the stimulation of the BSAA, in accordance with its therapeutic effect, mostly activates cortical and limbic regions that are part of the pain matrix.

The thumb point was identified with PPT which is a reliable and reproducible method used by acupuncturists to identify one or more ear acupoints related to ailments and dysfunctions in the body. It should be remarked that the representation of the human body on the auricle is probably "homunculus-like" and auricular diagnosis relies on the identification of more or less larger areas which are

proportional to innervation and functionality of the corresponding structure. In this respect, from the diagnostic point of view the thumb probably has a larger representation than the other fingers of the hand. Therefore, the identification and the treatment of the most tender point within this area may give the best therapeutic effect.

Whereas the TAA has the same indication, i.e. pain, overall on different auricular maps, the BSAA has a very different clinical significance according to Western and Chinese auricular maps. In Western maps it is considered as the atlas (C1) point, whereas according to Chinese standardized maps it holds the name of brain stem point *naogan* and is indicated for Ménière's disease, epilepsy, brain trauma, allergic dermatitis and headache. According to Romoli [8] this point seems to be active in insomnia, tension-type headache, depression, dizziness, vertigo and postural disorders with chronic cervical and lumbar pain. It is therefore interesting that the stimulation of this point may activate areas of the pain matrix involved in the processing of the affective-cognitive components of pain perception. Literature indicates that activity in regions belonging to the pain matrix are downregulated and upregulated in response to pain [4]. More specifically, the caudal part of the Anterior Cingulate Cortex (ACC) generally shows increase in BOLD response during pain while activity in the amygdala is generally downregulated after a noxious stimulus. In contrast to this and in apparent discrepancy with results on somatic acupuncture [1, 2, 13], we found an increase in BOLD response in the left amygdala and failed to find any significant activation in the caudal ACC. A possible explanation of our findings may rely on the fact that none of our subjects experienced pain during needle stimulation, so no adaptive strategies to pain were needed (see. "Results" on NRS pain scores). Furthermore, in light of the well-known function of the amygdala in processing the affective component of pain and in analgesia, these changes of activation may be due to the therapeutic effects characteristic of BSAA.

A further significant result is the increase of BOLD response found in the cerebellum. Vertigo, dizziness, ataxia or postural problems are symptoms related to a dysfunction of the vestibular system [14]. The activations found in the insula, extending to its posterior part in the left hemisphere, in the temporo-parietal cortex and the cerebellum, support the interaction of the acupoint stimulation with the vestibular network, in accordance with the mentioned additional therapeutic indications of BSAA.

The activation pattern found during BSAA stimulation, although involving symmetrical regions, show a clear predominance in the left hemisphere. This finding is in accordance with the hypothesis that auricular acupoints mainly project in the hemisphere homolateral to the stimulated ear.

The results of our pilot study show that specificity of auricular acupoints can be assessed by fMRI and that brain responses for the two acupoints tested (TAA, BSAA) might be linked to their respective therapeutic indications. The present study provide a basis for supporting the systematic investigation of other auricular points, especially areas of the outer ear, such as the tragus, antitragus and ear lobe which are supposed to be correlated with different parts of the central nervous system.

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ORAL COMMUNICATIONS

# Acupuncture in cluster headache: four cases and review of the literature

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**Abstract** Although cluster headache (CH) is the most disabling form of primary headache, little evidences regarding alternative and complementary therapies are available. Only few dated studies and some isolated cases are described. We describe four patients with CH treated with acupuncture as a preventive treatment, combined with verapamil or alone. All patients received acupuncture treatment twice/week for 2 weeks, then once/week for 8 weeks, and then once/alternate weeks for 2 weeks. According to Traditional Chinese Medicine the acupoints selected were: Ex HN-5 Taiyang, GB 14 Yangbai (both only on the affected side), GB 20 Fengchi (on both sides), LI 4 Hegu, LR 2 Xingjiang, SP 6 Sanyinjiao, ST 36 Zusanli (all on both sides). At each point, after the insertion of the needle, the feeling of "*De Qi*" was evoked; after obtaining this sensation the acupoints were not further stimulated for a period of 20 min, until their extraction. In all patients an interruption of cluster attacks was obtained. To our knowledge, this is the first report concerning acupuncture in CH patients which details the protocol approach, acupoints and duration of the treatment. Our results offer the opportunity to discuss the emerging role of acupuncture in the therapy of CH, assuming a possible influence on opioid system.

**Keywords** Acupoints · Acupuncture · Cluster headache · Preventive treatment

**Abbreviation**
CH Cluster headache

## Introduction

Cluster headache (CH) is a rare type of primary headache, probably the most disabling and painful [1]. It is characterized by strictly unilateral pain attacks in the orbital, supraorbital and temporal region (or in any combination of these sites), lasting 15–180 min and occurring 1–8 times/day [2]. The pain, described as 'burning', 'throbbing' or 'penetrating', is so severe that CH is also called 'suicide headache', because some patients contemplated committing suicide during an attack, or when afraid of another attack [3] (Fig. 1).

Although recurrent in most cases, CH has considerable impact on social functions, quality of life and use of healthcare so that lifestyle changes are described in 96 % of the patients. The use of specialists and off-hour services was significantly higher among cluster patients in comparison with the general population [4].

The employment of acute symptomatic therapies (subcutaneous sumatriptan, inhalation of 100 % oxygen, parenteral dihydroergotamine, and oral zolmitriptan) and prophylactic treatments (steroids, verapamil, lithium, valproic acid, topiramate, indomethacin, and others) is well

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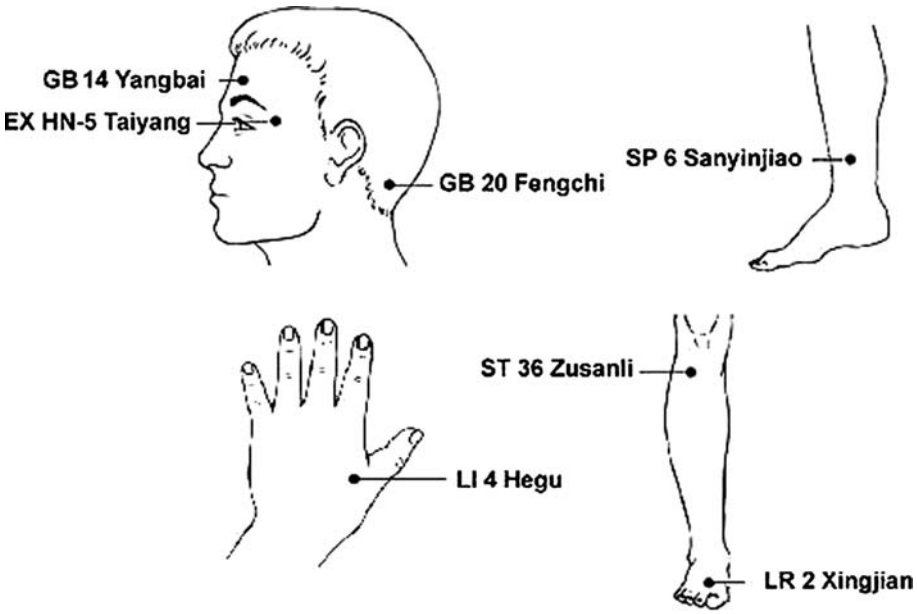


**Fig. 1** Name and location of the acupoints used in our patients affected by CH

documented. However, a proportion of patients does not respond to these conventional therapies or only partially responds, whereas others complain of significant side effects [1]. Some untreatable cases require invasive treatments [5] such as neurosurgical approaches or prescription of hallucinogenic substances [6].

There are little evidences about alternative and complementary non-invasive therapies for CH [7–9]. No other studies on the use of acupuncture in CH explain a detailed protocol or acupoints utilized.

To our knowledge, this is the first report which document the efficacy of acupuncture in CH and proposes an acupuncture treatment protocol.

## Materials and methods

We describe four patients with CH treated with acupuncture as a preventive treatment, combined with verapamil or alone. All patients were treated with the same acupuncture protocol. During the protocol all patients collected daily headache diaries.

### Acupuncture points and treatment protocol

The Traditional Chinese Medicine (TCM) describes a syndromic picture very similar to the CH called "Liver Fire", characterized by severe headache with "burning, throbbing, distending or penetrating" pain located in the oculo-temporal region, conjunctival injection, nausea, vomiting, runny nose, tearing, agitation, sensation of heat and sweating of the face.

For the acupunctural treatment we selected the acupoints according to TCM, as follows:

Local points: Ex HN-5 Taiyang, GB 14 Yangbai (both only on the affected side).

Regional points: GB 20 Fengchi (on both sides).

Distal points: LI 4 Hegu, LR 2 Xingjiang, SP 6 Sanyinjiao, ST 36 Zusanli (all on both sides).

All points were punctured by experienced acupuncturists with 0.3 mm diameter sterile disposable steel needles (lenght: 52 mm), that were inserted to a depth of 10–30 mm and manipulated until the patient reported the characteristic irradiating sensation, said to indicate effective needling, that is commonly called *De Qi*; after obtaining this sensation the acupoints were not further stimulated for a period of 20 min, until their extraction.

All patients received acupuncture treatment twice/week for 2 weeks, then once/week for 8 weeks, and then once/alternate weeks for 2 weeks.

### *Case report no. 1*

A 39-year-old male, reporting a 20 years history of episodic CH happening in July–August or November–December. Until 2008 he had one cluster period every 2 years (2–3 attacks/week), then the frequency increased and became annual. The pain was stabbing, strictly unilateral, localized on right orbital-supraorbital region, lasting 15–20 min and usually occurred during the night. Associated symptoms were photophobia, phonofobia, agitation, restlessness, and marked autonomic signs (ipsilateral tearing, rhinorrhea, conjunctival injection, miosis, forehead and facial sweating and flushing). During the last 3 years, verapamil (360 mg/day) was effective in suppressing the cluster period, until the last time when the attack frequency remained four per week, despite this treatment. For this reason he started acupuncture

according to our protocol while continuing verapamil. After the third acupuncture treatment a reduction of the number of attacks was observed, after the sixth treatment the verapamil dose was reduced to 240 mg/day, after the ninth treatment to 120 mg/day and stopped completely after the tenth treatment. Remission was maintained with one acupuncture/week for another 4 weeks.

A new cluster started after 45 days from the last treatment, so that acupuncture alone with the same protocol was promptly initiated with immediate benefit.

*Case report no. 2*

A 23-year-old male was diagnosed with chronic CH ab initio 5 years prior. The cluster frequency was 1–4 attacks/day and the attack duration was 120 min; the pain, localized on left orbital and fronto-temporal areas, was associated with ipsilateral tearing, conjunctival injection, palpebral oedema, agitation and irritability. Sumatriptan s.c. was rapidly effective for attacks, while oxigen mask therapy was not. For prevention, prednisone, lithium and verapamil (360 mg/day) were not effective; only verapamil (600 mg/day) was able to reduce the attacks, but not to induce remission (one attack on alternate days). The combination of acupuncture and verapamil (360 mg/day) led to a frequency of 1–4 attacks/month. The remission was maintained for 2 months after the end of the acupuncture treatment. Cluster headache attacks then returned with a frequency of one attack daily. Reintroducing acupunture, the frequency fell to one attack/week.

*Case report no. 3*

A 38-year-old male, presented the onset of episodic CH when he was 19 years old; cluster period: March–June; frequency from 2–3 attacks/day to 6–7/day with a duration of 20 min. The pain site was left temporo-parietal, frontal, orbital, rarely on upper dental arch. Pain was severe, throbbing and associated with rhinorrea, tearing, conjunctival hyperemia and palpebra oedema. Sumatritpan s.c. was effective as acute treatment. Generally at the beginning of the attacks he took verapamil (360 mg/day) which was able to progressively reduce the frequency to 1/day in 2 weeks and to stop the cluster. During a second cluster period, verapamil combined with acupuncture was prescribed and a complete remission was obtained. The following year, at the beginning of the cluster, he immediately started acupuncture alone, without verapamil, with the same scheduled protocol and after 2 weeks CH went into remission.

*Case report no. 4*

A 43-year-old female, with CH onset when she was 25 years-old. The attacks happened annually, in the period from January to March with a frequency of 1–2 attacks/day, mainly during the night and with a duration of 60–120 min. The pain site was localized on right ocular region, with irradiation to the root of the nose and to ipsilateral side of the head. The pain was penetrating, burning and associated with photophobia, body sweating, rhinorrea and omolateral tearing, nasal congestion and irritability. She obtained a complete resolution of pain with sumatriptan s.c., but did not respond to oxygen-therapy. For prophilactic therapy methysergide was prescribed, but it was immediately stopped for adverse effects. A 20 day verapamil treatment (360 mg/day) was effective in interrupting the cluster but the patient did not tolerate the drug.

So, at the onset of a new cluster period, a combined treatment of acupuncture and a low dose of verapamil (240 mg/day) was started. After 2 weeks verapamil was reduced to 120 mg/day because attacks decreased to 1 every 3 days. CH remission was obtained after 20 days of acupuncture and verapamil was discontinued.

She needed acupunture plus verapamil (120 mg/day) for six CH periods, after that, acupuncture alone was administered when necessary for the following 3 years.

## Discussion

Acupuncture is nowadays one of the most widespread forms of complementary medicine [10, 11] used for the treatment of chronic pain, including headaches [12, 13]. In the 1990s it was demonstrated that acupuncture was more effective than placebo for the treatment of headache and migraine [14]. In the last decade, acupuncture plus routine care in patients with headache, has been associated with marked clinical improvements compared with routine care alone [15]. The recent Cochrane Database Systematic review [13] suggests that acupuncture should be considered an effective treatment and a valuable option for patients suffering from migraine or tension-type headache, with fewer adverse effects.

Thereafter, during these years an increased use of complementary and alternative medicine in the treatment of primary headache disorders has been observed, but less is known about acupuncture in CH patients. Only few and dated cases [7–9] about acupuncture in CH patients are described. Melchart et al. [16], in an observational study on acupuncture in 2,022 patients with headache included 33 patients with CH, demonstrating an overall effect with relevant improvement after $8.6 \pm 3.0$ acupuncture treatments, but no specific results are available for the subgroup of patients with CH.

Our study proposed a protocol of acupuncture alone or combined with verapamil in four patients affected by CH, three with episodic CH and one with chronic CH. All

patients followed the same protocol (14 treatments) with a standardized set of acupuncture points and had a good response.

Acupuncture was identified as a possible alternative therapy in these patients, who responded to subcutaneous sumatriptan as acute treatment, but who did not respond well to common pharmacological preventive therapy. In our three patients with episodic CH, acupuncture was started because either the verapamil dose was not effective (2 pts) or, the verapamil caused side effects (1 pt). In these patients, acupuncture, initially started with verapamil and then continued alone, was effective in stopping cluster attacks.

In chronic CH (1 pt) acupuncture was started in association with low dose of verapamil because it could not completely stop the attacks.

The action mechanism of acupuncture therapy is complex. Studies demonstrated that electrical acupunture can increase endogenous opioid peptides (enkephalin, beta-endorphin) in supraspinal CNS regions and in the spinal cord [17, 18] while manual acupuncture can lead to the activations of the diffuse noxious inhibitory controls (DNIC) with an immediate suppression of pain transmission in neurons of the trigeminal caudalis and/or the spinal dorsal horn [19, 20].

Some biochemical studies evidenced significantly lower met-enkephalin levels in CSF [21] and lower peripheral blood beta-endorphin [22] in 65 patients with CH as compared to control, during the pain-free period as well. The authors speculated that these findings reflect reduced CNS levels of beta-endorphin due to an opioid system hypofunction [22]. On the other hand, CSF opioid levels may rise following manual acupuncture or electroacupuncture, as confirmed by Hardebo et al. [21] who evidenced that CSF met-enkephalin levels rose after acupuncture treatment.

Until now, the role of how acupuncture can act in CH patients is not known. Although the series is limited, this study provides good evidence of the integration of western medicine and traditional chinese medicine in the preventive treatment of CH.

**Conflict of interest** All the authors certify that there is no actual or potential conflict of interest in relation to this article.

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ORAL COMMUNICATIONS

# Study of parafunctions in patients with chronic migraine

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**Abstract** The purpose of this paper is to present the results of a questionnaire investigating parafunctions (particularly clenching and grinding) in patients with chronic migraine presenting sign of temporomandibular disorder. The questionnaire was elaborated by the Dental Clinic of the University of Milano and completed by 125 patients experiencing chronic migraine and attending the Neurological Institute Carlo Besta for an inpatient withdrawal protocol to treat medication overuse. Our results showed high percentages of parafunctions, which were present in 80 % of patients. We note that patient information on possible behaviours and coexisting conditions which may be involved in the mechanisms of chronic headaches, as well as education about these factors, are crucial aspects in the management of chronic headache patients. We suggest that patients suffering from chronic migraine with medication overuse headache should be evaluated in relation to the possible presence of parafunctions, and as far as the need for interocclusal devices, in order to limit the role of temporomandibular dysfunctions as trigger factors or coexisting conditions favouring the development/maintaining of headache chronification.

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**Keywords** Medication overuse (MO) · Chronic migraine (CM) · Gnathological evaluation · Parafunction · Clenching · Grinding

## Introduction

The mechanisms underlying progression from episodic to chronic migraine are not completely understood. It is generally accepted that several conditions and behavioural factors may contribute to this negative evolution, with a possible multifactorial model. Sometimes only one factor may be present, although more frequently local or systemic factors may be present in the same patient. Predisposing factors, such as dental–facial disharmony, triggering factors such as facial trauma and parafunctions [1] associated with psychological factors can, if not corrected, result in chronic painful symptomatology of temporomandibular disorders [2].

These disorders have a wide range of symptoms [3], characterized mainly by temporomandibular noise and pain, functional restrictions and other symptoms such as headache, neck pain, feeling of ear plugged and tinnitus, which if not examined by a gnathologist, may confuse patients and make them seek other types of specialist advice in search of a proper treatment, thus extending the time for correct diagnosis and therapy.

In particular, many patients suffering from chronic migraine do not consider the possibility that their headache may be associated with problems such as temporomandibular disorder [4, 5].

The aim of this study was to investigate the presence of parfunctions (particularly clenching and grinding) in patients with chronic migraine.

## Materials and Methods

A consecutive sample of patients with chronic migraine attending the Neurological Institute Carlo Besta for an inpatient withdrawal protocol to treat medication overuse were evaluated, and were enrolled in the study when the following inclusion criteria were satisfied:

- diagnosis of chronic migraine and medication overuse [6],
- temporomandibular pain,
- temporomandibular noise,
- palpation tenderness of masticatory muscles,
- difficulty in chewing or opening their mouth wide.

The control group was composed by 75 subjects attending the Department of Biomedical Surgical and Dental Sciences of University of Milano, 50 females and 25 males, mean age 41.2 years (ranging between 19 and 65, SD 11.7) and it is characterized by the following:

- no headache, facial pain,
- no previous gnathological treatments.

All the enrolled subjects filled in a specific medical questionnaire elaborated by the Dental Clinic of the University of Milano, focusing on parafunctions, particularly clenching, grinding and bad habits such as chewing gum for a long time.

The relationship between headache and parafunctions was evaluated using the Chi squared test. Results are presented with 95 % confidence intervals (CIs). For all analyses the level of significance was $p \leq 0.05$.

The following hypotheses were considered:

- hypothesis of independence of the "grinding" as cause of chronic migraine: hypothesis rejected; the alternative hypothesis of cause–effect relationship between grinding and headache is accepted with a level of confidence equal to 97.5 % ($p < 0.01$),
- hypothesis of independence of the "clenching" as cause of chronic migraine: hypothesis rejected; the alternative hypothesis of cause–effect relationship between clenching and headache is accepted with a level of confidence equal to 99 % ($p < 0.002$),
- hypothesis of independence of the "parafunction" as cause of chronic migraine: hypothesis rejected; the alternative hypothesis of cause–effect relationship between parafunction and headache is accepted with a level of confidence equal to 99.9 % ($p < 0.00003$).

## Results

A group of one hundred and twenty-five patients was enrolled. They were 105 females and 20 males, mean age 42.41 years (ranging between 18 and 63, SD 10.47) (Fig. 1).

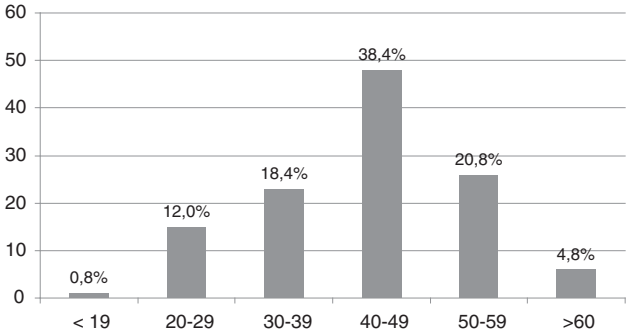


**Fig. 1** Age groups

**Table 1** Prevalence of parafunction

| | Sample group headache | % | 95 % CI | Control group no headache | % |
|---|---|---|---|---|---|
| TOT | 125 | 100 | $p < 0.05$ | 75 | 100 |
| Both parafunctions | 55 | 44 | $p < 0.01$ | 24 | 32 |
| Grindind only | 13 | 10.4 | $p < 0.01$ | 3 | 4 |
| Clenching only | 32 | 25.6 | $p < 0.002$ | 12 | 16 |
| No parafunction | 25 | 20 | | 36 | 48 |

One hundred (80 %) out of the 125 patients showed parafunctions: $n = 55$ (44 %) displayed clenching and grinding, $n = 32$ (25.6 %) clenching, $n = 13$ (10.4 %) grinding.

In addition, 60 patients (48 %) also reported regular use of chewing gum for a long time.

The analysis of the relationship between parafunctions and the presence of chronic migraine reveled a possible cause–effect relationship as the level confidence was 99.9 % ($p$ : 0.01) (Table 1).

## Discussion

Our data underline the important cause–effect relationship between parafunctions and chronic migraine, particularly for the presence of clenching and both parafunctions.

Furthermore the results of the present study reinforce the high prevalence of temporomandibular disorders among patients with chronic migraine and their possible role in migraine chronification. Overall, our data encourage the early diagnosis and treatment of muscular and mechanical aspects of temporomandibular disorder.

Grinding and clenching are two parafunctions that may involve the stomatognathic system in a "dynamic form" and a "static form", respectively.

An individual patient may be a "pure" grinder, other times only a clencher, other times the same patient may present episodes of clenching and grinding.

These parafunctions are a psychophysiological disorder that can be defined as a 'diurnal and/or nocturnal parafunctional activity which leads sufferers to clenching and/or grinding the teeth between them unconsciously. The nocturnal bruxism was defined by the American Sleep Disorders Association (ASDA), in its International Classification as a "stereotyped disorder characterized by grinding or clenching your teeth during sleep" [7]. The prevalence of bruxism in the general population ranges from 8 to 21 % if assessed with a questionnaire, and from 48 to 58 % when evaluated through the clinical oral examination [8].

Bruxism and other parafunctions are associated to the onset of cranial and facial articular temporomandibular pain according to previous studies [9, 10]. The etiology of bruxism is not completely clear. Bruxism has been suggested to be a multifactorial psychosomatic phenomenon [11]. Subjects with bruxism typically have increased levels of stress and tension [12, 13], sleep disturbance and depression. At present, bruxism is considered a phenomenon of neurological activity, centrally mediated and related to sleep disorders, and the presence of a link between the regulation of circulation and the rhythmic activation of masticatory muscles, especially if associated with body movements during sleep, has been suggested [15]. The prolonged contraction of the muscles determines the decrease in blood flow leading to muscle hypoxia, with the consequent production and accumulation of lactic acid. This would explain, at least in part, the subjective facial pain and headache history [16] and pain to palpation of the major stomatognathic and cranial postural muscles, particularly in the presence of a mandibular position that would force muscles to work in conditions of asymmetry and incorrect length/trajectory [13–21].

The treatment of grinding, which is only nocturnal, includes the administration of drugs such as muscle relaxants and anxiolitics [22]. The same drugs may be used in clenching. The application of an orthotic device or a bite can alleviate in part the structural damage and often may alleviate also headache.

The dysfunctional pathologies are frequently of delicate management when they become chronic and bring into serious difficulty even the most experienced doctor. Prevention is of primary importance, as recently suggested by the American Association for Dental Research guidelines.

Chronic migraine has a multifactorial origin, and the present study seems to confirm that parafunctions could play a primary role among other risk factors.

We suggest to make the patients aware about the centrality of the alterations of the stomatognathic system, before proceeding to a re-balancing therapy using an occlusal orthotic device [13–19]. Patients should be also educated to avoid bad habits (in particular the use chewing gum for several hours a day) that can force both the articular temporomandibular but particularly the muscles primarily responsible for the symptoms. We think that it is essential to ask to the patient about the above discussed aspects as well as to assess the presence of other habits, such as—spending hours to the computer in non-ergonomic positions—sitting several hours on an unsuitable chairs—talking on the phone holding the phone between neck and shoulders.

We therefore consider that the routine use of a questionnaire with specific items aimed to detect cranial mandibular disorders is essential in order to identify the (potentially) dysfunctional patients, with the possibility of implementing an effective prevention of the damages caused by bad habits and parafunctions.

The accurate analysis of these aspects, their prevention and/or correction will limit their role as trigger factors in headache patients and as coexisting condition able to influence the progression to from episodic to chronic migraine.

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ORAL COMMUNICATIONS

# Post-traumatic headaches: an epidemiological overview

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**Abstract** Post-traumatic headache (PTH) is the most common secondary headache disorder, corresponding to approximately 4 % of all symptomatic headaches. PTH, a cardinal feature of the post-concussive syndrome, usually shows a phenotype similar to migraine or tension-type headache. However, rare cases of PTH similar to trigeminal autonomic cephalalgias have been described. Many studies have investigated PTH prevalence and potential risk factors for its development and maintenance. In general population, the majority of PTH patients is female and has been involved in vehicle-related accidents. Generally, headache gradually disappears over few weeks or months; however, PTH could become persistent and very disabling in a minority of patients. This brief review will focus on PTH epidemiological aspects.

**Keywords** Post-traumatic headache · PTH · Epidemiological aspects · Epidemiology · Trauma

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## Introduction

Headache attributed to head and/or neck trauma or injury [1], the so-called post-traumatic headache (PTH), is the most common secondary headache disorder, corresponding to approximately 4 % of all symptomatic headaches [1, 2]. PTH is currently defined by International Classification of Headache Disorders (ICHD-3 beta version) [1], as a new headache starting within 7 days after head injury, whiplash, craniotomy or regaining of consciousness following trauma. Nevertheless, some patients may also experience a worsening of their pre-existing primary headache [3].

## Epidemiological aspects

Traumatic brain injury (TBI) is the major cause of morbidity and disability throughout the world. Approximately 80 % of non-fatal TBI are classified as mild, and the most common sequelae of mild TBI is a disabling PTH [2, 3]. In other terms, a very large number of subjects are at risk to have PTH, which should be considered an important public health issue.

Mild TBI is very frequent in general population, and it is usually correlated to motor vehicle accidents (45 %), falls (30 %), occupational accidents (10 %), recreational accidents (10 %), and assaults (5 %) [4, 5]. Although 50 % of subjects experiencing mild TBI are aged 15–34 years, PTH does not demonstrate a predilection for any specific age group [6, 7].

PTH intensity does not show a significant relationship with TBI severity, cause of injury or trauma dynamics, meaning that even a relatively mild TBI can be associated with debilitating headache symptoms [5]. These data are in line with a recent review [3] reporting that the prevalence

of post-traumatic chronic pain may be higher in subjects experiencing a mild (75.3 %) than in those having a severe TBI (32.1 %). However, due to a number of differences in definitions and methodological approaches, PTH prevalence ranges widely from 30 to 90 % [8].

It is well known that certain categories of people are more prone to PTH development [5]. Although males experience mild TBI more frequently than females (in a ratio of at least 2:1), PTH incidence is greater in females than in males. Specifically, female gender is a PTH risk factor stronger in subjects involved in vehicle-related accidents sustaining a moderate-to-severe TBI than in those following a mild TBI [5, 9, 10]. Furthermore, subjects with a history of headache were significantly more likely to report PTH in the first year after a mild TBI (45 %) compared to those without any history of primary headache [19]. In other terms, a pre-injury history of headache and female gender may represent significant risk factors for developing and maintaining PTH following vehicle-related accidents.

In general population, in approximately 10 % of amateur athletic competitions, mild TBI caused a persistent PTH [11] and several TBI episodes were more likely to predispose to persistent PTH [11]. In this context, an important role in PTH frequency is played by whiplash injury (i.e. a pain syndrome related to cervical damage secondary to significant acceleration–deceleration movements), which is reported in 30–90 % of acute PTH forms [12, 13].

In military population, the most frequent cause of PTH seems to be blast-induced TBI (67 %) [14] being responsible for persistent PTH in about 77 % of soldiers [15].

In this context, the occurrence of PTH following craniotomy, should also be considered which may occurs in up to 60 % of the surgeries, most frequently within the first 48 hours, even if it may persist after this time period in about 32 % of patients. Putative predisposing factors have been investigated in PTH following craniotomy and it has been demonstrated that female and young subjects are more prone to develop it. Specific surgical approaches, such as the "base of skull surgery", seem to be associated to an higher risk of developing PTH compared to other surgery procedures [16].

ICHD-3 (beta version) criteria suggested that PTH should start within 7 days after head injury, whiplash, craniotomy or regaining of consciousness following trauma. This is in line with epidemiological studies reporting that within 1 week after mild TBI, 90 % of individuals admitted to the hospital referred PTH [5, 17]. However, a longer latency between TBI and PTH onset has been frequently reported (up to 24.3 %) [14, 18]. In a recent study conducted among US Army soldiers, nearly 40 % of PTH occurred within 1 week, 20 % occurred within 1 month, and just over 40 % occurred after 1 month from TBI [9]. ICHD-3 (beta version) criteria contemplate that acute PTH lasts for <3 months, whereas a persistent PTH should be present for more than 3 months. Several studies demonstrated a high incidence of persistent PTH, showing that from 18 to 22 % of PTH lasted longer than 1 year [10]. Specifically, in the first year, more than 41 % of the subjects reported headache after a mild TBI and up to 71 % of subjects reported headache after moderate or severe TBI [5, 17, 19].

It is interesting to underline that, despite the frequent occurrence of PTH, little is known about its pathophysiology. Undoubtedly, PTH clinical presentation may reflect a coalescence of both organic and functional injury. Non-organic explanations for PTH have been proposed and explored, including psychogenic, psychosocial and sociocultural aspects [20]. Specifically, the role of compensation, litigation, and malingering in incidence, cause and persistence of PTH following a mild TBI remains still under debate [21].

It is well known that PTH may occur as an isolated symptom or as one of a constellation of symptoms known as post-concussive syndrome (PCS) [19]. After TBI approximately about 30 % of the subjects may experience PCS [6]. According to clinical diagnostic criteria [22], PCS includes different symptoms such as headache, dizziness, fatigue, irritability, difficulty in concentrating and reduced tolerance to stress. Similar to PTH, PCS may be very mild, self-limiting and alleviated by conservative measures or, conversely, it may be severe, persistent, resistant to treatment and associated with significant morbidity [6, 23]. Furthermore, several studies suggested the presence of a comorbid post-traumatic stress disorder (PTSD) in up to 75 % of patients suffering from PTH [24, 25]. Other studies confirmed PTSD high prevalence in PTH patients, compared to patients suffering from migraine (22–30 %) and general population (6.8 %) [26, 27].

To date, there are relatively few epidemiological studies regarding PTH clinical characteristics. All together, these studies demonstrated that migraine-like and tension-type headaches are considered the most commonly reported, followed by other unclassified headaches [7, 10, 28, 29]. A recent prospective epidemiological study, aimed to characterize phenotype and prevalence of PTH following mild TBI, has demonstrated that the majority of PTH exhibits moderate or severe intensity and frequency of headache attacks [8]. Indeed, migraine and probable migraine occur in 49 % of acute PTH patients, whereas a tension-type headache was present in approximately 40 % of the patients. Furthermore, migraine phenotype is characterized by more frequent headache attacks (from several times per week to daily) than tension-type headache (from one per week to one per month). Rare cases of acute PTH could be

phenotypically similar to cluster headaches [30], hemicrania continua [31], chronic paroxysmal hemicrania [32], and short-lasting, unilateral, neuralgiform headache attacks with conjunctival injection and tearing (SUNCT syndrome) [33].

In persistent PTH the most frequent phenotype is chronic tension-type headache (97 %) with a frequency of attacks of approximately 26 days/month and a moderate intensity (mean VAS score of about 5.9) that could be, eventually, complicated by medication overuse headache [34]. One-third of PTH patients have reported a combination of tension-type like and migraine like headaches [34].

PTH clinical features and prognosis in the general childhood population are not well documented.

However, a very recent study has demonstrated that about 11 % of the children reported PTH, at a mean of 15.8 days after TBI, which persisted up to 3 months after injury in approximately 7.8 % of the children. Although headache phenotype was very pleomorphic, PTH met migraine criteria in about 55 % of the children. Interestingly, 56 % of the children suffered from pre-existing not well-specified "headaches" while 18 % had experienced migraine before TBI. A family history of migraine was present in 82 % of the children [35].

## Conclusion

PTH, as a frequent complaint of individuals experiencing mild TBI, represents the most common secondary headache and is a serious medical and socioeconomic problem. However, despite its high frequency in general population, several PTH aspects, such as clinical phenotype, temporal latency between TBI and PTH and its duration, remain poorly understood. Similarly, the role of different predisposing or risk factors, such as coexisting primary headache or psychiatric disease, PCS, other chronic pain conditions and financial compensation is still under debate, contributing to hinder the understanding of PTH. Well-designed epidemiological and clinical studies are definitively needed to better identify PTH patients, to establish the severity of TBI impact on PTH intensity and to evaluate significant comorbidities [2, 36].

**Conflict of interest** The author certifies that there is no actual or potential conflict of interest in relation to this article.

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ORAL COMMUNICATIONS

# Sex-related differences in migraine

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**Abstract** This paper reviews sex-related differences in migraine epidemiology, symptoms, natural history and comorbid disorders. Migraine is more than twice as common in females as in males, and women experience more frequent, longer lasting and more painful attacks, have more disability and a risk of transition from episodic to chronic migraine greater than men, but the mechanisms behind these differences are still poorly understood. The role of sex hormones, genes, and the differences in brain function and structure are discussed. Finally, we evaluate the many gender-related questions about treatment of migraine in women. In future research data should be analyzed separately for men and women to ensure that differences between the sexes could be identified.

**Keywords** Migraine · Gender · Sex differences · Therapy

## Epidemiology

Many pain disorders are more prevalent in females than in males [1]. Gender differences in the epidemiology of migraine are well known. Stewart et al. [2] point out that migraine has a cumulative lifetime incidence of 43 % in women and 18 % in men. The American Migraine Prevalence and Prevention (AMPP) Study II [3] shows higher prevalence of migraine in women, with a female-male ratio in the order of 2.3:1. In the PArma CEfalea (PACE) study [4] the past-year definite migraine prevalence was 29.7 % in women and 11.4 % in men, with a female-male ratio of 2.6:1.

The ratio is not consistent across ages. Among children aged 7–9, migraine affects the same percentage of boys and girls (2.5 % boys, 2.4 % girls), but in older age groups, more girls are affected than boys (age 10–12: 3.9 % boys, 5.4 % girls; age 13–15: 4.0 % boys, 6.4 % girls) [5, 6]. At puberty, the incidence of migraine without aura rises in women and to a less extent in men. In women during their 30s and 40s, migraine prevalence peaks and in the following decades, especially after menopause, a gradual decline is observed. In adult men, the rise in prevalence is more gradual, the peak age and decline are similar to those in women but the absolute values remain smaller at all ages (see Fig. 1) [5–7].

Regarding specifically migraine with aura, Stewart et al. [8] show a lifetime prevalence of 5 %, with male to female ratio 1:2 and the PACE Study [4] finds a 1-year prevalence of 3.3 % in men and 5.3 % in women.

## Clinical manifestations and natural history

The natural history of migraine is worse in women. Women experience more frequent, longer lasting and more painful headaches compared with men and have a risk of transition from episodic to chronic migraine greater than men (OR = 2.9, 95 % CI = 1.2–6.9), even after adjusting data for triptan use and headache frequency [3]. Moreover, it is more common for female migraineurs to utilize healthcare resources and their migraine attacks cause more disability (each year across the USA, male migraineurs need 3.8 bed rest days versus 5.6 days for women) [9].

Similar findings have been reported regarding side symptoms of migraine attacks: women are more likely to

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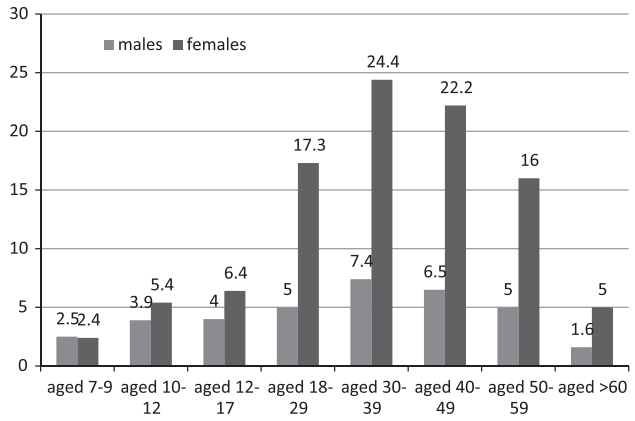


**Fig. 1** One-year period prevalence of migraine by age and sex (4–6)

experience light sensitivity (82 vs 74 %), sound sensitivity (77 vs 70 %), and nausea (75 vs 65 %) related to their headaches compared to men [10].

Some of the differences in clinical aspects of migraine between men and women may be due to menstrually related attacks, that are usually very severe. Granella et al. [11] report that 84 % of women with menstrual migraine engage in fewer social activities, 81 % have difficulty performing household chores, 58 % have to limit family activities, 55 % cannot engage in sports and 45 % have work-related disability. Work-related disability is more often reported for menstrual migraines than for non-menstrual attacks ($P = 0.006$).

Cutaneous allodynia (CA), defined as the perception of pain from an ordinary non-noxious stimulation of the skin, is a frequent complaint during migraine attacks and has been linked to central sensitization of nociceptive neurons at the level of the trigeminal nucleus caudalis [12]. CA has been found to be more common and severe in females [13] and it has been associated with migraine disability, poor response to triptans (that cannot reverse the central sensitization) [14], depression, and a particular personality profile, characterized by ''harm avoidance'' behaviour and anxious trait [13]. Finally it represents a risk factor for the disease progression [15].

## Comorbidities

Migraine is co-morbid with various medical disorders, including vascular diseases, depression, anxiety, epilepsy and many somatic conditions such as irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome [6].

Migraine with aura has a little but significant association with cardiovascular diseases and cerebrovascular diseases, particularly in women. The US Women's Health Study shows that subjects with migraine with aura (but not migraine without aura), have a significant increased risk of major cardiovascular disease, myocardial infarction, ischemic stroke, death due to ischemic cardiovascular disease, coronary revascularization, and angina compared to controls [16].

Many studies have been specifically addressed to evaluate the risk of ischemic stroke in healthy young women affected by migraine with aura. Carolei et al. [17] established that a history of migraine particularly with aura was the only significant risk factor for ischemic stroke in women below age 35 ($P = 0.003$). In a meta-analysis [18], the relative risk for subjects suffering from migraine with aura to develop an ischemic stroke is 2.16 (95 % CI, 1.53–3.03). Because ischemic stroke is a rare disease in young people and especially in young women, the absolute risk remains very low and no preventive therapies are advisable, while it is very important to remove additional risk factors if present. Use of estrogen-containing oral contraceptives (OCs) in women with migraine with aura is formally contraindicated because of an additional risk, even with low estrogen dose pills (<50 μg ethinyl estradiol), with a twofold increased risk of ischemic stroke [19]. Risk is further increased (until tenfold) for women with migraine with aura who smoke and use oral contraceptives [20]. MRI CAMERA study [21] observes that migraineurs, notably those with aura, had higher prevalence of subclinical infarcts in posterior circulation (OR = 13.7; 95 %CI 1.7–112) and female migraineurs have an independent increased risk of white matter lesions (WML; OR = 2.1; 95 % CI 1.0–4.1). Finally migrainous infarction, which is a rare but specific type of ischemic stroke developing during an attack of migraine with aura, affects women two to three times as often as men [22].

A recent metanalysis [23] suggests that subjects with migraine have an increased risk of hemorrhagic stroke too, with a risk that seems greater in females with any migraine (1.55; 95 % CI, 1.16–2.07; $P = 0.003$) and in female migraineurs aged <45 years (1.57; 95 % CI, 1.10–2.24; $P = 0.012$).

Several studies show that migraine is co-morbid with major depressive disorders, panic disorder and social phobia, but many studies do not find differences in the sex-specific prevalence of these conditions between migraneurs men and women [6, 24], even if others find rates of clinical depression and anxiety significantly higher among females [25].

Obesity is known to be a risk factor both for vascular diseases and chronic migraine. Scher et al. [26] observe that individuals with total body obesity and episodic headache have an increased risk of incident chronic daily headache over a 1-year period [OR = 5.3 (1.4–21.8)]. Furthermore, subjects with obesity have an increased risk of episodic migraine, especially among women and young (<50 years) adults of both sexes [27].

## Role of sex hormones

Female sex hormones are the principal candidate to explain differences in migraine between men and women. Various clinical evidences support their role [6]. During women life migraine prevalence is related to fluctuating levels of ovarian steroids, but this relationship is complex. Migraine frequency is lower before puberty and after natural menopause, when the level of ovarian hormones in serum is stable and low, and increases during menstruation, when serum levels of estradiol and progesterone abruptly decline. On the other hand, surgical menopause may be associated with worsening of migraine. Pregnancy also influences migraine but the response may be different between migraine with and without aura. In migraineurs without aura, attacks usually significantly decrease during pregnancy when the levels of ovarian hormones in serum are stable and high, but aura may worsen or appear for the first time. High-estrogen states seem to be in general associated with the development of migraine with aura also in women who have not previously had migraine or have had only migraine without aura. This may occur not only during pregnancy but also in women starting combined OCs. Continuous combined OCs, suppressing the natural ovarian cycle, may have a beneficial effect on menstrual migraine that is usually without aura and may be, on the contrary, induced or deteriorated by their intermittent use.

Pringsheim and Gooren [28] find that transsexuals who were using antiandrogens to suppress male sex characteristics and estrogens to induce female sex characteristics have a migraine prevalence (26 %) similar to the one expected in women. This supports the idea that hormonal changes, exogenous as well as endogenous may be more important than genetic differences between men and women.

To understand the complex relationship between hormones and migraine and other pain conditions, preclinical and clinical studies have focused on pro and antinociceptive effects of estrogen [29] as well as on effects of sex hormones on central neurotransmission and cortical excitability [30].

The experimental approach to this problem has various limitations: there is no evidence that estrogens directly affect calcitonin gene-related peptide (CGRP) or 5-$HT_{1D}$ receptors in the trigeminal system, but it seems possible that estradiol affects neuropeptide release, or receptor coupling, rather than altering gene expression. At the level of trigeminal nucleus caudalis (TNC), estradiol significantly modifies the expression of several other genes. Among others, it activates the extracellular signal-regulated kinase (ERK), whose upregulation is consistent with increased nociception, but it downregulates bradykinin B2 receptor and interleukine-1b receptor, that induce CGRP release from sensory neurons. This results in a decreased release of CGRP with an antinociceptive effect. Progesterone seems to affect neurotransmission within the TNC as well as to decrease plasma extravasations in animal models of migraine [29].

About neurotransmission, the predominant effect of estrogen appears to be facilitation of the glutamatergic and serotonergic systems as well as inhibition of the sympathetic nervous system, while it has both facilitatory and inhibitory effects on the opiatergic, GABAergic and noradrenergic systems. The main effect of progesterone and its metabolites seems to be activation of GABAergic systems [29].

In addition, regarding neuronal excitability, estradiol and progesterone seem to have an opposite effect, with estradiol being excitatory (so enhancing susceptibility to cortical spreading depression) and progesterone and its derivative allopregnanolone being inhibitory [30].

## Role of genes

Various researchers suggest that migraine is a genetically determined disorder [31]; however, how it might transmit remains controversial. Mendelian models of transmission, i.e. autosomal dominant, autosomal recessive, or X-linked, have been indicated as a trait of migraine, but, looking at the different expression of the disease in females and males, some authors have regarded migraine as a more complex genetic disorder, proposing the hypotheses of a mitochondrial DNA transmissible disease [32] or related to sex-chromosome inheritance [33], or, finally, a sex-influenced model, autosomal dominant in females and autosomal recessive in males [34]. Research on the genetics of migraine has yielded several migraine genes [31], first in monogenic familial hemiplegic migraine and, more recently, in common migraine too; differences between men and women, however, have not been found or frequently have not been looked for. Of course a possible explanation for the sex difference in migraine is that women have greater genetic loading than men to express the disorder, but this hypothesis does not be confirmed by twin and family studies [35]. Furthermore, a different migraine susceptibility between genders may be associated to genetic polymorphisms with a different expression in women and men. Estrogen and progesterone receptors genes are good candidates in this field. Rodriguez-Acevedo et al. [36] find that three haplotypes in estrogen receptor 1 are associated with migraine, providing a support to the hormone-mediated pathogenesis model.

A recent review [37] will focus on the role that epigenetic mechanisms may play in migraine etiology. Epigenetic mechanisms may explain how non-genetic

endogenous and exogenous factors such as female sex hormones, drugs and inflammation trigger may modulate attack frequency.

## Differences in brain function and structure

Several hypotheses have been proposed to explain the differences in migraine and other pain conditions observed between the sexes, including, as we have seen, fluctuations in sex hormones and receptor binding, genetic factors and differences in exposure to environmental stressors as well as response to stress and pain perception. Many of these factors mirror the brain structure.

Various functional MRI studies observe differences in pain processing between the sexes in healthy subjects [38, 39]. Maleki et al. [40] analyse sex differences in brain function and structure in migraineurs. They find that disease-related structural changes in insula and precuneus regions seem specific to female migraineurs, while disease-related structural changes in parahippocampal gyrus seem specific to male migraineurs. Moreover, within the migraine group, functional changes in response to noxious heat show more pronounced responses in female migraineurs in regions such as amygdala and parahippocampus. In female migraineurs, insula, which is a structure involved in interoception, emotional processing and pain perception, is thicker, its activation to painful stimuli is decreased, and there is a significant negative connectivity between the posterior insula and the primary somatosensory area. Similarly, in healthy subjects, previous functional MRI studies found greater pain activation of the insular cortex in males [41]. In Maleki's study, female migraineurs also display significant thickening in the dorsal and ventral portion of the precuneus, a structure that is involved (anterior precuneus) in sensorimotor processing (functional connection with the superior parietal cortex, paracentral lobule and motor cortex) and (central precuneus) in cognition and associative processing (functional connection with the dorsolateral prefrontal, dorsomedial prefrontal and multimodal lateral inferior parietal cortex). Moreover, female migraineurs have a greater activation in brain regions involved in emotional processing such as the amygdala and parahippocampus and in regions corresponding to the contralateral main sensory nucleus and spinal trigeminal nucleus in the brainstem.

Liu et al. [42] examine the resting networks in chronic migraine suffers and find various gender-related differences. In female patients, brain functional networks show worse resilience, more regions exhibit decreased nodal centrality, and more functional connections reveal abnormalities, than in male patients. This indicates that the functional networks in females are more vulnerable to disruption induced by migraine and this may result in an abnormal integration during the experience and the anticipation of pain. Already in the healthy subjects differences there exist in the brain network organization, between genders [43]: it seems possible that women's cortical networks have a higher risk of developing migraine.

The studies about sex difference in pain processing in healthy subjects and migraineurs support the notion of a 'sex phenotype' in pain perception and migraine. The disease affects male and female brains in a different manner and emotional circuitry appears involved to a greater degree in female than male.

## Treatment

Treatment of migraine in women poses many gender-related questions: how to treat menstrual migraine? How to treat pregnant migraine-affected women? How can perimenopausal period change migraine and its treatment? And how a diagnosis of migraine in a fertile aged woman can affect the choice of the contraceptive?

Regarding the treatment of menstrual migraine, a recent pooled analysis of three double-blind, randomized, crossover, multicenter studies confirms the superior efficacy of frovatriptan versus other triptans in lowering the risk of early recurrence (over 24 and over 48 h from intake) and similar efficacy on the other endpoints (time to and entity of pain relief, recurrence in the first 24 h) [44]. One randomized-control trial conducted by Silberstein et al. [45] demonstrates the efficacy of frovatriptan for short-term prophylaxis of menstrual migraine. Participants took placebo, frovatriptan 2.5 mg daily, or frovatriptan 2.5 mg twice daily for 6 days, starting 2 days before the expected onset of menstrual relates migraine. Both frovatriptan dosing regimens were superior to placebo ($P < 0.0001$) in reducing menstrual migraine incidence with no evidence of a delayed or rebound headache after frovatriptan was discontinued. Another possible approach to menstrual migraine without aura in women without contraindication to oral contraception could be to avoid hormone fluctuations, using an extended cycle combined OCs, with continuous assumption of oral contraception for 168 days instead of 21 before the seven days pause. A clinical trial [46] confirms the efficacy of this regimen, but further evidences about efficacy and lack of collateral effects on more patients are needed.

During pregnancy the majority of patients experience a substantial reduction of migraine, especially in the second and third trimesters [47]. There are a few women that instead worse their symptoms during pregnancy: the treatment of these patients is a real challenge.

Many usual therapies for migraine, used in acute attack and as daily prevention, are contraindicated during pregnancy (category X, or D): NSAIDs in the first trimester, ergotamines, methysergide, Ergot derivatives, dihydroergotamine, divalproex sodium, carbamazepine, topiramate, and atenolol.

Paracetamol is frequently indicated as the first choice in the treatment of migraine attack during pregnancy, but a recent retrospective epidemiological study on 64,322 pregnancies is getting a shadow on this drug [48]: the maternal acetaminophen use during pregnancy is associated with a higher risk for Hyperkinetic Disorders and Attention-Deficit/Hyperactivity Disorder -like behaviors in children. Because the exposure and outcome are frequent, these results are of public health relevance but further investigations are needed.

Current pregnancy outcome registers about the use of triptans are available: sumatriptan, being the most old one, has major data; there is no evidence so far of teratogenicity but the use of triptans during pregnancy [49, 50] is not recommended because data are not sufficient to exclude it at all. Furthermore, data from the Danish Medical Birth Registry find an association between preterm delivery and sumatriptan use [51].

Some drugs are in B/C categories as long as paracetamol, and those could be used in pregnant women if expected risks are lower than benefits: opioids, butalbital, NSAIDS in second and third trimester, metoclopramide.

Regarding supplements, according to the European Federation of Neurological Societies, magnesium is the only one [52] that can be used safely during pregnancy.

Different approaches could be considered: botulinum toxin is not approved for the use during pregnancy, while data exist about the efficacy and sustained improvement after treatment with biofeedback and relaxation [53] and nerve blocks with a local anesthetic could be another safe option to consider.

Perimenopausal period may be associated with a worsening of frequency and severity of migraine, and migraine beginning in this period has also been reported. The majority of the data seem to focus on the fluctuations of estrogen blood rate and testosterone blood rate, that can became more important and erratic in this phase of life. During the subsequent menopausal period in fact the majority of patients with a previous diagnosis of menstrual migraine experience a substantial relief from their disease.

Some studies suggest the possibility of treating patients in perimenopausal period using transdermal hormonal supplementation with testosterone (54), and with transdermal estradiol, whose use is actually supported by several case–control studies [55–57].

Finally, migraneurs need an accurate evaluation in choosing a contraceptive. As we have seen earlier, use of estrogen-containing OCs in women with migraine with aura is formally contraindicated because of an additional risk even with low estrogen dose pills (<50 μg ethinyl estradiol), with a twofold increased risk of ischemic stroke [19]. Risk is further increased (until tenfold) for women with migraine with aura who smoke and use oral contraceptives [20, 58]. A consensus statement from both headache and stroke experts suggests screening for and treatment of all traditional stroke risk factors in women with migraine without aura but does not state that low-dose OCs use is contraindicated [59].

**Conflict of interest** The authors declare that there is no actual or potential conflict of interest in relation to this article.

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ORAL COMMUNICATIONS

# Development of spatial integration depends on top-down and interhemispheric connections that can be perturbed in migraine: a DCM analysis

**Eleonora Fornari · Romana Rytsar · Maria G. Knyazeva**



**Abstract** In humans, spatial integration develops slowly, continuing through childhood into adolescence. On the assumption that this protracted course depends on the formation of networks with slowly developing top-down connections, we compared effective connectivity in the visual cortex between 13 children (age 7–13) and 14 adults (age 21–42) using a passive perceptual task. The subjects were scanned while viewing bilateral gratings, which either obeyed Gestalt grouping rules [colinear gratings (CG)] or violated them [non-colinear gratings (NG)]. The regions of interest for dynamic causal modeling were determined from activations in functional MRI contrasts stimuli > background and CG > NG. They were symmetrically located in V1 and V3v areas of both hemispheres. We studied a common model, which contained reciprocal intrinsic and modulatory connections between these regions. An analysis of effective connectivity showed that top-down modulatory effects generated at an extrastriate level and interhemispheric modulatory effects between primary visual areas (all inhibitory) are significantly weaker in children than in adults, suggesting that the formation of feedback and interhemispheric effective connections continues into adolescence. These results are consistent with a model in which spatial integration at an extrastriate level results in top-down messages to the primary visual areas, where they are supplemented by lateral (interhemispheric) messages, making perceptual encoding more efficient and less redundant. Abnormal formation of top-down inhibitory connections can lead to the reduction of habituation observed in migraine patients.

**Keywords** Children · Effective connectivity · Inhibition · Predictive coding · Visual cortex · Functional magnetic resonance imaging

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## Introduction

The developing brain provides a unique opportunity to investigate its functional networks in consecutive temporal windows. Due to the interregional heterochronicity of maturation, the role of long-developing functional circuits and their dysfunction in pathology can be understood. The top-down influences are based on such circuits with protracted development [1, 2]. Their extended development through adolescence has been shown for prefrontal top-down influences underlying voluntary behavioral control [3, 4]. However, top-down effects are involved in all types of cognitive activities, including perception, where they reshape interactions between distributed networks under different perceptual contexts.

Moreover, their deviant or delayed development might be suspected in the pathological conditions that affect distributed brain regions and have age-dependent prevalence. For instance, migraine, which is a frequent cause of headache in children, can be among such neurological disorders. Indeed, as MRI-based studies in adults show distributed cerebral networks are changed in chronic migraine patients [5, 6]. The prevalence of migraine increases from 3 to 19 % in children between 5 and 12-year-old, and then drops to some extent [7], suggestive of a link to certain protracted developmental processes.

The predictive coding hypothesis [8] persuasively offers a framework for the role of top-down effects in the hierarchical processing of sensory stimuli. This hypothesis suggests that at each level of signal processing, neural networks form internal models of the natural world based on its regularities. These representations generate predictions of how the sensory evidence should be interpreted and send them via descending connections upstream, where the model information is compared to the stimulus-driven activity. At the lower processing level, the well-predicted activity is removed by inhibition, and the residual error between the prediction and sensory evidence is calculated. The signal deviations from the predictions are sent to the higher processing centers for adjusting the model. Importantly, by inhibiting the predictable and, therefore, excessive activity, such a hierarchical mechanism optimizes processing of a stimulus.

Top-down influences can be studied non-invasively in terms of effective connectivity, which evaluates the influence that one local neural system (source) exerts on another (target) by means of dynamic causal modeling (DCM) [9]. For the analysis of feedback effects, it is important that DCM differentiates positive and negative couplings. Positive modulation expresses functional excitation in a target region in the case of activity increase correlated with the source, while negative modulation manifests functional inhibition in the target in the case of source activation. In this study, we examine the top-down and interhemispheric modulatory connections in a visual network, using a perceptual task that involves interhemispheric spatial integration [10, 11]. Spatial integration refers to the brain processes that implement a global representation of spatially extended objects by assembling local information across the visual field. In contrast to the majority of visual functions that achieve adult levels within a few months from birth, spatial integration develops at least until mid-adolescence [12–15]. Migraine interferes with the development of spatial integration such that, compared to age-matched controls, children with migraine show reduced improvement in the performance of contour integration task between 6 and 14 years [16].

Our task contrasts colinear and orthogonal bilateral gratings, of which only the first generates a Gestalt such that the stimulus parts are fused between hemispheres. In agreement with predictive coding theory, a more coherent (colinear) stimulus would cause activations in higher-order and deactivations in lower-order visual areas [17]. Indeed this phenomenon has been observed in adults performing visual integration tasks [10, 11, 18–20]. As recently shown with DCM, such dynamics in adults depends on top-down and lateral inhibition [21, 22] and is weakened with age and all the more so in Alzheimer's disease [22]. Yet nothing is known about the development of top-down effects within the human visual cortices.

We hypothesized that the functional circuits providing top-down effects continue to advance during the second decade of human life. In addition to characterizing their developmental changes from a network perspective, we aimed at linking them to structural brain maturation as manifested by interhemispheric callosal connectivity. Here, we report the DCM-based evidence of this process in healthy children, a necessary step for the evaluation of the state of long-developing networks in children with neurological disorders including migraine. Some of these results have been mentioned elsewhere in relation to the corpus callosum development [23].

## Materials and methods

### Subjects

The data from 13 children (4 girls, 9 boys, mean age 11.0 years, range 7–13 years) with normal vision and without known neurological or psychiatric illness have been analyzed in the study. Previously we have used the data from this population to track the functional and morphological maturation of interhemispheric connectivity with a combined MRI technique [15]. Fourteen normal adults (6 women and 8 men; mean age 29.8 years, range of 21–42 years) without known neurological or psychiatric conditions and with normal or corrected-to-normal vision also participated in the study. The study followed the protocol approved by the Lausanne University Ethics Committee and written informed consent was obtained from children and their parents as well as from the adult participants. All the instrumental procedures conformed to the Declaration of Helsinki (1964) of the World Medical Association concerning experimentation on humans.

### Stimuli

Subjects viewed bilateral sinusoidal black-and-white gratings with a spatial frequency of 0.5 Hz, a contrast of 70 %,

a size of a lateral patch of 11° × 19°, and drifting with a temporal frequency of 2 Hz. The stimuli either obeyed Gestalt grouping rules [iso-oriented colinear gratings (CG)] or violated them [non-colinear orthogonally oriented (NG)]. The stimulus conditions were alternated with background (uniform gray screen of the same space-averaged luminance as the stimuli) in a balanced pseudo-randomized order, five (for children) or six times (for adults), 15 s each (for a detailed description of the stimuli and eye movement control see [10, 11]).

### fMRI data acquisition and pre-processing

For children, the protocol was performed on a 1.5 Tesla Siemens Magnetom Vision. Functional MRI images were acquired with an EPI gradient echo sequence (FA 90°, TE 66 ms, pixel size 3.75 × 3.75 $mm^2$, acquisition time 1.7 s, 22 slices, 5 mm thick) with a TR 3 s.

The adults were imaged on a 3T Siemens Trio scanner with the same type of sequence (FA 90°, TE 30 ms, pixel size 3 × 3 $mm^2$, acquisition time 1.7 s, 32 slices, 3 mm thick, TR 2 s). As the structural basis for brain segmentation and surface reconstruction, we acquired high-resolution T1-weighted 3D gradient echo sequence (MPRAGE), 160 slices (1 × 1 × 1 mm voxel size). In both experiments, we prevented head movements by cushioning the participant's head in a padded coil.

Both fMRI datasets were pre-processed and analyzed using Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK), first, for standard single-subject and group statistics, then for DCM-specific design. Functional images were realigned to the first scan using a six-parameter rigid-body transformation and co-registered to the respective anatomical acquisition. To minimize inter-subject anatomical differences and increase the signal-to-noise ratio, each subject's images were normalized to the Montreal Neurological Institute template (MNI) using a 12-parameter affine transformation [24], re-sampled to 2 × 2 × 2 $mm^3$, and smoothed with an isotropic Gaussian kernel (FWHM = 6 mm).

It should be mentioned that moderately stronger and more extensive activations that can be recorded with the 3T compared to 1.5T scanner in a visual perceptual task [25] do not compromise the validity of comparative DCM analysis, since the method models the temporal dynamics of BOLD signals rather than their intensity. Furthermore, the local character of the modeled network situated within the visual cortex suggests the homogeneity of magnetic field across the regions of interest (ROIs). Finally, our ROIs (for details see "ROIs for DCM") are similarly located in the adult data from 1.5T [10, 11] and 3T (here), and, therefore, represent the same network.

Single-participant analysis was performed by adjusting the general linear model to our block design experiment. The signal drift across acquisitions was removed with a high-pass filter. Statistical parametric maps of the contrasts of interest were computed for each subject and were used as input values for the group statistics based on random field theory. In particular, the inferential statistics included between-condition $t$ tests. To identify the nodes for DCM analysis (hereafter referred to as ROIs), we considered centers of clusters surviving a statistical threshold for peak height at $P < 0.05$ [family wise error (FWE) corrected] and satisfying an extent threshold of $k > 30$ contiguous voxels in the group SPMs.

### Dynamic causal modeling

DCM serves to assess condition-dependent interactions within the distributed brain network based on an fMRI time series. To this end, DCM considers the brain as a dynamic system, in which external inputs cause changes in neuronal activity, which, in turn, cause changes in the distributed fMRI signals [9]. Mathematically, DCM for fMRI includes a bilinear model of neural dynamics and an extended balloon hemodynamic model of the transformation of neural activity into a measured BOLD response [9, 26]. A fixed set of ROIs, possible connections between them, and driving inputs are prerequisites for determining effective connectivity, which is defined by the influences that one node in a model exerts over another. Effective connections are divided into the intrinsic connections, i.e., the influences between ROIs in the absence of a modulating context, and the modulatory connections, i.e., the changes due to the experimental context. Effective connections can be positive, i.e., excitation in a source region induces increase in activity in the target, and negative, i.e., functional activation in the source causes target inhibition. Since the theoretical and practical issues of DCM were recently reviewed, we refer interested readers to these sources for details of the method and underlying theory [27–29].

### Roles for DCM

The results of standard GLM analysis of SPMs reported earlier [10, 15] served as the basis for ROI selection. Both children and adults showed extensive activations in the striate and extrastriate areas under CG and NG conditions. In the primary visual cortex, we have chosen ROIs centered on the local group maxima from the conjunction maps of CG > background and NG > background contrasts. In the extrastriate areas, we defined ROIs from the CG > NG contrast, which revealed bilateral activations in the lingual gyrus (V3v, Fig. 1) in both groups. At the group level, the local maxima within these activated clusters served as ROI

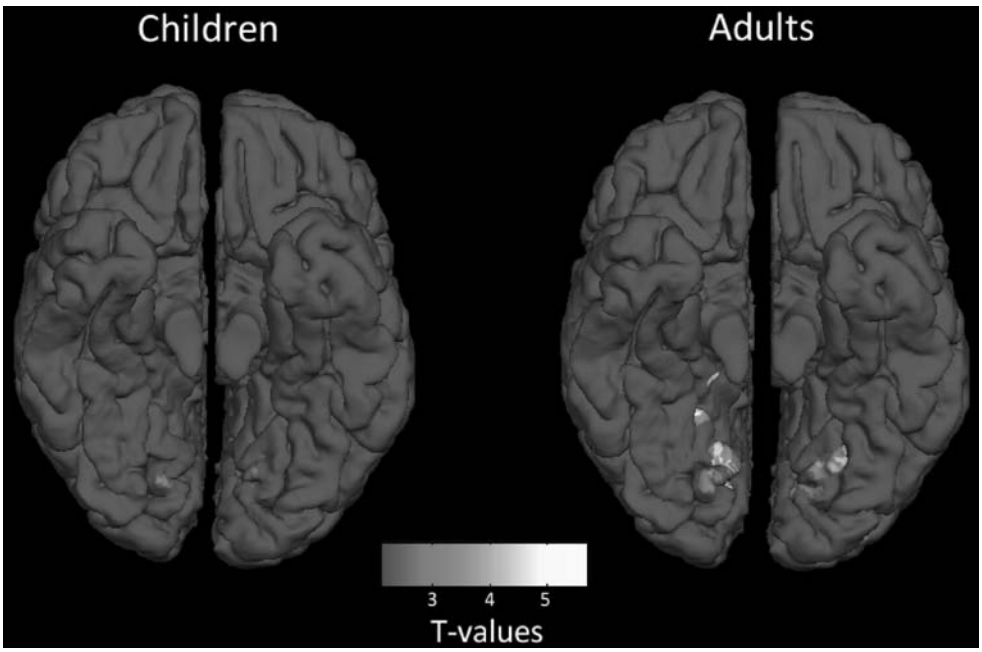


**Fig. 1** Interhemispheric integration effects as revealed by fMRI activation. The 3D representation of statistical maps for the contrast between colinear and non-colinear gratings in the groups of children and adults ($P < 0.001$, extent threshold $k = 30$ voxels) is rendered on the MNI canonical brain. The *bottom view* of a pial surface is presented. In adults, the MNI coordinates ($x$, $y$, $z$) of the center of left-hemisphere cluster (178 voxels) are −12, −70, −10 and those of right-hemisphere cluster (133 voxels) are 16, −76, −14. In children, the coordinates are −18, −78, −14 (left hemisphere, 88 voxels) and 10, −76, −6 (right hemisphere, 95 voxels). *Hot scale* shows $T$ values. In both groups, BOLD response is located within the lingual gyri, but the clusters are larger and more significant in the adult group. The centers of the clusters ($P < 0.05$, FWE corrected) define the V3 locations for DCM analysis

**Table 1** Anatomical locations of regions activated by gratings

| Group | CG > background | | CG > NG | |
|---|---|---|---|---|
| | Hemisphere | | | |
| | Left | Right | Left | Right |
| Adults | 59 % V1, 41 % V2 | 66 % V1, 34 %V2 | 58 % V3v, 42 % V4 | 65 % V3v, 35 % V4 |
| Children | 62 % V1, 38 % V2 | 69 % V1, 31 % V2 | 51 % V3v, 49 % V4 | 70 % V3v, 30 % V4 |

Functional locations of the centers of activated clusters are given according to a probabilistic atlas [61]. The percentage represents each center's mean probability of belonging to the mentioned visual areas across subjects

centers. In individual subjects, the location of an ROI center was determined as a local maximum closest to the respective group location.

For each subject and ROI, the first principal component of the original time series of all voxels within a 4-mm radius sphere was extracted. In the primary visual cortex, ROIs were located at the V1/V2 border (Table 1). The ROIs in the extrastriate cortex occupied territory in V3v/V4. Hereafter, for the sake of simplicity, these two pairs of ROIs are referred to as $V1_L$, $V1_R$, $V3_L$, and $V3_R$, where the "L" and "R" designate the left and right hemispheres, respectively.

## Dynamic causal model

For the sake of compatibility between children and adults, we applied a single model to both groups (Fig. 2). This is a fully connected model of intrinsic connections, which has also been a winning one for the group of aged healthy adults under the same perceptual task [22]. In this model, the stimuli > background contrast serves as a driving input. The signals induced by the bilateral stimuli travel via crossed visual pathways and directly affect the left and right primary visual cortices. The induced activity then spreads through the system according to the intra- and interhemispheric reciprocal connections. On the assumption that each intrinsic connection can be modulated by the task, we reproduced the architecture of intrinsic connections for modulatory connections (Fig. 3). We modeled the CG > stimuli contrast, since in our experiment the interhemispheric integration is a source of modulatory effects.

## Group statistics for DCM

To test for differences in the coupling parameters between developing and mature brain networks, we applied mixed between-within analysis of variance (ANOVA). The developmental affects were analyzed with a between-

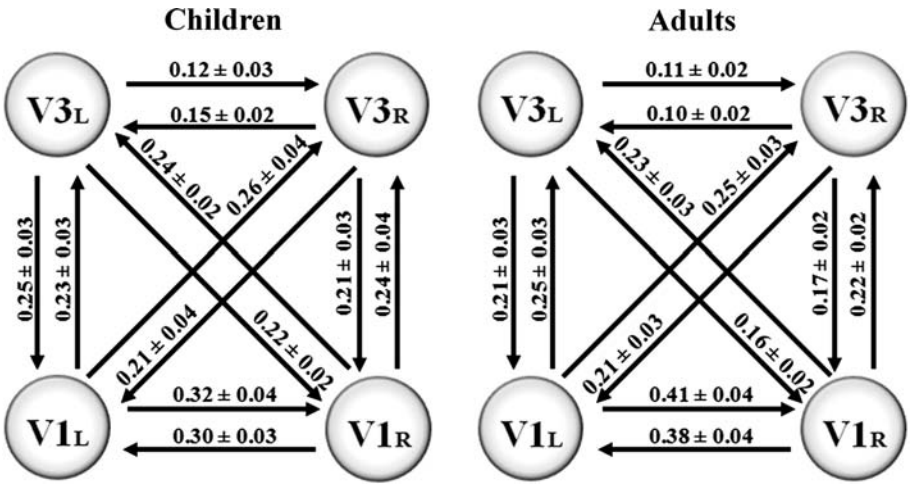


**Fig. 2** Intrinsic connections in children and adults. The schematized representation of the modeled networks includes *gray-filled circles*, which denote ROIs for DCM analysis, and *arrows*, which stand for intrinsic connections. The ROIs are located in the $V1_L$, $V1_R$, $V3_R$, and $V3_L$. The average strength of a connection in Hertz is shown together with a standard error next to the respective connection. For the sake of simplicity, the driving inputs provided by the right visual field gratings to $V1_L$ and by the left visual field gratings to $V1_R$ are not shown

subject age factor (children vs. adults). According to our hypothesis, developmental effects might differ depending on the topography of connections, which, in terms of ANOVA, can be shown with an interaction of the topography of connections with the age factor. The planned between-group comparisons of connection parameters were performed by means of a two-sample two-tailed $t$ test. For descriptive statistics of each parameter, we used a one-sample two-tailed $t$ test. Significant effects are reported at $P < 0.05$ corrected for multiple comparisons with the Bonferroni method.

The links between the coupling parameters of the DC model and morphometric measurements of the corpus callosum (CC) were assessed by the Pearson correlation coefficient $\rho$ with corresponding $P$ value. All the statistical tests were implemented with SPSS 17.0 for Windows.

## Results

### Intrinsic connections and driving inputs do not change with age

Group-averaged estimates of the strength of intrinsic connections are shown in Fig. 2. All the parameters significantly differ from zero at $P < 0.05$ (two-tailed $t$ test, Bonferroni corrected). To explore the age-related changes in vertical effective connections between striate (V1) and extrastriate (V3) areas, including both intra- and interhemispheric connections, we applied a three-way between-within ANOVA with factors of age (children vs. adults), direction (top-down vs. bottom-up), and topography (4 levels: $V1_L - V3_L$, $V1_L - V3_R$, $V1_R - V3_L$, and $V1_R - V3_R$). Neither the main effect of age, nor its interactions with the other two factors proved significant. We also failed to find age-related changes in horizontal interhemispheric connections at the striate and extrastriate levels, within the framework of a three-way between-within ANOVA with factors of age (children vs. adults), hierarchy (V1 vs. V3), and direction [$V1(3)_L \rightarrow V1(3)_R$ vs. $V1(3)_L \leftarrow V1(3)_R$].

Similarly, we found no differences in driving inputs between the groups or hemispheres as shown with a two-way between-within ANOVA with factors of age (children vs. adults) and hemisphere (left vs. right).

### Modulatory connections strengthen with age

All the modulatory connections turned out to be inhibitory (Fig. 3). Six out of 12 connections in children and all but one in adults significantly differ from zero at $P < 0.05$ (two-tailed $t$ test, Bonferroni corrected). Note that significant connections in children are mostly bottom-up. The vertical modulatory connections were analyzed with a two-way between-within ANOVA, which includes the age and topography factors described for intrinsic connections. The main effect of age was significant at $P = 0.037$ ($F = 4.88$, $df = 1$, $\eta^2 = 0.163$). As Fig. 3b shows, the strength of inhibitory top-down connections builds up with age. A three-way between-within ANOVA with the age, hierarchy, and direction factors (described for horizontal intrinsic connections) revealed the main effect of age ($P < 0.001$, $F = 18.289$, $df = 1$, $\eta^2 = 0.422$) for horizontal modulatory connections, which appeared to be stronger in adults.

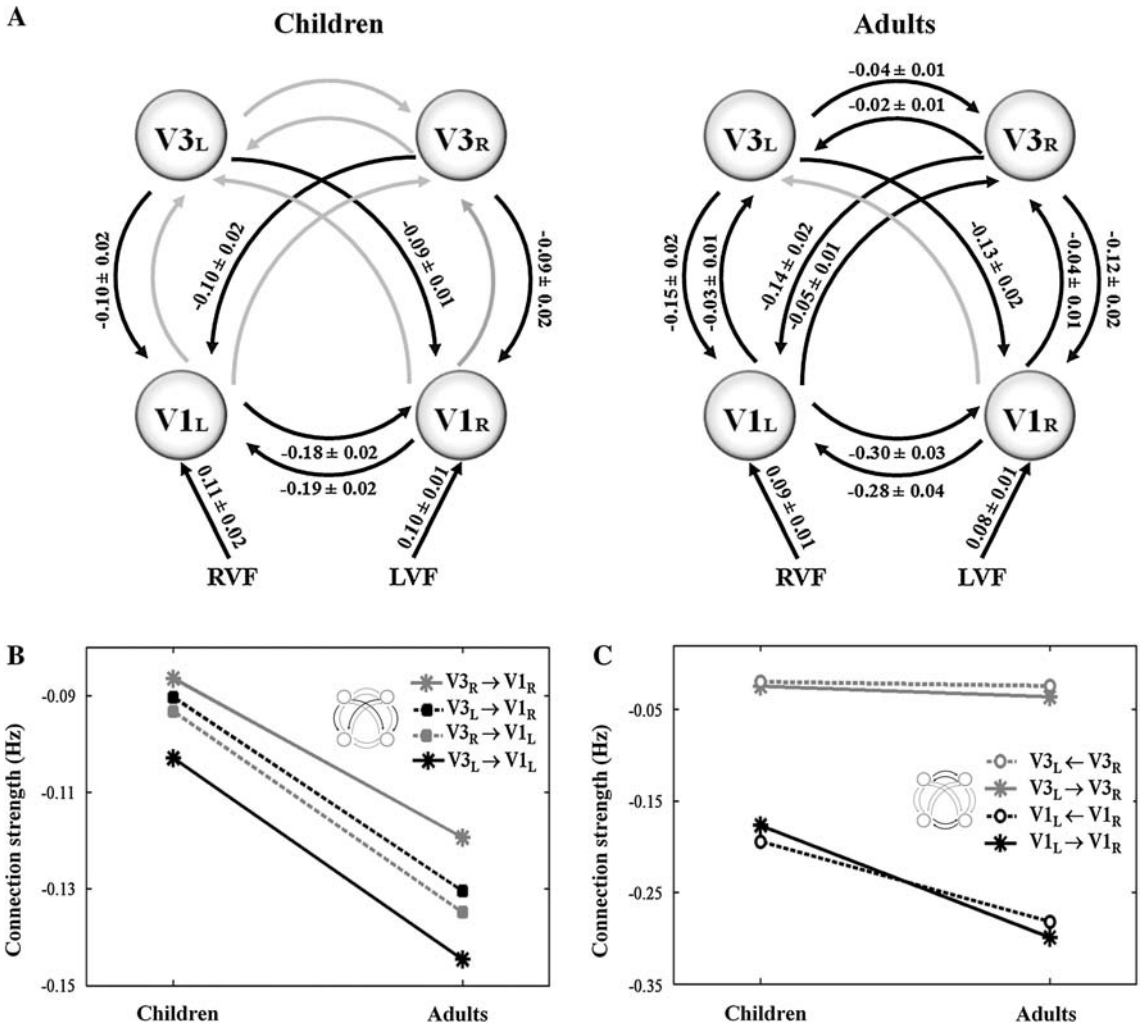


**Fig. 3** Modulatory connections for children and adult groups. **a** The average estimates of modulatory parameters in Hertz with standard errors are shown alongside the respective connections. Other designations are as in Fig. 2. **b** The main effect of age on top-down modulatory connections. Connections from left and right hemispheres are in *black* and *gray*, respectively. **c** The main effects of the age factor and the interaction of age × hierarchy on the striate (in *black*) and extrastriate (in *gray*) interhemispheric connections

This effect interacted with a hierarchy factor at $P = 0.007$ ($F = 8.589$, $df = 1$, Greenhouse–Geisser corrected; $\eta^2 = 0.256$). The planned between-group comparisons showed that only striate connections are significantly stronger in adults than in children ($P = 0.001$, $V1_L \rightarrow V1_R$; $P = 0.013$, $V1_L \leftarrow V1_R$, Fig. 3c).

## Effective coupling is associated with brain maturation

To visualize the developmental trajectory for interhemispheric effective connectivity and to link it to structural brain maturation, we applied a polynomial regression analysis to the effective connections between primary visual areas that were significantly stronger in adults than in children. To this end, age and the CC area assessed on the basis of a midsagittal slice served as estimators of general development and of structural maturation, respectively. The average strength of the $V1_L \rightarrow V1_R$ and $V1_L \leftarrow V1_R$ modulatory connections was used as a dependent variable. We found that both linear and quadratic regression models are significant for age ($P = 0.002$; Fig. 4a) and for the CC area ($P = 0.004$ for the linear and $P = 0.001$ for the quadratic model; Fig. 4b). The quadratic models showed better fit to the data (41.1 and 44.9 % of variance for age and CC area, respectively) than the linear models (34.3 and 30.3 %).

Although the CC area correlates with age ($\rho = -0.62$, $P = 0.001$), the latter is a more general index, accumulating all the developmental changes. To assess the contribution of the individual variations of the CC area, while controlling for age, we applied hierarchical multiple regression analysis. Preliminary analysis ensured no violations of the assumptions of normality, linearity, and multi-colinearity (tolerance = 0.62). In the hierarchical

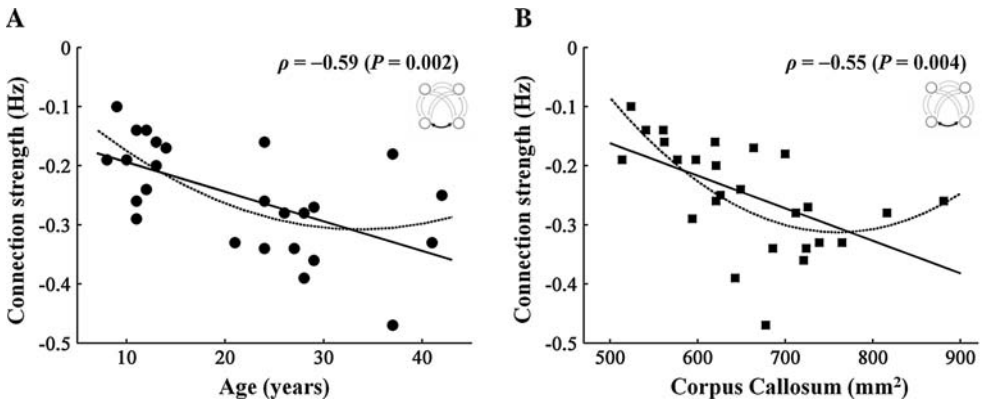


**Fig. 4** Effective connectivity and structural brain maturation. The *plots* show scatter diagrams and developmental trajectories fitted with the first- and second-level polynoms (*solid* and *dashed line*, respectively) for age (**a**) and the CC area (**b**). Pearson regression coefficient $\rho$ with corresponding $P$ value represents a measure of bivariate correlation. The CC area was assessed from a midsagittal slice. The connection strength refers to the average value of reciprocal modulatory connections between the primary visual (*black line* on the connection scheme)

regression model with the two variables, which turned out to be significant at $P = 0.003$ and explained 40 % of the variance in connection strength, the CC area predicted only 5.7 % in addition to what age predicted. Therefore, being controlled for the effect of age, the CC area failed to explain a significant amount of variance.

## Discussion

### Development of spatial integration and changes in top-down effective connections

In children, the key mechanisms of spatio-temporal integration are functional beginning in infancy. In particular, newborns looking at point-light animations prefer biological motion to non-biological motion and, among the biomotion animations, distinguish between upright and inverted displays [30]. Beginning at 2 months of age, infants combine the coherently moving components across large areas of space and treat them as connected wholes [31]. By 3–4 months of age, they are able to perceive the global structure of various arrays [32]. Further development of visual spatial integration continues through middle childhood and, probably, adolescence. Sensitivity to the global structure of Glass patterns with a different percentage of noise approximates that of adults at 9 years of age [33]. The capacity to integrate spatially distant line segments based on their colinearity improves until 10 years of age [34]. Spatial integration tested in contour-detection tasks improves until about 14 years of age [12]. A similar trajectory was shown for sensitivity to biological and global motion [35]. Furthermore, the processing of global shape in paradigms including compound displays still differs in adolescence from that in adults [36, 37].

These behavioral changes are paralleled by the development of functional connectivity in neural networks as manifested by EEG synchronization [38–41]. To show the transformations of neural networks underlying the protracted maturation of integrative mechanisms, here we have applied the DCM method to an fMRI time series under a passive perceptual task, which contrasted bilateral colinear gratings (Gestalt) to bilateral orthogonal gratings (no Gestalt), of which only the first stimulus can be interhemispherically integrated.

Our analysis is implemented in the framework of predictive coding theory, which provides an elegant model of the hierarchical optimization mechanism. It is based on feedback connections that carry predictions of lower-level neural activity and feed-forward connections that carry residual errors between predictions and actual lower-level responses [8, 17]. Indeed, a DCM analysis of fMRI activations induced by coherent or meaningful stimuli compared to random ones has shown inhibitory modulatory effects from the higher-order to the lower-order visual areas in adult subjects [21].

Here, we have shown that intrinsic effective connections within the visual areas do not differ between children older than 7 years and young adults, suggesting that basic visual networks integrated via long-distance reciprocal excitatory pathways are established at this age. The intrinsic connections were modulated by the coherent CG stimulus both in children and in adults. All the descending and lateral modulatory connections turned out to be inhibitory. Therefore, here we have shown for the first time that inhibitory backward effective coupling recently reported in adults [21, 22] works in children as well.

This result agrees with a large body of literature reporting the higher-order effects on V1 via feedback connections originating within the visual system and/or via

long-range local horizontal connections [42, 43]. Although low-level integration has been predominantly studied intrahemispherically as a contextual modulation in the neighborhood of the classical receptive field [44, 45], in adults it likely operates at a long range as well, e.g., across the cerebral hemispheres. In this regard, Ban and colleagues have demonstrated that interhemispheric integration can result in changes of V1 activation [20]. They have found a significantly lower BOLD response to two arcs located symmetrically in the lower visual field quadrants (i.e., to a pattern following the Gestalt principle of good continuation) compared to their asymmetrical (diagonal) location. In the absence of direct interhemispheric V1 connections between the low and high visual quadrants, this modulation of V1 activation is likely due to the top-down influences from the extrastriate areas.

The finding that the top-down modulatory effects in adolescents differ from those in adults suggests their slow formation in human ontogenesis. The available data on the structural maturation of feedback connections, which might be a part of the neural network that enables colinearity detection in humans [12], are limited to those between V2 and V1 [1, 2]. According to this postmortem anatomical study, the upper layers of V1, which receive the feedback connections, seem to be immature even at 5 years of age. In contrast, we found no evidence supporting the immaturity of effective connections downstream of V1, which have also been proposed to underlie the slow progression of perceptual integration in human ontogenesis [35].

The abnormal development of top-down connections in children can explain a well-known interictal phenomenon of reduced habituation to repetitive visual and auditory stimuli in migraine patients [46–48]. Sensory habituation, characteristic for healthy adults and children, refers to progressive reduction in the cortical response to repetitive stimuli. It is manifested as a gradual decrease in the amplitude of evoked potentials. Habituation can be considered as a mechanism protecting against the accumulation of potentially toxic metabolites in the brain. According to the predictive coding hypothesis, the repetition reduces cortical response due to increasing predictability of successive stimuli emerging as a direct result of predictive processing in the brain [49]. Since this effect is sustained through inhibitory feedback connections, their formation in children, which suffer from migraine, should be thoroughly explored in future studies.

## Interhemispheric modulation in V1

In addition to feedback connections strengthening with age, we found increasing interhemispheric inhibitory effects in the primary visual cortex. More precisely, according to the probabilistic cytoarchitectonic atlas, our ROIs designated as V1 included a portion of V2 as well (Table 1). The effects relevant to these DCM results have been recently shown in animal and human electrophysiological studies. Regarding animals, interhemispheric modulatory effects near the V1/V2 border have been observed in a ferret model [50]. As in our experiment, colinear or orthogonal gratings were presented to the two visual hemifields. They induced desynchronization of the local field potential, which could be modulated by reversible cooling of the opposite V1 under the colinear condition.

In adult humans, interhemispheric inhibition in the primary visual cortex has been shown with unilateral transcranial magnetic stimulation of V1, which increased (by means of disinhibition) the amplitude of EEG potentials, evoked by gratings, in the contralateral hemisphere [51]. Another example of transcallosal inhibition in the human primary visual cortex has been demonstrated in binocular rivalry. During perceptual transitions, a dominant stimulus can spread across the visual field in a wave-like manner. These traveling waves of rivalry dominance are delayed when passing from one visual hemifield to another. In a diffusion tensor imaging study, the diffusion properties of callosal fibers connecting the left and right V1 reliably predicted this across-hemifield delay [52]. Since perceptual alternation during binocular rivalry is likely to result from inhibitory interactions between neural representations of the different percepts [53], this finding links the CC to interhemispheric inhibition.

Hypothetically, the insufficiency of interhemispheric inhibition between the primary visual areas could be among the factors behind the reduced habituation (the increased amplitude of visual evoked potential) in patients with migraine. However, until now only the late components of visual evoked potentials, generated in the extrastriate areas, are shown to be different (e.g., [54]).

From an ontogenetic perspective, immature transcallosal modulation between the primary visual areas in the absence of age-dependent interhemispheric effects in the extrastriate areas challenges the conventional view that posits the prior maturation of the early visual cortex as a precondition for the later development of higher-order ventral stream regions [55]. Yet our finding is supported by the association between the indices of effective connectivity and brain maturation. The interhemispheric interaction in the ventral visual stream is implemented via fibers that form the splenium of the CC [56, 57]. Poorly myelinated fibers of small diameter with a protracted course of myelination are abundant in this region [58]. The CC area depends on the number of axons, their size, and the thickness of the myelin sheaths [15, 59], providing a reasonable cumulative index of interhemispheric connectivity. As we found, its age-dependent changes explain about 40 % of the variance in

interhemispheric effective inhibition between the primary visual areas.

Since interhemispheric effective inhibition is presumably implemented via polysynaptic pathways with long-distance excitatory and local inhibitory components, this correlation reflects only the development of the long-distance part. As far as local inhibitory mechanisms in the primary visual cortex are concerned, they were recently analyzed postmortem [60]. Consistently with our results, this study revealed the protracted development of GABAergic mechanisms, which continues well into the second and third decades of life.

In sum, our results suggest that feedback connections from the extrastriate to the primary visual areas together with the interhemispheric connections between primary visual areas strongly contribute to spatio-temporal feature integration in the mature brain. Both feedback and horizontal effective connectivity have a long developmental trajectory extending into the adolescence. This wide developmental window suggests a protracted period of the vulnerability to neuropathological disorders including migraine. For better understanding of the mechanism inducing migraine, the DCM can be used. The method seems to be especially efficient for the analysis of brain networks providing habituation.

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**Conflict of interest** All the authors certify that there is no actual or potential conflict of interest in relation to this article.

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POSTERS

## Surgical treatment of headache: personal procedure

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**Introduction:** During the last few years multiple studies have demonstrated the efficacy of surgical treatment in patients who suffer with migraine: by removing the hyperactive surrounding muscles, the trigeminal trigger point is being eliminated. Guyuron et al. have reported the elimination or improvement in forehead migraine headaches through surgical decompression of the peripheral branch of trigeminal nerve (N. Supratrochlearis and Supraorbitalis) following removal of hyperactive corrugator supercilii muscles, and in occipital migraine headaches through surgical decompression of cervical plexus—C2 (Lesser and Greater Occipital Nerves) following removal of hyperactive surrounding muscles. The aim of this study is to demonstrate the efficacy of surgical decompression by means of both endoscopic and open surgery, through innovative and improved technique compared with beforehand evaluated surgical techniques.
**Patients and methods:** Thirty-three patients who complained of chronic migraine headaches underwent a frontal bilateral selective miotomy procedure of Procerus, Depressor Supercilii and Corrugator Supercilii Muscles by means of video-assisted endoscopic surgery, and an occipital selective miotomy procedure of Occipital, Trapezius, Sternocleidomastoid and Semispinalis Capitis Muscles by means of open surgery.
**Results:** Of the 33 patients included in the study (range 18–73 years), 24 were women and 9 were men. Twenty-eight of 33 patients (85 %) reported a positive response to the surgery: 13 of 33 patients (40 %) observed complete elimination, 15 patients (45 %) experienced significant improvement (at least 50 % reduction in intensity or frequency), and 5 patients (15 %) did not notice a change in their migraine headaches.
**Conclusions:** This study confirms previous data in literature, strengthening the role of a peripheral mechanism (trigger points) in migraine headaches. Since the operation has not caused any serious complication or side effects, it can be recommended to patients who suffer from moderate to severe chronic migraine not responding to medications. Moreover, the minimally invasive procedure we described is easy, fast and cost-effective, relying on the use of a single instrument, also reducing the numbers of postoperative scars from five to one.

## When medication overuse headache overlaps with hypnic headache: a case report

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Hypnic headache is a rare primary headache characterized by recurrent attacks developing during sleep, appearing usually beyond 50 years. This condition is poorly recognized and probably underestimated. The etiology and pathogenesis is still unknown but the efficacy of lithium therapy support the hypothesis of a chronobiological disorder. We report the case of a 64 year old woman who suffered for a 3-years history of headache attacks occurring every night. She had previously suffered for mild episodic migraine since the adolescence but the frequency of the migraine attacks became more frequent after the age of 30. At the age of 51 she developed a chronic medication overuse headache but the majority of the attacks started to occur during the night. She was treated with different prophylactic therapies (valproic acid and topiramate) with only temporary relief. At the age of 60 the attacks became exclusively nocturnal and fulfilled the diagnostic criteria of hypnic headache.

An MRI examination, a prolonged pressure monitoring and a polysomnography excluded secondary causes for the headache. Since the overuse of symptomatic drugs the patient underwent a wash-out treatment after which a prophylactic therapy with lithium was introduced, resulting in a great reduction of the attacks. In this case symptoms fulfilled both "hypnic headache" and "medication overuse headache" diagnostic criteria. The diagnosis of hypnic headache should not be ruled out because of a pre-existing medication overuse headache.

## A case of Tolosa Hunt syndrome associated with multifocal chronic recurrent ostemyelitis in a child: a possible common pathogenesis for two rare disorders

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Tolosa–Hunt syndrome (THS) is a rare ophthalmoplegic syndrome due to a non-specific granulomatous inflammation of the cavernous sinus or orbital apex. A 13-year old child developed a THS consisting of right eye ptosis associated with orbital and temporal pain. The sierological and biochemical findings highlighted an increase of the acute-phase proteins with a normal immunological and infective screening. The MRI confirmed the diagnostic suspicion. The patient was treated with prednisone for the next 9 months until the resolution of the symptoms and of cavernous sinus lesion on MRI. However the patient developed a swelling of right wrist and diffuse arthralgias; further investigations (MRI, Computerized Bone Mineralometry, liquor examination and osteomedullary biopsy) revealed the presence of diffuse areas of osteorarefaction but excluded a lymphomatous or steroidrelated condition. A biopsy of the wrist lesion revealed an inflammatory aspecific infiltration of the bone. A conclusive diagnosis

of Chronic Recurrent Multifocal Osteomyelitis (CRMO) was postulated. A treatment with indometacine (75 mg/day) was introduced with resolution of the symptoms. We report the first paediatric case of THS associated with CRMO, suggesting a possible common pathogenesis. We want to highlight that a typical THS may occur also in paediatric population and that a careful follow up is mandatory.

## A clinostatic headache with Horner's syndrome

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**Introduction:** It is widely recognized that secondary headache should be considered in patients presenting with new onset headache or headache that differs from usual headache. Focal neurological symptoms and headache that changes with posture are other red flag features. We describe an atypical case of postural headache in association with Horner's syndrome.
**Case:** A 53-year-old man, with a history of migraine without aura, came to our attention for the evaluation of new-onset headache attacks in the last 6 days. The pain was pulsating, localized in the right temporal region and occurred as the patient assumed the clinostatic position. Non-steroidal anti-inflammatory drugs were ineffective. However, the pain spontaneously improved as the patient assumed the orthostatic position and fully resolved within 30 min. Additionally, 2 weeks before the appearance of this headache, the patient had noticed right ptosis and miosis. A brain MRI performed at onset of symptoms was interpreted as normal. Neurologic examination revealed right incomplete Horner syndrome (ptosis, miosis, absent anhidrosis). The remainder of the neurologic examination was unremarkable. In particular there were no diplopia or temporal artery abnormalities (tender or reduced pulsation). Due to persisting pain and Horner's syndrome, the man was admitted to the emergency department for further investigations. A thoracic CT ruled out an apical lung mass and blood tests revealed abnormal C-reactive levels. An angio-CT revealed right internal carotid artery dissection (ICAD).
**Conclusion:** This case highlights the need to suspect secondary headaches in patients who develop new atypical symptoms as paradoxical postural headache. In particular internal carotid artery dissection should be ruled out in case of "Painful Horner's Syndrome". Internal carotid artery dissection classically presents with unilateral head/neck pain, focal cerebral ischemic symptoms, and partial Horner syndrome. To our knowledge, the occurrence of clinostatic headache secondary to internal carotid artery dissection has never been reported.

## Temporary and recurrent visual disturbance in a brainstem lesion: a migrainous disorder?

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Symptomatic migraine or migraine-like headache can be secondary to a brainstem lesion, commonly in mesencephalon or pons, but rarely these conditions may be caused by a bulbar lesion.

These headaches are usually controlateral to the side of the lesion but also some cases of omolateral pain were reported. The pathogenetic mechanism probably involves a disfunction in the descending inhibitory activity of certain nuclei (LC, PAG, NC), possibly causing hyperexcitability in the trigeminovascular system.

In a recent report of a patient suffering from migraine with aura, developed after a lesion in medulla oblongata, pain was contralateral and aura was not lateralized. The authors hypothesized that the aura might be related to an impaired habituation, secondary to a brainstem lesion with reduced activity of trigeminal nucleus and cortical hyperexcitability which would in turn cause cortical spreading depression (CSD) and visual symptoms.

We describe the case of a young man, previously healthy, who developed only visual disturbances without pain after left vertebrobasilar thrombosis. The symptoms, arised 20 days after the vascular lesion, had a daily frequency and usually lasted one hour; they disappeared one year later.

Some characteristics of this case let us speculate that these symptoms might be of migraine nature and we try to formulate some pathogenetic hypotheses.

## Spontaneous intracranial hypotension (SIH) headache in allergic singer woman with congenital sacral meningocele

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**Introduction:** Spontaneous intracranial hypotension (SIH) is characterized by orthostatic headache and low CSF pressure. Other symptoms include diplopia, neck stiffness, alterations in hearing, nausea, rarely leading to numbness and coma.
Meningocele is a congenital malformation characterized by protrusion a meningeal sack, covers atrophic skin, sometimes with hair and angioma, across a spinal column defect. Meningeal sack is full of CSF. Generally roots are not interested.
**Case report:** A 40 year old young woman was admitted to our hospital for severe constrictive headache, an usual from her normal headache, associated with vomiting made worse in orthostatic postural position. In the morning, after repeatedly sneezed by allergic rhinitis, followed lumbosacral pain and moderate migraine without aura and tension-type headache.
In the evening, after she had sung appeared violent pain to right ear with severe headache.

In medical history: hair cat allergy and migraine without aura. Urgent basal TC brain and neurological examination were normal. In the second day, brain MRI with contrast showed widespread, symmetric and linear meningeal enhancement, with dura mater thickening. The patient was treated with intravenous corticosteroids therapy and rest in bed. Spinal cord MRI with mdc documented sacral extension of the dura mater sack until S3. Lipomatosis formation between S4 to coccygeal bone. Nerve roots until S4. Cleft arch back last sacral vertebra. Findings compatible with sacral meningocele. Lack of fistola.
**Discussion:** Traumatic factors representing 30 % of syndromes CSF hypotension. In this case the sneezing and the vocalization have caused an increased thoracic-abdominal pressure with traction, trauma and tearing of the sacral roots causing an headache by spontaneous intracranial hypotension.

Cleft interested a meninx locally fragile with little protection for the congenital disease.

The patient was submitted after five days with complete restitutio ad integrum with oral corticosteroids terapy, but without treatment with epidural blood patch (EBP).

## Impact of headache in the workplace: a pilot study

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**Background:** The aim of this study was to evaluate the negative consequences of headache in the workplace, and to investigate the possible correlations with specific factors related to the workplace.
**Methods:** This study was conducted at UNIQA Insurance Company (Milano). A self-administered questionnaire designed to investigate the presence of headache during the previous three months was sent by e-mail to all 300 employees. It included the ID migraine screener and the MIDAS questionnaire, as well as questions about trigger factors, prescription of therapy and relative satisfaction, medical resource utilization, presence of other disorders.
**Results:** Twenty-one employees responded to the questionnaire. Among these 18 reported headache, 88 % were female, mean age 39 years (22–49); 61 % reported headache during the morning hours, 44 % had attacks lasting >3 days; 38,8 % had a migraine diagnosis according to the ID screener, and 73 % had never received a previous diagnosis; the main triggers of headache were: stress (in 89 %), and specifically stress on the workplace, in 62 % of subjects, fatigue in 55 %, lack of satisfactory sleep in 39 %. Only 17 % of subjects had consulted their physician or a neurologist; 89 % used NAIDS for symptomatic treatment of headache, and none of them took a prophylactic therapy. The MIDAS was correctly completed by 72 % of headache subjects: the 18 % of the sample reported absence from work and the 72 % reported a 50 % or more reduction in productivity.
**Discussion:** The main limitation of the study was the low rate of response to the specific questionnaire. However, our results allow some considerations: most headache sufferers did not have a headache diagnosis; only a minority consulted a physician, and no subject in the sample used headache-specific medications which could reduce the impact on work and have not sought health treatment and rely on over the counter medications to manage symptoms; headaches occurred often during the working hours; workplace stress and fatigue were among the most represented trigger factors; presenteism was reported by majority of subjects, while absenteeism was not common.
**Conclusion:** Our results confirm that headache sufferers may experience relevant limitations in the workplace. They also confirm the high level of underdiagnosis and undertreated—two factors that are likely to cause a remarkable impact of headache on work, due to the lack of appropriate education and treatment.

## Meningioma and typical migraine without aura: description of a case

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We described the case of a female patient of 50 years old, suffered for years from a bilateral,orbital frontal and throbbing headache, sometimes with nausea, photo and phonophobia. The headache worsed after physical activity.

The average monthly frequency was 1 severe attack, while milder attacks were more than 15 days a month.

She took NSAIDs and rizatriptan, with moderate benefit within 2 h.

A typical, episodic migraine without aura with chronic tension type headache associated (according to the ICHD 2 criteria) was diagnosed.

The patient was then prescribed a prophylactic treatment with amitriptyline 25 mg p.o. daily for three months, with benefit on the frequency and intensity of the attacks.

After more than a year she was admitted to the Emergency Room for a generalized epileptic seizure.

A Tc brain scan was performed, showing the presence of a massive right temporal meningioma, surrounded by oedema.

The patient has been thus transported in the Neurosurgery Departement and submitted to a surgical intervention of partial removal of the tumor. After the surgical procedure she complained of a mild left hemiparesis, with slow but complete recovery.

At subsequent assessments, the patient reported the complete regression of migraineurs symptoms, with only few tension type headache attacks.

This is an unusual clinical case in which a typical migraine without aura seemed to be caused by a meningioma.

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