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INVITED LECTURE

# Redefining primary headaches

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**Abstract** In the light of the pathophysiologic knowledge acquired in the recent years, a tentative redefinition is now possible of some types of headache until now defined as idiopathic, and indistinctly described as primary headaches. Cluster headache and trigeminal neuralgia are known examples of diseases classified as primary, which are, in contrast, well-defined diseases to be distinguished from headaches without any recognized anatomic site of lesion or pathogenesis. Another still debated condition, chronic migraine, is proposed here as the consequence of "processes" to be ascribed to mechanisms activated by other comorbid conditions. The observations supporting the possibility that allodynia represents the implicit process leading to pain progression, which occurs in some migraineurs, are discussed.

**Keywords** Primary headaches · ICHD · Transformed migraine · Chronic migraine · Allodynia

## Introduction

The title "Redefining primary headaches" is a title with a great ambition. It indicates that the writer should possess two capacities:

1. thoroughness in conceptual and semantic analysis;
2. an extensive, meticulous knowledge of headaches in all its forms.

This could lead to a reclassification of primary headaches, with all the semantic and conceptual doubts and uncertainties that whoever suggests an overthrow or a simple minor change in an existing, largely shared codification such as that proposed by the International Headache Society (IHS) in 2004 [1] must be coping with.

We shall start from point (1) with a question: what do we mean by primary? Anything that corresponds to the "earliest in time or order of development". This definition may be read in most dictionaries, which may add: "first in a causal order, being the first in order of one or more other items", and again: "in medicine, synonym of initial in morbid processes that may be clinically subdivided into several stages".

It may already be inferred that this is not the definition used by the IHS when it distinguished primary (36 codified forms) from secondary headaches (143 codified forms).

According to the IHS, and not only to it, the distinction is between morbid conditions that have headache as the only phenotypic expression within a coexisting or immediately preceding or following syndromic context on the one hand, and on the other, etiologically defined morbid conditions in whose syndromic context headache may or may not be present, or else may be dissociated from other symptoms or signs.

Headaches that we define today as secondary are not controversial, if there is an accurate diagnostic and therapeutic reference to the definition.

The lesion leading us to the definition of secondary headache will be different (either inflammatory or neoplastic, either traumatic or caused by intra- or extraparenchymal

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hemorrhage, etc.), but it will always be indicated in anatomic terms, based on the history of a clinical medicine that today appears to be scarcely elaborated when looked in retrospection.

The progress of experimental and applied research confuses the issues, and raises new doubts. This is the path trodden by the scientific research in its most-recent history, and it calls into question another definition, crucial to reach a consensus on the concept of "primary": the definition of *observation*. Jean Baptiste Le Rond d'Alembert, creator, together with Denis Diderot, of the *Enciclopedie*, must be credited as the first to ever provide a rigorous definition of observation in the scientific domain.

According to d'Alembert, a physicist and mathematician, "scientific observation is a simple verification, a collection of raw data, a sort of taking note of facts. Hence, it must be distinguished from the experiment, which is an elaborate study of the unknown."

If we relate the considerations above to the activities of a researcher (clinical or other), which may only be defined as such if he/she resolves to reveal for the first time what is not known, we are no longer dealing with the observation of raw data, but with a more or less elaborate experiment. The result of this is the individuation of previously unknown causal factors, and of previously controversial pathogenetic mechanisms. However, the greater elaboration of the experiment as compared to unprogrammed observation has an additional advantage: that of allowing for a macroscopic as well as microscopic anatomic view of the lesional substrate of the symptom or sign. The biochemical lesion tackled with by Sir Rudolph Peters in 1937 becomes a substitute and elaborate lesional substrate for the anatomic damage.

All this leads to informally give up the idea of defining as primary any headache that, based on the current knowledge *under evolution*, might be defined as a *secondary headache to processes* having complex and multiform phenotypes, in which headache is one of the non-obligatory clinical variables. Migraine aura without any migraine is one such example.

All this might look like little more than an intellectual *divertissment*, although it is not so. Any headache defined today as primary by the IHS, which is in the need of a present recodification as headache disease, is going to require an adequate treatment (pathogenetic and/or causal, as well as symptomatic) that will engage the clinical researcher in increasingly complex experiments with the purpose of finding a cure, without which there is no doctor, as Rudolph Virchow used to remind.

To make it brief, the attempt is that of creating a nosography that, once symptomatic headaches are individuated in the context of morbid processes with a well-defined anatomic basis, should classify headaches currently defined as primary into two large classes:

1. disease headaches with a well-defined pathogenesis that might show an etiological uncertainty; and
2. headaches without an anatomic basis and without a well-defined pathogenesis.

Such a distinction could lead us to re-analyze the studies conducted on comorbidities, which may only be considered as such in the presence of morbid conditions, when two pathogenetically if not etiologically defined diseases coexist [2].

## Redefining primary headaches

An increasing number of cases show the difficulty in continuing to classify some headache conditions within the indistinct context of primary diseases. Cluster headache and trigeminal neuralgia are two examples of headaches that should be reconsidered. The much debated chronic migraine concept is presented in this paper with greater detail as an example of a still incomplete although practicable route.

### Cluster headache

Until recently, the pathophysiology of cluster headache has escaped any attempt at definition of its mechanisms, and has lately been traced back to alterations in specific hypothalamic structures, where functional as well as anatomic anomalies take place [3, 4]. Transforming the newly acquired knowledge into new therapeutic options such as the deep brain stimulation (DBS) of the posterior hypothalamus has only been possible when it was decided to assign to the hypothalamic dysfunctions a causative connotation, and to pain a secondary syndromic value, despite its stereotyped specific presentation. Today, anxiety, psychomotor agitation in the course of a crisis, and hypersexuality, all present in these subjects [5], may be reconsidered within a syndromic context that includes pain, and that is not subordinate to it.

### Trigeminal neuralgia

At present, trigeminal neuralgia is believed to be produced, in almost all cases, by the presence of a neurovascular conflict within the posterior fossa [6]. The presence of this causative conflict, suggested by Peter Jannetta back in 1977, has had to wait for over two decades before clinical experience codified it as possible cause. Hence, it was only in 2004 that the term "idiopathic" was substituted by "classic", a necessary balancing to maintain the distinction

between forms associated with the conflict (or without any demonstrable cause), and those in which an identical phenotype presents in larger syndromic contexts, such as those of expansive lesions of the cerebellopontine angle or those of multiple sclerosis [7].

## Chronic migraine

Chronic migraine, a condition whose taxonomic collocation is still debated [8–11], represents a perfect example of the problems that arise when a headache is defined as primary. Classified under subchapter 1.5-complications of migraine, chronic migraine is still considered as a primary condition, to the point that when it is associated with an analgesic overuse, it has to be distinguished from medication overuse headache (MOH)—a condition classified among the secondary forms that is nosographically separate, although clinically indistinguishable [12]. It is well known that this distinction requires a 2-month clinical observation after medication withdrawal. Only in case of missed return to an episodic pattern is the clinician authorised to formulate a diagnosis of chronic migraine; if that does not happen, the latter diagnosis will be excluded, and a diagnosis of MOH will be confirmed. Therefore, the standard classification clearly separates a progression "secondary" to overuse from a "primary" one, unequivocally excluding any other possibility [1]. The complex clinical procedures needed for a distinction between the two forms are not free from negative consequences, mostly related to the difficulty of inviting the patient, unquestionably disabled by his/her problem, to spend a long observation period without medicaments, and to the consequent difficulty of recruiting subjects for a clinical trial.

Is a system that determines such a high-cost in terms of consequences on clinical practice and research justified? And at present, how trustworthy may we believe the considerations that led to the implementation of this complex diagnostic system are?

### *Chronic migraine and analgesic overuse*

It is interesting to note that a pre-existing episodic migraine is a necessary condition for developing chronic pain in the presence of drug overuse [13], although non sufficient, as it is only observed in a minority of migraine sufferers who take NSAIDs daily due to rheumatologic problems [14]. Drug overuse is noticed in most cases observed in the outpatient's department, although data reported on population studies indicate that 1/3 [15] to 2/3 [16] of subjects with chronic migraine do not abuse analgesics. After an isolate suspension of overuse, a return to an episodic pattern only occurs in 45% of patients with probable MOH [17]. Taken all together, these observations suggest that overuse is neither necessary nor sufficient to determine the progression of pain, but it has to be considered as an important risk factor in subjects with a history of migraine who are likely to be subject to a specific comorbid predisposition.

Which hypotheses may be formulated on the nature of this predisposition?

From a biochemical viewpoint, there is evidence of a downregulation of the trigeminal serotoninergic receptors [18], and of a reduced serotonin synthesis at the level of the dorsal raphe nucleus [19], associated with analgesic overuse. The finding on PET of a hypometabolism of the orbitofrontal cortex, an area involved in the processing of pain, which persists even after overuse withdrawal, has led to the assumption that a primitive hypofunction of the orbitofrontal cortex affects the development of MOH in a number of migraineurs. Alternatively, orbitofrontal hypometabolism could represent a prolonged, or even persistent, effect of alterations in the pain pathways, produced by a long-standing overuse [20]. The latter possibility is supported by the results of an important neurophysiologic study conducted on subjects with MOH. Through a simultaneous evaluation of the nociceptive blink reflex (nBR) and of the pattern reversal-evoked potential (PREP) before and after overuse suspension, it was possible to prove that central sensitization is a causative mechanism involved in MOH, reversible upon suspension, not confined to the trigeminal areas but extending to the thalamocortical ones [21].

Hence, the mechanism through which acute medication overuse induces the progression of migraine could focus on a central facilitation of nociception, a phenomenon believed to be at the basis of allodynia.

These considerations lead us to have some reservations about the appropriateness of the nosographic distinction attributed to MOH. Downgrading MOH to a mere complication of migraine (and of tension-type headache) occurring in predisposed subjects is starting to be seen as a taxonomic priority. This operation could solve to its root the problem of neatly differentiating, only on a clinical basis, diagnoses considered to be of the same hierarchic level even though virtually relating to disorders having a considerable symptom overlap.

### *Allodynia and migraine progression*

While in episodic migraine allodynia only occurs during the attack [22–24], in the chronic forms it has also been detected intercritically, which suggests that the neurons of the trigeminal nuclear complex are chronically sensitized in these patients [25]. The frequency of the crises is related to central sensitization [26, 27], and there is evidence that an increased sensitivity to pain in migraineurs is a

consequence of pain repetition [28]. A recent study indicates that allodynic phenomena are bilaterally detected during the intercritical phase in over 70% of subjects suffering from chronic headache [29].

These observations support the theory that central sensitization of the pain pathways is involved in the progression of migraine pain, and it provides a possible explanation of the similar clinical presentation of different forms of headache, once pain has reached a daily or almost-daily frequency. However, at present this hypothesis, which requires meticulous research, is supported by the possibility of tracing back to allodynic mechanisms the action of the main risk factors for chronic migraine [30, 31] validated by the recent literature, such as: the high frequency of crises at baseline [26, 27]; obesity [27, 32]; comorbidity with psychiatric disorders [27, 33, 34]; and female gender [35], as well as the above-mentioned medication overuse.

On the basis of the proposed facts and considerations, chronic migraine may also be included among the conditions whose primary character might be debated, being headache the event occurring at the end of a pathogenetic sequence typical of a peculiar individual susceptibility to allodynia. The latter, on its turn, is largely conditioned by the individual comorbidity profile; hence, it may only in part be defined as primary in itself.

## Conclusions

Much of this dissertation has been dedicated to chronic migraine, chosen to simultaneously illustrate a practicable route and the need for further debate. Defining a headache as primary should only be a transient step in history, as happened for other neurologic diseases, even though with an unavoidable slowness.

None of us can help not wishing for quick routes in science, but even during what has been defined by Erik J. Hobsbawn as the "short century", this has not happened with the speed we would have wanted and keep on wishing for.

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## References

1. Headache Classification Subcommittee of the International Headache Society (2004) International classification of headache disorders, 2nd edn. Cephalalgia 24[Suppl 1]:1–160
2. Bonavita V, De Simone R (2008) Towards a definition of comorbidity in the light of clinical complexity. Neurol Sci 29(Suppl 1):S99–S101
3. May A, Bahra A, Büchel C et al (1998) Hypothalamic activation in cluster headache attacks. Lancet 352(9124):275–278
4. May A, Ashburner J, Büchel C et al (1999) Correlation between structural and functional changes in brain in an idiopathic headache syndrome. Nat Med 5(7):836–838
5. D'Andrea G, Nordera GP, Perini F et al (2007) Biochemistry of neuromodulation in primary headaches: focus on anomalies of tyrosine metabolism. Neurol Sci 28(Suppl 2):S94–S96
6. Jannetta PJ (1977) Observations on the etiology of trigeminal neuralgia, hemifacial spasm, acoustic nerve dysfunction and glossopharyngeal neuralgia. Definitive microsurgical treatment and results in 117 patients. Neurochirurgia (Stuttg) 20(5):145–154
7. Jensen TS, Rasmussen P, Reske-Nielsen E (1982) Association of trigeminal neuralgia with multiple sclerosis: clinical and pathological features. Acta Neurol Scand 65(3):182–189
8. Silberstein SD, Lipton RB, Sliwinski M (1996) Classification of daily and near-daily headaches: field trial of revised IHS criteria. Neurology 47:871–875
9. Olesen J, Rasmussen BK (1996) The International Headache Society classification of chronic daily and near-daily headaches: a critique of the criticism. Cephalalgia 16:407–411
10. Headache Classification Committee, Olesen J, Bousser M-G et al (2006) New appendix criteria open for a broader concept of chronic migraine. Cephalalgia 26:742–746
11. Olesen J (2007) Reply: new appendix criteria open for a broader concept of chronic migraine. Cephalalgia 27:469–470
12. Silberstein SD, Olesen J, Bousser MG et al (2005) The international classification of headache disorders, 2nd Edition (ICHD-II)-revision of criteria for 8.2 Medication-overuse headache. Cephalalgia 25:460–465
13. Lance F, Parkes C, Wilkinson M (1988) Does analgesic abuse cause headaches de novo? Headache 28:61–62
14. Bahra A, Walsh M, Menon S et al (2003) Does chronic daily headache arise de novo in association with regular use of analgesics? Headache 43:179–190
15. Castillo J, Munoz P, Guitera V et al (1999) Kaplan Award 1998: epidemiology of chronic daily headache in the general population. Headache 39:190–196
16. Colás R, Muñoz P, Temprano R et al (2004) Chronic daily headache with analgesic overuse. Epidemiology and impact on quality of life. Neurology 62:1338–1342
17. Zeeberg P, Olesen J, Jensen R (2006) Probable medication-overuse headache: the effect of a 2-month drug-free period. Neurology 66:1894–1898
18. Reuter U, Salomone S, Ickenstein GW, Waeber C (2004) Effects of chronic sumatriptan and zolmitriptan treatment on 5-HT receptor expression and function in rats. Cephalalgia 24:398–407
19. Dobson CF, Tohyama Y, Diksic M, Hamel E (2004) Effects of acute or chronic administration of antimigraine drugs sumatriptanand zolmitriptan on serotonin synthesis in the rat brain. Cephalagia 24:2–11
20. Fumal A, Laureys S, Di Clemente L et al (2006) Orbitofrontal cortex involvement in chronic analgesic-overuse headache evolving from episodic migraine. Brain 129:543–550
21. Ayzenberg I, Obermann M, Nyhuis P et al (2006) Central sensitization of the trigeminal and somatic nociceptive systems in medication overuse headache mainly involves cerebralsupraspinal structures. Cephalalgia 26:1106–1114
22. Burstein R, Cutrer MF, Yarnitsky D (2000) The development of cutaneous allodynia during a migraine attack. Clinical evidence for the sequential recruitment of spinal and supraspinal nociceptive neurons in migraine. Brain 123:1703–1709
23. Burstein R, Collins B, Jakubowski M (2004) Defeating migraine pain with triptans: a race against the development of cutaneous allodynia. Ann Neurol 55(1):19–26

24. Ashkenazi A, Sholtzow M, Shaw JW et al (2007) Identifying cutaneous allodynia in chronic migraine using a practical clinical method. Cephalalgia 27:111–117
25. Cooke L, Eliasziw M, Becker WJ (2007) Cutaneous allodynia in transformed migraine patients. Headache 47(4):531–539
26. Buchgreitz L, Lyngberg AC, Bendtsen L, Jensen R (2006) Frequency of headache is related to sensitization: a population study. Pain 123(1–2):19–27
27. Bigal ME, Ashina S, Burstein R et al (2008) Prevalence and characteristics of allodynia in headache sufferers. A population study. Neurology 70:1525–1533
28. Buchgreitz L, Lyngberg AC, Bendtsen L, Jensen R (2007) Increased pain sensitivity is not a risk factor but a consequence of frequent headache: a population-based follow-up study. Pain 137(3):623–630
29. Filatova E, Latysheva N, Kurenkov A (2008) Evidence of persistent central sensitization in chronic headaches: a multi-method study. J Headache Pain 9:295–300
30. Scher AI, Midgette LA, Lipton RB (2008) Risk factors for headache chronification. Headache 48:16–25
31. Bigal ME, Lipton RB (2006) Modifiable risk factors for migraine progression. Headache 46(9):1334–1343
32. Bigal ME, Lipton RB, Holland PR, Goadsby PJ (2007) Obesity, migraine, and chronic migraine. Possible mechanisms of interaction. Neurology 68:1851–1861
33. Wang SJ, Fuh JL, Lu SR, Juang KD (2007) Outcomes and predictors of chronic daily headache in adolescents. A 2-year longitudinal study. Neurology 68:591–596
34. Luconi R, Bartolini M, Taffi R et al (2007) Prognostic significance of personality profiles in patients with chronic migraine. Headache 47:1118–1124
35. Gazerani P, Andersen OK, Arendt-Nielsen L (2005) A human experimental capsaicin model for trigeminal sensitization: gender-specific differences. Pain 118:155–163

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SECONDARY HEADACHES

# Alterations in the cerebral venous circulation as a cause of headache

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**Abstract** The alterations of the cerebral venous circulation are a rare but clinically important cause of headache. Although any process involving the cerebral veins or sinuses may cause headache, the most frequent and important are cerebral venous thrombosis and idiopathic intracranial hypertension. The headache of cerebral venous thrombosis does not have specific features and may be isolated; therefore, all patients with headache and risk factors for venous thrombosis should undergo the appropriate neuroradiologic examinations to rule out the diagnosis. In fact, early anticoagulant treatment may dramatically change the clinical outcome. Also idiopathic intracranial hypertension, if untreated, may have serious clinical consequences such as permanent visual loss. The pathogenesis of this disorder has not been clearly established and several possibilities involving the cerebral circulation are discussed.

**Keywords** Headache · Cerebral venous thrombosis · Idiopathic intracranial hypertension

## Introduction

Headache is a cardinal manifestation of a number of clinical conditions involving the cerebral venous system. In particular, any functional or structural impairment of the dural sinuses can cause a reduction of CSF drainage and hence lead to an increase of intracranial pressure; the latter in turns causes a stretching of nervous terminations in the dura perceived as pain at the head or neck. One well-known cause of venous obstruction is cerebral venous thrombosis (CVT). The headache is present is in the majority of patients and is the presenting symptom in many; since it has no specific feature, any headache in patients at high thrombotic risk should raise the clinical suspect of CVT. Another frequent conditions in which headache might be related to alterations of venous function is idiopathic intracranial hypertension (IIH). However, in this disorder the physiopathologic mechanisms are probably more complex and less clearly established; in particular, whether the alterations in venous outflow are the primary cause of the diseases or just the consequence of some other alteration is yet to be determined. The diagnosis of IIH has a high clinical relevance as it may prevent visual loss.

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## Anatomy of the venous system

The venous drainage of the brain can be essentially divided into two main districts: a superficial system which receives blood from the brain convexity (mainly from the cerebral cortex), and a deep system, which instead drains the deep white matter and the grain nuclei. The superficial veins drive blood from the frontal and parietal lobes into the superior sagittal sinus, while blood from the temporal and occipital lobes is drained by the left and right transverse sinuses. The deep cerebral veins, on the other end, drain blood into the straight sinus through the Galen vein or into the transverse sinuses. The venous circulation of the neural structure in the posterior region, including the brainstem and cerebellum have a more variable and inconstant anatomy; however, the veins of this region ultimately end in the transverse sinuses. Finally, the venous blood from the

antero-inferior areas of the brain (inferior surface of the fontal lobes) and from the face is collected in the cavernous sinuses, and from there is driven to the transverse sinuses through the petrous sinuses. The superior sagittal, transverse and straight sinuses are connected in the confluence of sinuses in the posterior fossa; therefore, thrombotic processes affecting this area can impair the venous drainage of most of the brain and are thus responsible of dramatic, and often fatal, clinical syndromes. Further anastomotic connections are often present: the superficial system is connected with the deep system through the vein of Trabant, while the superior sagittal and transverse sinuses are in communication through the vein of Labbè. These pathways may provide some collateral flow in case of venous occlusions, explaining the mild clinical conditions observed in many patients.

Most of the venous blood of the brain is eventually collected to the transverse sinuses, which continue into the sigmoid sinuses and deep jugular veins.; one of the later sinuses is often prevalent and conveys more blood flow. A minority of venous blood is also drained through anastomotic connections with the vertebral plexus.

## Pathophysiology of headache in cerebral venous thrombosis

Headache is the most frequent symptom in cerebral venous thrombosis. It is present in over 80% of patients and is the presenting symptom in nearly 70% [1]. Although the headache is associated with other neurologic signs in the majority of patients, it can also occur isolated [20% in the international Study on Cerebral Venous Thrombosis (ISCVT)] [2]. The pain is thought to be due to the elevation of intracranial pressure, which may result from different mechanisms: the reduction of liquoral absorption resulting from sinus occlusion or to the mass effect of swollen brain areas or brain hematomas. These mechanisms often coexist and their relative prevalence depends on the extent and site of the thrombotic process: if the occlusion is limited to one sinus, parenchymal damage may be restricted to a localized oedema without ischaemic lesions; in this case, the head pain may be absent. If the thrombotic process is more widespread and involves more than one sinus, collateral flow is insufficient to allow venous drainage; the first consequence is a dramatic increase in capillary pressure, leading to leakage of fluids in the extracellullar compartment, brain swelling and intracranial hypertension [3, 4]. Instead, in the case of thrombosis of a cortical vein, brain ischaemia develops rapidly and a venous stroke is invariably present. Venous strokes have peculiar characteristics compared with arterial ones: the degree of oedema is usually greater and haemorrhagic complications, ranging from small petechial lesions to a proper haemorrhagic infarction are much more frequent [5, 6]. The higher degree of brain oedema is probably due to the present of a vasogenic component, which is absent in arterial strokes, as demonstrated by MRI imaging techniques [7, 8]. Both the diffuse brain oedema and the development of a stroke may lead to headache, which may be diffused or localized. The localization of the pain is not predictive of the site of the stroke or of the sinus occlusion.

The pain may be associated with other signs of intracranial hypertension, such as vomiting or a reduced consciousness. These signs are more often observed in patients with large supratentorial lesions with severe mass effect or in patients with occlusion of vessels of the deep circulation. In fact, in case of occlusion of an internal cerebral vein or of the straight sinus the diencephalic structure responsible for awareness is directly injured, leading to early loss of consciousness in these patients. Furthermore, oedema of these centroencephalic area leads rapidly to compression of the brainstem endangering patient survival.

Finally, a rare possibility is that the headache may be secondary to a meningeal irritation. In fact, subdural and even subarachnoid haemorrhages have been described as a consequence of venous thrombosis [9, 10]. In this case, the onset is sudden and the pain is particularly intense; meningeal signs can be found at the neurologic examination. However, an acute onset is present in nearly 7% of cases and thurderclap headache has been reported in cases of CVT without subarachnoid haemorrhage [11, 12].

Since the identification of headache features associated with CVT has a high clinical relevance, we studied a group of 49 patients with a diagnosis of CVT and headache and compared them with 90 control patients with headache of other cause [13]. Unfortunately, headache associated with CVT has no specific features, as it can have an acute, subacute or chronic onset, be localized or diffuse and have any severity. The pain can be associated with nausea and vomiting and can be both continuous or pulsating. When pain is lateralized and pulsating, an erroneous diagnosis of migraine is often made [14]. We found a positive correlation between CVT, acute headache onset ($P < 0.005$) and severe headache ($P = 0.024$). These data were confirmed in a small prospective study on 27 subjects, as we found a positive correlation between CVT, acute headache onset ($P = 0.001$) and severe headache ($P = 0.004$). Therefore, in patients with acute or subacute onset headache of severe intensity, CVT should always be considered. However, since headache has no specific feature, all cases of unexplained headache in patients at high risk, such as subjects with known states of hypercoagulation or women in pregnancy-puerperium or who consume oral contraceptives, should raise the clinical suspicion of cerebral venous occlusion.

## The venous system in idiopathic intracranial hypertension

Idiopathic intracranial hypertension is a clinical syndrome due to an increase in cerebrospinal fluid pressure in the absence of intracranial mass or vascular lesions and with normal ventricular size. It is an uncommon disorder, with an incidence around 1–2 per 100,000 persons/year [15, 16]; this value rises to 15–19/100,000 in young obese women, who are at an increased risk for this disease [15]. Headache is present in 70–90% of patients [16, 17], and is the presenting feature in the majority [15]. Like the pain in CVT, it has no specific features and may be constant, progressive or fluctuating, mimicking tension type or migraine headache [18]. The pain may be exacerbated by couching, straining or Valsalva manoeuvres, but this feature is not present in all patients [19].

The pathogenesis of idiopathic intracranial hypertension is still undefined and several different mechanisms have been proposed, including increase in CSF production, reduced absorption or systemic venous hypertension. The first mechanism is now thought to be present only in the rare instance of patients with a papilloma of the choroid plexus, while those with true IIH have been shown to have a normal rate of CSF production [20]. On the other hand, impairment of CSF clearance has been demonstrated in several studies [21, 22] and is currently considered a more likely explanation for the disease. Moreover, in a recent study with NMR venography abnormalities in the intracranial venous system such as bilateral stenosis of the transverse sinus have been shown in 27 of 29 [23]. However, whether these anatomical alterations are the primary alterations or are secondary to the increased intracranial pressure is yet to be established. Some authors reported that such abnormalities may be reversed by intracranial pressure lowering with surgical procedures [24], but other studies showed the persistence of transverse sinus stenosis after CSF diversion [25]. Moreover, some authors have reported the reduction of intracranial pressure after dilatation and stenting of the stenosed sinuses, supporting the notion that the abnormal venous anatomy may be the primary pathogenic mechanism. Interestingly, partial sinus thrombosis lining the arachnoid villi has been proposed to explain the pathogenesis of the disease in patients without detectable stenosis. This hypothesis, which in fact considers IIH as a peculiar clinical syndrome of cerebral venous thrombosis, has been proposed on the basis of studies showing an increased rate of coagulation abnormalities in patients with idiopathic intracranial hypertension [24, 25], but more recent reports failed to confirm such findings [26].

A third possibility is that venous pressure may be increased as a result of systemic venous hypertension. As a matter of fact, as high right atrial pressure has been shown in some patients with IIH (27). Venous pressure may be raised in obese patients as a result of diaphragmatic elevation, increase in pleural pressure and consequent impairment of venous outflow from the brain. This hypothesis, albeit intriguing, cannot explain the cases of IIH in non-obese patients.

## Final remarks

Headache is the most frequent symptom in all processes involving the dural venous system, whatever their aetiology, and is largely due to the consequent development of intracranial hypertension. For this reason, the pain does not have any specific feature; more than the characteristics of the headache itself, what should raise the suspicion of the clinician is the association with other symptoms, such as loss of vision due to papilloedema, or the presence of risk factors for venous thrombosis. An early diagnosis is crucial in both disorders: in CVT to establish anticoagulant treatment, which has been shown to improve the course of the disease and reduce disability, and in IIH to avoid visual loss with CSF shunting techniques.

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## References


1. Bousser Marie-Germaine, Ferro José M (2007) Cerebral venous thrombosis: an update. Lancet Neurol 6:162–170
2. Ferro JM, Canhao P, Stam J, Bousser MG, Barinagarrementeria F (2004) Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). Stroke 35:664–670
3. Schaller B, Graf R (2004) Cerebral venous infarction: the pathophysiological concept. Cerebrovasc Dis 18:179–188
4. Provenzale JM, Joseph GJ, Barboriak DP (1998) Dural sinus thrombosis: findings on CT and MR imaging and diagnostic pitfalls. AJR Am J Roentgenol 170:777–783
5. Poon CS, Chang J-K, Swarnkar A, Johnson MH, Wasenko J (2007) Radiologic diagnosis of cerebral venous thrombosis: pictorial review. AJR Am J Roentgenol 189(6 Suppl):S64–S75
6. Corvol JC, Oppenheim C, Manai R et al (1998) Diffusion-weighted magnetic resonance imaging in a case of cerebral venous thrombosis. Stroke 29:2649–2652
7. Yoshikawa T, Abe O, Tsuchiya K et al (2002) Diffusion-weighted magnetic resonance imaging of dural sinus thrombosis. Neuroradiology 44:481–488
8. Sigh S, Koumar S et al (2005) Cerebral venous sinus thrombosis presenting as subdural haematoma. Australas Radiol 49(2):101–103
9. Shad A, Rorke TJ et al (2008) Straight sinus stenosis as a proposed cause of perimesencephalic non-aneurysmal haemorrhage. J Clin Neurosci 15(7):839–841 Epub 2008 Apr 10
10. De Brujin SFTM, Stam J, Kappelle LJ, for CVST Study Group (1996) Thunderclap headache as first symptom of cerebral venous sinus thrombosis. Lancet 348:1623–1625

11. Landtblom AM, Fridriksson S, Boive J et al (2002) Sudden onset headache: a prospective study of feature, incidence and causes. Cephalalgia 22:354–360
12. Agostoni E (2004) Headache in cerebral venous thrombosis. Neurol Sci 25:S206–S210
13. Newman DS, Levine SR, Curtis VL, Welch KMA (1989) Migraine like visual phenomena associated with cerebral venous thrombosis. Headache 29:82–85
14. Durcan F, Corbett J, Wall M (1988) The incidence of pseudotumour cerebri: population studies in Iowa and Louisiana. Arch Neurol 45:875–877
15. Radhakrishnan K, Thacker AK, Bohlaga NH, Maloo JC, Gerryo SE (1993) Epidemiology of idiopathic intracranial hypertension: a prospective and case-control study. J Neurol Sci 116:18–28
16. Wall M, George D (1991) Idiopathic intracranial hypertension: a prospective study of 50 patients. Brain 114:155–180
17. Mathew N, Ravishankar K, Sanin L (1996) Co-existence of migraine and idiopathic intracranial hypertension without papilledema. Neurology 46:1226–1230
18. Corbett J, Savino P, Thompson H et al (1982) Visual loss in pseudotumour cerebri. Arch Neurol 39:461–474
19. Malm J, Kristensen B, Markgren P, Ekstedt J (1992) CSF hydrodynamics in idiopathic intracranial hypertension: a long-term study. Neurology 42:851–858
20. Martins A (1973) Resistance to drainage of cerebrospinal fluid: clinical measurement and significance. J Neurol Neurosurg Psychiatry 36:313–318
21. Orefice G, Celentano L, Scaglione M, Davoli M, Striano S (1992) Radioisotopic cisternography in benign intracranial hypertension of young obese women: a seven-case study and pathogenetic suggestions. Acta Neurol 14:39–50
22. Fera F, Bono F, Messina D et al (2005) Comparison of different MR venography techniques for detecting transverse sinus stenosis in idiopathic intracranial hypertension. J Neurol 252:1021–1025
23. Esack A, Thompson G, Burmester H (1989) Benign intracranial hypertension and essential thrombocythaemia. J Neurol Neurosurg Psychiatry 52:914–922
24. Orefice G, De Joanna G, Coppola M, Brancaccio V, Ames PRJ (1995) Benign intracranial hypertension: a non-thrombotic complication of the primary antiphospholipid syndrome? Lupus 4:324–326
25. Backhouse OC, Johnson M, Jamieson DR et al (2001) Familial thrombophilia and idiopathic intracranial hypertension. Neuro-ophthalmology 25:135–141
26. Sugerman H, DeMaria E, Felton W, Nakatsuka M, Sismanis A (1997) Increased intra-abdominal pressure and cardiac filling pressures in obesity-associated pseudotumour cerebri. Neurology 49:507–511

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SECONDARY HEADACHES

# Clinical features and outcomes in spontaneous intracranial hypotension: a survey of 90 consecutive patients

**E. Mea · L. Chiapparini · M. Savoiardo · A. Franzini · G. Bussone · M. Leone**

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**Abstract** Spontaneous intracranial hypotension (SIH) is a rare disabling condition whose main clinical manifestation is orthostatic headache. We analysed clinical characteristics in relation to time to resolution in 90 consecutive patients diagnosed with SIH at our centre between 1993 and 2006. After excluding 7 patients lost to follow-up, the remaining 83 cases were divided into four groups: Group A (53 cases) with progressively worsening orthostatic headache; Group B (3 cases) with severe acute-onset orthostatic headache; Group C (9 cases) with fluctuating non-continuous headache, of mild severity, that, in 33% of cases, did not worsen on standing; Group D (18 cases), 5 with a previous history of headache, 14 with orthostatic headache, and 10 with altered neurological examination. Complete symptoms and neuroradiological resolution occurred during follow-up in Groups A, B and D, but was longer in Group D probably in relation to more severe clinical picture with altered neurological examination. However, after a mean of 52 months (range 24–108), none of the nine Group C patients had MRI indicating complete resolution. The main characteristic of Group C related to incomplete resolution was delayed diagnosis. These preliminary findings suggest that early diagnosis of SIH correlates with better outcome, further suggesting that patients with a new headache that may worsen on standing or sitting should undergo MRI with contrast to expedite a possible SIH diagnosis, even if the pain is relatively mild.

**Keywords** Spontaneous intracranial hypotension · Orthostatic headache · Prognosis · Delayed diagnosis

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## Introduction

Spontaneous intracranial hypotension (SIH) is a rare condition caused by spontaneous spinal cerebrospinal fluid leak; it is often misdiagnosed or under-diagnosed [1]. The prototypical clinical manifestation is orthostatic headache. Typical MRI findings are (a) subdural fluid accumulation, (b) pachymeningeal enhancement, (c) venous engorgement, (d) pituitary hyperaemia, and (e) brain sagging [1–8]. SIH is often highly disabling, although clinical characteristics and severity vary. Outcome is usually favourable (complete resolution), but there are exceptions [2]. We retrospectively reviewed consecutive SIH cases in order to identify clinical features correlating with a favourable outcome.

## Patients and methods

Ninety cases presenting consecutively at our institute between 1993 and 2006 with a diagnosis of SIH confirmed by cerebral MRI with contrast were reviewed: 35 male (39%) and 55 female (61%). Mean age at first examination was 45 years (range 15–71). Median follow-up was 3 years (range 8 months to 14 years). Median time from symptoms onset to diagnosis was 4 months (range 15 days to

**Table 1** International Headache Society criteria for headache attributed to spontaneous intracranial hypotension (IHS-2004: 7.2.3/ ICHD-II, 2004)

| |
|---|
| A. Diffuse and/or dull headache that worsens within 15 min after sitting or standing, with at least one of the following and fulfilling criterion D: |
| 1. Neck stiffness |
| 2. Tinnitus |
| 3. Hypacusia |
| 4. Photophobia |
| 5. Nausea |
| B. At least one of the following: |
| 1. Evidence of low CSF pressure on MRI (e.g. pachymeningeal enhancement) |
| 2. Evidence of CSF leakage on conventional myelography, CT myelography or cisternography |
| 3. CSF opening pressure <60 mm$H_2O$ in sitting position |
| C. No history of dural puncture or other cause of CSF fistula |
| D. Headache resolves within 72 h after epidural blood patching |

*CSF* cerebrospinal fluid, *MRI* magnetic resonance imaging, *CT* computed tomography

54 months). Headache and other clinical characteristics were recorded during semi-structured interview. In 70 (78%) patients, the headache interview occurred at initial admission; in the remaining 20 patients (22%), the interview was completed later by telephone. IHS [3] criteria for headache attributed to SIH (Table 1) were applied. We assessed clinical features in relation to favourable outcome (complete resolutions of symptoms and normalisation of MRI findings).

SIH diagnosis was confirmed by cerebral MRI when at least one of the following was present: subdural fluid accumulation, pachymeningeal enhancement, and sagging of the brain [1, 2, 4–6]. Additional MRI findings were venous engorgement and pituitary hyperaemia [1, 2, 4–6].

Seven patients were lost to follow-up and were, therefore, excluded from the subsequent analyses.

## Results

Analysis of clinical characteristics, MRI findings and outcomes in the 83 evaluable patients showed that they could be divided into four groups.

Group A (53/83 = 64%)

None of these patients had a previous history of headache. The headache worsened slowly over time, was of medium severity, worsened on standing or sitting, involved the entire head and was accompanied by at least one of the following: neck stiffness, tinnitus, hypacusia, photophobia, or nausea. In all cases, cerebral MRI revealed at least one of the following: brain sagging, dural enhancement, or subdural fluid accumulation. Additional signs in some cases were venous engorgement and pituitary engorgement. In none of these patients did the symptoms or MRI findings persist for more than 12 months from onset. Mean time to complete symptoms and MRI remission was 7 months (range 3–12). Thirty-seven of these patients received medical treatment (hydration and steroids with bed rest); the remaining 16 were given epidural blood patch. Mean time between symptoms onset and diagnosis was 2.5 months (range 1–8).

Group B (3/83 = 3.6%)

This group had severe, acute-onset headache that worsened on sitting or standing and was accompanied by at least one of the following: neck stiffness, tinnitus, hypacusia, photophobia, and nausea. In all cases, cerebral MRI showed subdural fluid accumulation. Symptoms resolved spontaneously in two patients and after epidural blood patch in the other. Mean time between symptoms onset and complete resolution was 8 months (range 3–11). Mean time between symptoms onset and diagnosis was 4 months (range 2–8). None of these patients had a previous history of headache.

Group C (9/83 = 11%)

In this group, the headache was sub-continuous and of mild severity that worsened on sitting or standing in six patients. Four of these patients had a previous history of headache. In all cases, at least one of the following was present: neck stiffness, tinnitus, hypacusia, photophobia, and nausea. Compared to patients of Group A, patients of Group C had vaguer and milder symptoms. In all except one, cerebral MRI showed typical signs of SIH. The clinical course was characterised by periods of symptoms worsening alternating with periods of improvement, but the headache never resolved completely, irrespective of the treatment (medical in six; epidural blood patch in three) and during the period they were followed (mean 52 months; range 24–108); in no case did the MRI picture resolve completely. Mean time between symptoms onset and diagnosis was 12 months (range 2–36).

Group D (18/83 = 22%)

Five of these patients had a previous history of headache. Fourteen had orthostatic headache, 10 had at least one of the following accompanying symptoms: neck stiffness, tinnitus, hypacusia, photophobia, and nausea. In 10, the neurological examination was altered (vertigo, visual

disturbances, cognitive disturbance, cranial nerve deficit, cerebellar symptoms). Sixteen had typical MRI findings. Mean time between symptoms onset and diagnosis was 10 months (range 2–25). Ten patients received blood patch and eight received medical treatment only. In all 18 cases, symptoms were resolved and MRI was normalised in a mean of 33 months (range 14–60).

## Discussion

This study on a large series of SIH patients shows that outcomes were favourable (i.e. complete resolution) in most cases (74/83 = 88.2%) in agreement with literature findings [2, 9]. Also in most patients (Group A plus Group C; 62/83 = 74.7%), symptoms at onset were gradually worsening orthostatic headache accompanied by typical SIH signs on MRI. However, although patients of Groups A and C had similar clinical and radiological features, outcomes differed. In fact, complete resolution was not obtained in any of the nine Group C patients after a mean follow-up of 52 months (range 24–108). Group C patients were also characterised by longer time between symptoms onset and diagnosis and this seems attributable to their milder and less clear-cut symptoms which were, presumably, not clearly pointed out or evident to the clinician. It is noteworthy that, in Group C, lack of symptoms/signs resolution seemed unrelated to treatment (medical in 6, epidural blood patch in 3). Illness duration was considerably longer in Group C than the other groups. The delay in diagnosis in Group C, therefore, seems to be related to long illness duration and incomplete resolution, which not only have a negative impact on the patient's quality of life, but also necessitate more visits to the doctor and more MRI examinations with consequently greater direct costs. Group C patients also resumed work later than those of Groups A and B resulting in increased indirect cost of the illness. With regard to Group D, the time between symptoms onset and diagnosis was closely similar to that in Group A, and their longer time to complete radiological and clinical resolution is likely to be in relation to their more severe clinical picture with neurological signs or symptoms in a considerable proportion of cases.

These preliminary observations suggest the need to perform cerebral MRI in patients who present with new headache that worsens on sitting or standing even if the severity is mild, in order to expedite a possible SIH diagnosis.

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## References

1. Schievink WI (2006) Spontaneous spinal cerebrospinal fluid leaks and intracranial hypotension. JAMA 295:2286–2296
2. Mokri B (2003) Headaches caused by decreased intracranial pressure: diagnosis and management. Curr Opin Neurol 16:319–326
3. Headache Classification Subcommittee of the International Headache Society (2004) The International Classification of Headache Disorders: 2nd edn. Cephalalgia 24(Suppl 1):1–160
4. Mokri B (2004) Spontaneous low cerebrospinal pressure/volume headaches. Curr Neurol Neurosci Rep 4:117–124
5. Schwedt TJ, Dodick DW (2007) Spontaneous intracranial hypotension. Curr Pain Headache Rep 11:56–61
6. Mea E, Savoiardo M, Chiapparini L, Casucci G, Bonavita V, Bussone G, Leone M (2007) Headache and spontaneous low cerebrospinal fluid pressure syndrome. Neurol Sci 28:S232–S234
7. Savoiardo M, Minati L, Farina L, De Simone T, Aquino D, Mea E et al (2007) Spontaneous intracranial hypotension with deep brain swelling. Brain 130:1884–1893
8. Chiapparini L, Ciceri E, Nappini S, Castellani MR, Mea E, Bussone G et al (2004) Headache and intracranial hypotension: neuroradiological findings. Neurol Sci 25:S138–S141
9. Mea E, Chiapparini L, Savoiardo M, Franzini A, Grimaldi D, Bussone G, Leone M (2009) Application of IHS criteria to headache attributed to spontaneous intracranial hypotension in a large population. Cephalalgia (in press)

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SECONDARY HEADACHES

# Headache induced by the use of combined oral contraceptives

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**Abstract** Although combined oral contraceptives (COCs) are a safe and highly effective method of birth control, they may also give rise to problems of clinical tolerability in migraine patients. Indeed, headache is among the most common side effects reported with the use of COCs, frequently leading to their being discontinued. The latest International Classification of Headache Disorders identified at least two entities evidently related to the use of COCs, i.e., exogenous hormone-induced headache and estrogen-withdrawal headache. As to the former, the newest formulations of COCs are generally well tolerated by migraine without aura patients, but can worsen headache in migraine with aura patients. Headache associated with COCs, generally, tends to improve as their use continues. However, although it is not yet clear if there is an association between headache and the composition of COCs (both in the type and amount of hormones), it has been observed that the incidence of headache during COC use seems greater if migraine is associated with menstrual trigger. The estrogen-withdrawal headache is a headache that generally appears within the first 5 days after cessation of estrogen use and resolves within 3 days, even if in some cases it may appear on the sixth or seventh day after pill suspension and lasts more than 3 days.

**Keywords** Combined oral contraceptives · Clinical features · Migraine · Exogenous hormone-induced headache · Estrogen-withdrawal headache

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## Introduction

It is commonly believed that combined oral contraceptives (COCs) may aggravate a pre-existing headache, or trigger its new onset. Moreover, headache is among the most common side effects reported with COC use and frequently leads to it being discontinued [1]. The question is further complicated by the fact that migraine, in particular, has a higher prevalence during the fertile phase of life and, obviously, this is the period when COCs are more commonly used. It is, therefore, often not clear whether headache existed prior to, or was a consequence of, using COCs in general population studies. Be this as it may, data as to headaches of new onset and pre-existing headaches that change their clinical features during COC intake is not easy to collect from an analysis of existing literature.

The International Classification of Headache Disorders, second edition (ICHD-II) [2] identifies at least two entities evidently related to the use of COCs: *exogenous hormone-induced headache* (code 8.3.1) and *estrogen-withdrawal headache* (code 8.4.3). Even if it is clear, from a clinical point of view, that this two types of headaches are completely different one another and that both of them may lead to discontinuation of COCs, published studies are of no guidance as to the real prevalence of these two forms of headaches, or as to which of these two forms is more represented in the subgroup of "new onset headaches" and that of "preexisting headaches that exacerbate". Many studies of migraine during COC administration are retrospective and lack a clear description and/or classification of the headaches observed. Other methodological biases include the duration of the observation period and the absence of a clear statement of the interval between the commencement of pill intake and the first occurrence of headache. Moreover, some studies are very old and deal

with COCs containing ≥50 μg ethinylestradiol (EE), with only a few studies differentiating between the two types of oral contraceptives available, i.e., the combined oral contraceptive pill and the progestogen-only pill.

## Exogenous hormone-induced headache

The major diagnostic criteria for this headache are shown in Table 1.

Loder et al. [1] reviewed literature to assess any evidence of an association between COC use and new onset or worsening of headache. An analysis of clinical trials including an active, untreated, or placebo control group, revealed only small and not always significant increases in headache activity during the early treatment stages. Indeed, most migrainous women find that COC use does not substantially change their headaches, even if almost 25% of women with migraine without aura (MO) reported an exacerbation [3–7]. The situation worsens in patients suffering from migraine with aura (MA) in which an aggravation of the symptoms has been observed in at least 50% of these cases [6, 7].

As to the new onset headaches, Granella et al. [7] reported this phenomenon in 1.2% of MO and in 11.4% of MA, whilst the study by Cupini et al. [6] reported much higher values, rising to as high as 16.2% for MO and 22.2% for MA. Nevertheless, Loder et al. [1] found that, regardless of its cause, headache associated with COCs tended to improve as their use continued. Also the ICHD-II acknowledges that COCs may trigger, or worsen migraine, while their suspension may arrest it, or restore its previous state [2]. Although suspension of COCs when migraine starts due to its use may be followed by immediate relief, in other cases there is a delay of 6–12 months, with some patients reporting that migraine persists on a long-term basis [8].

The relationship between headache and the COC estrogen dose is complex. A lower dose seems to be less associated with headache: 20 μg EE combined with 150 μg desogestrel resulted in a headache incidence of <2% by the sixth course [9]. Although it might be reasonable to hypothesize that COCs containing lower EE doses are less likely to provoke headache, as they minimize the magnitude of estrogen withdrawal, some trials in which women on COCs switched to a lower EE dose reported no improvement [10], or even a worsening of headache [11]. Moreover, Sulak et al. [12] assumed that very low estrogen doses may fail to completely suppress ovarian function.

Recently, a large population-based cross sectional study [13] did not report any significant effect of the estrogen content (ranging from 30 to 50 μg EE) on migraine prevalence: irrespective of the EE dosage, the OR for developing migraine was in the order of 1.4. Massiou et al. [8] suggested that studies of COCs containing second-generation progestogen, such as levonorgestrel, report headaches in approximately 10% of all cycles [14]. In contrast, fewer headaches have been reported with the use of the newer third-generation progestogens, with a headache incidence of approximately 5% [15]. More recently, Loder et al. [1] claimed that the dose, or type of progestin in a COC formulation does not seem to have any influence on headache, but that further confirmation is required.

Although several studies have been carried out on the various clinical features that may be predictive of a worsening of migraine in COC users, to date, there is no agreement amongst authors. Ryan [16] reported that the incidence of headache during COC use was greater when migraine was associated with menstruation, or appeared for the first time after pregnancy, or if the patient had relief of migraine during the last trimester of pregnancy. Also Mueller [3] reported a worsening of migraines with COC use, associated with a menstrual trigger, while, on the contrary, she reported a non-statistically significant worsening during pregnancy.

**Table 1** International Headache Society diagnostic criteria for "Exogenous hormone-induced headache" and for "Estrogen-withdrawal headache"

| |
|---|
| 8.3.1 Exogenous hormone-induced headache |
| A. Headache or migraine fulfilling criteria C and D |
| B. Regular use of exogenous hormones |
| C. Headache or migraine develops or markedly worsens within 3 months of commencing exogenous hormones |
| D. Headache or migraine resolves or reverts to its previous pattern within 3 months after total discontinuation of exogenous hormones |
| 8.4.3 Estrogen-withdrawal headache |
| A. Headache or migraine fulfilling criteria C and D |
| B. Daily use of exogenous estrogen for ≥3 weeks, which is interrupted |
| C. Headache or migraine develops within 5 days after last use of estrogen |
| D. Headache or migraine resolves within 3 days |

## Estrogen withdrawal headache

The major diagnostic criteria for this headache are shown in Table 1.

Headache in COC users may well be a withdrawal symptom. Indeed, migraine is more likely to occur, or worsen, during the pill-free week, especially in long-term COC users [12].

Recently, the characteristics of this oral contraceptive-induced menstrual migraine (OCMM) were described by us

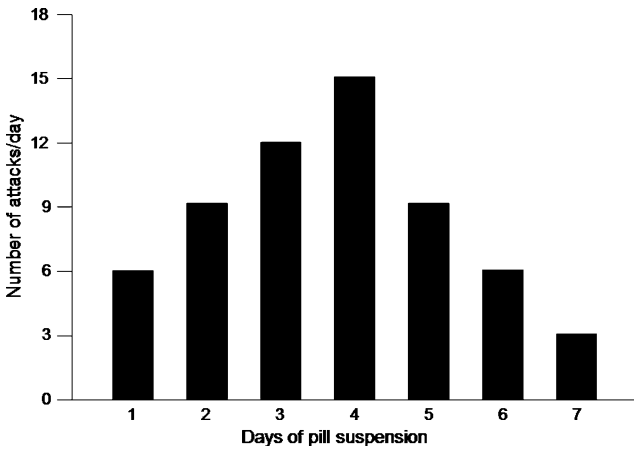


**Fig. 1** Distribution of the first day of oral contraceptives-induced menstrual migraine attacks in a selected study population during 7-day pill suspension

[17], in order to ascertain if the clinical characteristics defined by the ICHD-II are in line with the real picture of this headache. In our sample (20 women suffering exclusively from pure OCMM, average age 32.2 ± 7.0 years, range 22–46), all the attacks, with typical MO features, were of moderate or severe intensity at baseline. Migraine appeared within the first 5 days after cessation of estrogen use in 85% of cases, in line with what was reported by the ICHD-II [2], whereas in 15% of cases attacks were delayed to the sixth or seventh day after pill suspension (see Fig. 1). In the majority of patients, headache usually lasted at least 48 h in the presence of usual symptomatic drug treatment, but in 3/20 patients the length of the attack exceeded the 72-h upper limit proposed for MO by the ICHD-II [2].

In conclusion, on the basis of our data, although existing diagnostic criteria are extremely useful, they do not cover all realities and, above all, there is a lack of epidemiological studies on large female cohorts able to clearly define the real incidence and clinical characteristics of this often disabling disease.

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## References

1. Loder EW, Buse DC, Golub JR (2005) Headache as a side effect of combination estrogen–progestin oral contraceptives: a systematic review. Am J Obstet Gynecol 193:636–649
2. Headache Classification Subcommittee of the International Headache Society (IHS) (2004) The International Classification of Headache Disorders (2nd edition). Cephalalgia 24(Suppl 1):1–151
3. Mueller L (2000) Predictability of exogenous hormone effect in subgroups of migraineurs. Headache 40:189–193
4. Granella F, Sances G, Pucci E, Nappi RE, Ghiotto N, Nappi G (2000) Migraine with aura and reproductive life events: a case control study. Cephalalgia 20(8):701–707
5. MacGregor EA, Igarashi H, Wilkinson M (1997) Headaches and hormones: subjective versus objective assessment. Headache Q 8:126–136
6. Cupini LM, Matteis M, Troisi E, Calabresi P, Bernardi G, Silvestrini M (1995) Sex-hormone-related events in migrainous females. A clinical comparative study between migraine with aura and migraine without aura. Cephalalgia 15:140–144
7. Granella F, Sances G, Zanferrari C, Costa A, Martignoni GC (1993) Migraine without aura and reproductive life events: a clinical epidemiological study in 1300 women. Headache 33:385–389
8. Massiou H, MacGregor EA (2000) Evolution and treatment of migraine with oral contraceptives. Cephalalgia 20:170–174
9. Fotherby K (1992) Clinical experience and pharmacological effects of an oral contraceptive containing 20 micrograms oestrogen. Contraception 46:477–488
10. Gerais AS, Rushwan H (1985) A crossover pill study among Sudanese women. Int J Gynaecol Obstet 23:229–233
11. Edelman DA, Kothenbeutel R, Levinski MJ, Kelly SE (1983) Comparative trials of low-dose combined oral contraceptives. J Reprod Med 28:195–200
12. Sulak PJ, Scow RD, Preece C, Riggs MW, Kuehl TJ (2000) Hormone withdrawal symptoms in oral contraceptive users. Obstet Gynecol 95:261–266
13. Aegidius K, Zwart JA, Hagen K, Schei B, Stovner LJ (2006) Oral contraceptives and increased headache prevalence. The Head-HUNT study. Neurology 66:349–353
14. Guillebaud J (1983) The 150/30 formulation. Experience in the United Kingdom. J Reprod Med 28(1 Suppl):66–70
15. Fotherby K (1995) Twelve years of clinical experience with an oral contraceptive containing 30 μg ethinyloestradiol and 150 μg desogestrel. Contraception 51:3–12
16. Ryan RE (1978) A controlled study of the effect of oral contraceptives on migraine. Headache 17:250–252
17. Allais G, Bussone G, Airola G, Borgogno P, Castagnoli Gabellari I, De Lorenzo C et al (2008) Oral contraceptive-induced menstrual migraine. Clinical aspects and response to frovatriptan. Neurol Sci 29(Suppl 1):S186–S190

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SECONDARY HEADACHES

# Migraine as a visceral pain

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**Abstract** Migraine is a reversible brain dysfunction characterized by pain and passive coping strategies consistent with sickness behaviour. The brain contains no pain fibres and the only way it may signal pain is through the trigemino-vascular system. Here, it is postulated that migraine is an example of genetically determined behavioural responses and that sickness behaviour, a pan-mammalian adaptive response to internal and external stressors, characterizes the migraine attacks. Sickness behaviour is manifested in withdrawal and motor quiescence, sympatho-inhibition and lethargy, in which visceral pain signals a homeostatic imbalance of the brain. The sickness behavioural response is associated to pain felt as inescapable visceral pain, and depends upon brain networks involving different brainstem, hypothalamus and forebrain regions, that encode evolutionarily conserved adaptive genetic responses. This hypothesis, still speculative, may offer a more coherent view of migraine as an adaptive biobehavioural response triggered by a threatened brain.

**Keywords** Migraine · Visceral pain · Interoception · Adaptive behavioural response

## Introduction

Migraine is a syndrome of recurrent headaches manifesting in attacks lasting 4–72 h (if untreated) with typical unilateral localization, a pulsating quality, moderate to severe pain, aggravation by or avoidance of routine physical activities, and association with nausea and/or vomiting and photo- and phono-phobia [1]. The migraine attack consists of several phases: prodromal symptoms, aura, headache phase with pain and nausea/vomiting, resolution, and recovery (or postdrome) [2]. Migraine is highly prevalent in the general, especially female, population and carries a substantial genetic pre-disposition. Pain and symptoms attributed to involvement of the autonomic system feature prominently in the symptomatology of the migraine attack, but their mechanisms and in general the (patho)physiology of migraine are still debated and remain enigmatic because the actual theories of pathogenesis fail to account for the quality of symptoms, their complexity and their slow development. The voluminous scientific literature on migraine clearly points out that the mechanisms of migraine are located in the brain and that most migraine triggers affect the brain directly by modulating an internal migraine threshold which in turn may vary with anxiety, sleep or circadian rhythms. However, there is little information about the actual causes of migraine and on the reason why all individuals have the potential to suffer a migraine attack at some time in life under particular circumstances.

Although pain represents just the tip of the migraine iceberg, migraine is usually portrayed as a pain disorder. This short review is focused on the possible meaning of pain of migraine, the latter conceptualized as a bio-behavioural response genetically engendered to restore a disturbed homeostasis of the brain.

The present view of migraine represents a bio-behavioural hypothesis of migraine [2–4] framed, however, in a Darwinian perspective. It has already been presented in summary [5, 6].

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## The pain of migraine

Pulsating unilateral moderate to severe pain marks the headache phase of migraine, associated with nausea and/or vomiting and phono- and photo-phobia, and gastric paresis and osmophobia. Remarkably, pain during the migraine attack is aggravated by or causes avoidance of even light routine activity, such as walking or climbing stairs, and this is a diagnostic criterion required by the ICHD [1]. The behaviour of migraine patients during the attack is characteristic, with patients looking forward to lying down as immobile as possible and dozing, in order to avoid all kinds of physical and mental exercise. The resolutory phase is characterized by tiredness, fatigue, head pain, difficulties in concentrating, "hangover", gastrointestinal symptoms, mood changes, yawning and somnolence, and may end with sleep [7–9].

The brain contains no pain fibres and the only way it may signal pain is through the trigemino-vascular system [10]. Sensory fibres to cranial structures derive from the trigeminal nerve and ganglion and supply the meninges and their vessels, in particular the pial arterioles in the region of the pial/glial limitans [10]. Activation of the trigemino-vascular system results in the release of CGRP in the blood of the jugular vein, and, since CGRP release in the external jugular vein is found during the attacks of migraine, this has been taken as evidence of the activation of the trigeminal system during the attack. Trigeminal afferents form an axon reflex on meningeal vessels, whereby antidromic activity in the sensory terminal results in plasma protein leakage and mast cell degranulation (neurogenic sterile inflammation) in the dura mater. Orthodromic conduction along the trigeminal afferent feeds forward to the brain the sensation responsible for the migraine pain. The trigeminocaudal nucleus forms part of the so called trigeminocervical complex, a structure equivalent to the dorsal spinal horn and extending down to the C1 and C2 spinal levels. Stimulations of the superior sagittal sinus, dura mater, and cerebral vessels all result in activation of the trigeminocervical complex, which also receives convergent afferents from face, teeth, oral mucosa, and even from the greater occipital nerve originating from the C2 root, possibly accounting for the pain referred from cervical structures [11]. This nucleus thus probably represents for primates the nucleus that mediates the pain of migraine. Remarkably, trigemino-vascular stimulation also activates brain stem structures such as the superior salivatory nucleus [12] and the periaqueductal gray (PAG) [13]. Nociceptive dural input is modulated by several neurotransmitters, including orexin A via the orexin 1 receptor [14]. These observations demonstrate the involvement of the PAG and the orexin A containing hypothalamic region in the regulation of trigeminally transmitted pain. By contrast, vagus nerve stimulation has an antinociceptive effect on trigeminal nerve pain and reduces activation in the trigeminocaudal nucleus [15].

In summary, the pain of migraine has the characteristics of visceral pain that has different neurological mechanisms and psychophysics (perception and psychological processing) from that of somatic pain [16]. To better understand this concept, we have to introduce the new concept of visceral pain as homeostatic emotion.

## Pain and the autonomic central network: homeostatic pain and the interoceptive brain

A visceral system of feeling is essential for the representation of the physiological conditions of all tissues in the body, and for the maintenance of homeostatic activity [17]. Distinct interoceptive pathways exist in primates [17], whose activation leads to the generation, mainly in the cingulate and insular cortices, of both a sensation and a motivation, in some instances felt as pain. The network of the brain regions activated during pain, the so-called pain neuromatrix, strikingly overlaps with the regional network involved in visceral afferent information [18]. Deep pain arising from the body viscera should therefore be viewed as a homeostatic emotion like thirst, hunger, itching and temperature [18, 19], and may be considered to represent a monitor of the internal bodily world. This goes together with visceral pain having a fundamental adaptive role, as well as representing a powerful motivator of behaviour. Visceral homeostatic pain, different from cutaneous (non-burning) pain that is felt superficially and is usually sharper and briefer in duration, is felt deep in the viscera and lasts longer [20].

Migraine is a reversible brain dysfunction and no structural central or peripheral nervous system lesion has been shown to underlie the pain in the typical migraines. Therefore, migraine pain should be conceived as a visceral non-neuropathic pain, serving a homeostatic function in the interoceptive brain, that signals this dysfunction through the trigemino-vascular system.

## The behavioural meaning of pain: cutaneous/escapable versus visceral/inescapable pain

If pain, in particular visceral pain should be viewed as a powerful homeostatic emotion, headache pain too must need be understood according to its behavioural significance and ability to restore the brain homeostasis. We must acknowledge that the behavioural context is different according to whether the pain is perceived as escapable, or instead as inescapable, i.e. a pain that can or cannot be

controlled by the subject (active versus passive coping). Different types of pain are encoded by different sensitive pathways. While A-fibre nociceptors convey the first pain signal (pricking, well localized), C-fibres convey the second (burning, diffuse) pain [21]. Pain that is felt as escapable results from the activation of A-delta fibres, originating from the skin and transmitting cutaneous pain. Pain instead felt as inescapable (visceral pain) results from the activation of C fibres from the deep viscera, and has a homeostatic function [22–25]. These two kinds of pain activate distinct sensory pathways in the brain, in particular the PAG, the hypothalamus, amygdala and forebrain. C-fibres mainly project to the ventrolateral PAG, while A-delta fibres activate the dorsolateral/lateral PAG [22, 25]. Likewise different is the activation of more rostral networks in the hypothalamus, amygdala and forebrain [25]. Activation of different networks results in different behaviours, whereby escapable pain leads to a fight-or-flight defense reaction (so-called active emotional coping), while inescapable pain to motor quiescence, decreased vigilance and vasodepression (so-called passive emotional coping or sickness behaviour) [23]. Indeed, deep noxious afferent fibres from the superior sagittal sinus (thought to represent a model of migraine-like vascular head pain) activate the ventrolateral PAG region [26]. The behavioural significance of pain in the primary headaches is therefore different, according to whether it is perceived as escapable or inescapable, and this could explain the opposite behaviours (frantic agitation versus motor quiescence) displayed by the patients during the cluster headache and the migraine attacks.

In this scenario, migraine considered in its complete presentation and not only as pain of the head, can be interpreted as the response of a threatened brain [27]. In fact the brain as any other viscera, when threatened has to evaluate the value of the threat in order to coordinate appropriate behavioural and autonomic response to avoid or mitigate the harm. The difference with what occurs in other viscera when they are threatened is that the brain instead of being only the coordinator of the appropriate defensive response is itself the target of the threat. Again, another important difference between the brain and other viscera is that the emotional "sufferance" of the brain can be translated in pain only by means of the trigemino-vascular system.

## Migraine headache as a genetically determined adaptive Darwinian behavioural response (sickness behaviour)

Welch [3] proposed the so-called biobehavioural model for migraine, whereby migraine represents a biobehaviourally based dysautonomia involving principally the intrinsic noradrenergic system and its putative orbitofrontal connections. This model unifies the multifaceted phenomena of the migraine attack and the migraine natural history around a principal pathogenic role played by the central autonomic network (CAN) that is responsible not only for the pain during the attack, but also for the prodromic and resolution symptoms so often overlooked in the pathogenesis of migraine. The biobehavioural model of migraine makes useful sense also of the comorbidity of migraine with anxiety, depression, and even autoimmune dysfunction (allergy)—all in some way governed by the central autonomic network—and helps to explain the evolution of sporadic migraine into transformed migraine, a condition in which clinical studies and functional imaging experiments implicate the orbitofrontal regions [28]. The biobehavioural model may also usefully incorporate the interictal (susceptibility) traits characteristic of the migraine brain. Such traits include the predisposing factors of hypoxia or deficient brain energy metabolism [29], the abnormal habituation in information processing [30], and the characteristic high placebo responder rate of migraineurs [31], thought to involve the prefrontal cortices [32]. Within this explicative model, migraine pain may be considered as having a protective event, in accordance with the general function of pain as a sensory modality having an evolutionary advantage [33]. Indeed sickness behaviour represents a pan-mammalian behavioural response to a disturbed body homeostasis, and as such, a genetically determined behavioural response [34]. Migraine pain is accordingly fundamentally adaptive. If migraine pain is adaptive, what noxious-to-the-brain factor does migraine pain specifically warn against in order to curtail? This question must remain unanswered and speculative. However, since Nature does nothing in vain and since neurons and glia are primarily oxidative, we can speculate that, the migraine attack being neuronal in origin, glucose and oxygen should be our main concerns here. Insufficient supply or excess utilisation of these chemicals could be the threat to the brain that triggers the migraine attack, which in turn has the function to restore the lost homeostatic equilibrium. Why a threatened brain should select migraine as the most adaptive biobehavioural response in particular circumstances, what pain is warning against and what it is protecting, remains however still a mystery.

## Conclusions

The biobehavioural model expanded in a Darwinian perspective views the migraine attack as adaptive behavioural responses engendered out of a genetic (evolutionary conserved) repertoire by a network of pattern generators in the

central autonomic motor system for the maintenance of brain homeostasis. Such a view even if mainly speculative leads to several final considerations: (1) pain of migraine is a visceral signal of the brain with a consequent behavioural significance; (2) pain of migraine and, more generally, the sickness behavioural responses associated with it belong to a physiologic evolutionary conserved repertoire, are actually adaptive, and serve the purpose of recovering the body's homeostasis and, more generally, of "healing"; (3) the results of functional brain imaging during the migraine attack may just reflect activity in the autonomic structures organizing the appropriate behavioural response to a threat to the brain rather than the activation of a "generator" for pain; (4) migraine may not be only of the brain and by the brain, but also for the brain.

The challenge posed by this view of the pain of migraine is to try to identify the characteristics of the migraine brain that, being the real (patho)physiological factors, trigger the development of the attack under appropriate conditions.

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## References


1. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders (2004) Cephalalgia 24:1–160
2. Blau JN (1992) Migraine: theories of pathogenesis. Lancet 339:1202–1209
3. Welch KMA (1986) Migraine: a biobehavioural disorder. Cephalalgia 6:103–110
4. Schoenen J (2006) Neurophysiological features of the migrainous brain. Neurol Sci 27(Suppl 2):S77–S81
5. Montagna P (2008) The primary headaches: genetics, epigenetics and a behavioural genetic model. J Headache Pain 9:57–69
6. Montagna P, Cortelli P (2008) Migraine and the autonomic nervous system. In: Low PA (ed) Clinical autonomic disorders: evaluation and management. Lippincott. Williams and Wilkins, Philadelphia, pp 612–624
7. Blau JN (1982) Resolution of migraine attacks: sleep and the recovery phase. J Neurol Neurosurg Psychiatry 45:223–226
8. Kelman L (2006) The postdrome of the acute migraine attack. Cephalalgia 26:214–220
9. Quintela E, Castillo J, Munoz P, Pascual J (2006) Premonitory and resolution symptoms in migraine: a prospective study in 100 unselected patients. Cephalalgia 26:1051–1060
10. Moskowitz MA (1990) Basic mechanisms in vascular headache. Neurol Clin 8:801–815
11. Le Doare K, Akerman S, Holland PR, Lasalandra MP, Bergerot A, Classey JD, Knight YE, Goadsby PJ (2006) Occipital afferent activation of second order neurons in the trigeminocervical complex in rat. Neurosci Lett 403:73–77
12. Knight YE, Classey JD, Lasalandra MP, Akerman S, Kowacs F, Hoskin KL, Goadsby PJ (2005) Patterns of fos expression in the rostral medulla and caudal pons evoked by noxious craniovascular stimulation and periaqueductal gray stimulation in the cat. Brain Res 1045:1–11
13. Hoskin KL, Bulmer DCE, Lasalandra M, Jonkman A, Goadsby PJ (2001) Fos expression in the midbrain periaqueductal grey after trigeminovascular stimulation. J Anat 98:29–35
14. Holland PR, Akerman S, Goadsby PJ (2006) Modulation of nociceptive dural input to the trigeminal nucleus caudalis via activation of the orexin 1 receptor in the rat. Eur J Neurosi 24:2825–2833
15. Bohotin C, Scholsem M, Multon S, Martin D, Bohotin V, Schoenen J (2003) Vagus nerve stimulation in awake rats reduces formalin-induced nociceptive behaviour and fos-immunoreactivity in trigeminal nucleus caudalis. Pain 101:3–12
16. Cerbero F, Laird JMA (1999) Visceral pain. Lancet 353:2145–2148
17. Craig AD (2003) Interoception: the sense of the physiological condition of the body. Curr Opin Neurobiol 13:500–505
18. Saper CB (2000) Pain as a visceral sensation. In: Mayer EA, Saper CB (eds) Progress in brain research, vol 122. Elsevier, Amsterdam, pp 237–243
19. Craig AD (2003) A new view of pain as a homeostatic emotion. Trends Neurosi 26:303–307
20. Craig AD (2003) Pain mechanisms: labeled lines versus convergence in central processing. Annu Rev Neurosci 26:1–30
21. Parry DM, MacMillan FM, Koutsikou S, McMullan SM, Lumb BM (2008) Separation of A- versus C-nociceptive inputs into spinal-brainstem circuits. Neuroscience 152:1076–1085
22. Keay KA, Bandler R (2001) Parallel circuits mediating distinct emotional coping reactions to different types of stress. Neurosci Biobehav Rev 25:669–678
23. Keay KA, Bandler R (2002) Distinct central representations of inescapable and escapable pain: observations and speculations. Exp Physiol 87:275–279
24. Lumb BM (2002) Inescapable and escapable pain is represented in distinct hypothalamic-midbrain circuits: specific roles for Ad- and C-nociceptors. Exp Physiol 87:281–286
25. Lumb BM (2004) Hypothalamic and midbrain circuitry that distinguishes between escapable and inescapable pain. News Physiol Sci 19:22–26
26. Keay KA, Bandler R (1998) Vascular head pain selectively activates ventrolateral periaqueductal gray in the cat. Neurosci Lett 245:58–60
27. Maren S (2007) The threatened brain. Sciente 317:1043–1044
28. Fumal A, Laureys S, Di Clemente L, Boly M, Bohotin V, Vandenheede M, Coppola G, Salmon E, Kupers R, Schoenen J (2006) Orbitofrontal cortex involvement in chronic analgesic-overuse headache evolving from episodic migraine. Brain 129:543–550
29. Montagna P, Sacquegna T, Cortelli P, Lugaresi E (1989) Migraine as a defect of brain oxidative metabolism: a hypothesis. J Neurol 236:124–125
30. Schoenen J (1994) Pathogenesis of migraine: the biobehavioural and hypoxia theories reconciled. Acta Neurol Belg 94:79–86
31. Lewis DW, Winner P, Wasiewski W (2005) The placebo responder rate in children and adolescents. Headache 45:232–239
32. Wager TD (2005) Expectations and anxiety as mediators of placebo effects in pain. Pain 115:225–226
33. Loder E (2002) What is the evolutionary advantage of migraine? Cephalalgia 22:624–632
34. Hart BL (1988) Biological basis of the behaviour of sick animals. Neurosci Biobehav Rev 12:123–137

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SECONDARY HEADACHES

# Headache and multiple sclerosis: clinical and therapeutic correlations

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**Abstract** Headache is not generally considered as a symptom of multiple sclerosis (MS), but several studies have showed that it is more frequent (about 50%) in MS patients than in controls or general population. Headache may occur at onset and during the course of the disease. Tension-type headache and migraine without aura are the most commonly reported primary headaches; occipital neuralgia or cluster-like attacks have also been described, the location of demyelinating lesions (cervical or brain stem) could be strategic in these cases. Furthermore, disease-modifying therapies, such as interferons, may cause or exacerbate headache. These data suggest that MS patients have an increased risk of headache. Preventive therapies may be evaluated in selected patients during chronic treatments to ameliorate compliance.

**Keywords** Headache · Multiple sclerosis · Prevalence · Migraine · Tension-type headache · Cluster headache · Occipital neuralgia · Magnetic resonance imaging · Interferon

## Introduction

Headache is not generally considered as a symptom of multiple sclerosis (MS), but several studies have investigated the association between these two conditions. Conflicting results have been reported on the lifetime prevalence of headache and frequency of headache as MS onset symptom [1–19]. Attention has been drawn to de novo headache and exacerbation of pre-existing headache in interferon-treated MS patients [20–22]. Furthermore, recent neuroimaging studies have suggested a correlation between the location of the demyelinating lesions and headache [13, 23].

The aim of this study is to review the published data on headache in MS patients, in order to clarify the clinical–radiological correlations and the influence of MS therapies on headache incidence.

## Headache and multiple sclerosis: clinical aspects

Since 1950 [1] several studies have investigated the occurrence of headache in MS patients: variable frequencies ranging from 4 to 61.8% have been reported (Table 1) [1–19]. These discrepancies may be explained by differences on study design and patients' inclusion criteria. The results of the more recent studies, most of them prospective and/or case control survey, based on International Headache Society criteria for diagnosis and classification of headaches, have showed that the lifetime prevalence of headache is higher in MS patients (more than 50%) than in controls and general population, suggesting an increased risk of headache and a possible association between these two conditions [12, 14, 18].

Headache features seem to be non-specific for MS: migraine without aura and tension-type headache are the most commonly reported primary headaches [14, 18]. Ophthalmoplegic migraine-like [24], complicated migraine [25], cluster headache-like [26], have also been described in single cases.

The prevalence of headache in general was not related to MS form, illness duration or disability score [10, 19]. However, a correlation between type of MS and types of

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**Table 1** Summary of results of studies on the prevalence of headache in MS patients

| References | No. of patients/ controls | Percentage with headache | Percentage with headache as onset symptom |
|---|---|---|---|
| Adams et al. [1] | 389 | NR | 2.1 |
| McAlpine and Compston [2] | 250 | NR | 2 |
| Abb and Schaltenbrand [3] | 1,420 | 37.5 | 8 |
| Bonduelle and Albaranes [4] | 145 | 5.5 | 2 |
| Poser et al. [5] | 111 | 8 | NR |
| Kurtzke et al. [6] | | | |
| Retrospective | 293 | NR | 9.9 |
| Prospective | 234 | NR | 26.1 |
| Watkins and Espir [7] | 100/100 | 27/12 | NR |
| Clifford and Trotter [8] | 317 | 5 | NR |
| Freedman and Gray [9] | 1113 | 4 | 1.6 |
| Rolak and Brown [10] | 104/100 | 52/18* | 6.7 |
| Pollmann [11] | 157 | 40 | NR |
| D′Amico [12] | 116 | 57.7 | 1.7 |
| Gee [13] | 277 | 55.6 | NR |
| Vacca [14] | 238/238 | 51.3/23.9* | 5.5 |
| Villani [15] | 102 | 61.8 | NR |
| Yetimalar [16] | 21 | – | 28.5 |
| Martinelli Boneschi [17] | 428 | 35.5 | NR |
| Nicoletti [18] | 151/101 | 57.4/37.2* | NR |
| Putzki [19] | 491/447 | 56.2/72.7 | NR |

*NR* not reported

* Significant comparison

primary headaches has been showed, migraine being more frequent in relapsing–remitting and tension-type headache in progressive MS patients [12, 15, 17]. Female patients have a higher risk of tension-type headache and migraine [17].

Kurtzke [6] considered headache as a "minor" MS onset symptom and variable frequencies have been reported, ranging from 1.6 to 28.5% (Table 1). Headache has been also described as "unusual primary manifestation" in 6 out of 21 "asymptomatic MS patients" [16] and in 20 out of 30 "preclinical MS" patients, with MRI suggestive for MS, 11 of them had clinical conversion after a mean time of 2–3 years [27]. On the other hand, severe headache associated with diplopia or trigeminal neuralgia, or cluster-like attacks have been reported in single patients with isolated brain stem demyelinating lesions, usually responsive to steroid treatment [28–31].

## Headache and location of demyelinating lesions

Kurtzke [6] already showed that headache was most common in MS patients with visual or brain stem symptoms. Freedman and Gray [9] found that half of patients with headache during an attack of MS had clinical signs of brain stem involvement. These clinical correlations have been clarified by the more recent imaging studies. Gee [13] has showed that MS patients with a plaque within the midbrain/periaqueductal gray matter area had a four-fold increase in migraine-like headaches when compared to MS patients without a lesion in the same region. Tortorella [23] has showed that migrainous MS patients have more significant involvement of the substantia nigra and periaqueductal gray matter compared with MS patients without migraine and migrainous patients.

On the other hand, the location of the demyelinating lesions could be strategic in some cases. Acute trigeminal autonomic cephalalgia, occipital neuralgiform pain may be symptomatic of demyelinating lesions of the brain stem or of the upper spinal cord (C1–C2) area [32–34].

## Headache in MS-treated patients

Interferon-$\beta$ (IFN) is commonly used for long-term treatment of MS. Flu-like syndrome, dermal injection site reactions are the most common side effects [35]. A systematic review showed that headache is significantly more frequent in MS patients treated with IFN as compared to placebo [36]. Furthermore, several studies have evaluated the influence of chronic therapies on headache development or aggravation: variable frequencies, ranging respectively

**Table 2** Summary of the results of studies on the incidence of headache in MS-treated patients

| References | IMA, de novo headache Type of IMA, *N*/tot (%) | Worsening of pre-existing headache *N*/tot (%) |
|---|---|---|
| Brandles [20] | IFN 9/51 (17) | 1/51 (2) |
| Pòllman [21] | IFN 9/53* (17) | IFN 18/53* (34) |
| | COP 1/49 (2) | COP 3/49 (6) |
| La Mantia [22] | IFN 38/79* (48) | IFN 17/41* (41) |
| | COP/aza 0/22 | COP/aza 0/22 |
| Vacca [14] | IFN 7/92 (8%) | IFN 13/92 (14) |
| | COP 0/14 | COP 1/14 (7) |
| Martinelli Boneschi [17] | NR | IFN migraine 48.6, TTH 63.3 |
| | | COP migraine 0, TTH 25 |
| Nicoletti [18] | IFN 7/49 (14.2) | IFN 4/49 (8) |
| Villani [15] | IFN 7/64 (11) | IFN 24/64 (37.5) |
| Putzki [19] | Not studied | NR |
| | Headache prevalence rates | |
| | IFN 28.3%, Cop 26.4% | |

*COP* Glatiramer acetate, *aza* azathioprine, *IMA* immunomodulating agents, *NR* not reported

* Significant comparison

from 8 to 48% and from 2 to 41% have been reported in MS patients treated with IFN, while glatiramer acetate seems to have a minor headache-inducing potential (Table 2) [14, 15, 17–22].

## Discussion

This review shows that the relationship between headache and MS is complex, since several aspects have been analyzed by the investigators: (1) the lifetime prevalence of primary headaches in MS patients; (2) the correlation between different types of headaches and the clinical features of MS; (3) the occurrence of headache at the onset of the disease; (4) the correlation between headache and central lesions; (5) the occurrence of headache during chronic MS treatments.

The main conclusion of this review is that primary headaches are common in MS patients, occurring in more than 50% of the cases, a higher proportion than reported in the matched controls or in the general population. The reasons for this significant association have not been clarified. Recent evidences suggest that demyelinating brain stem lesions might be among the factors responsible for the presence of migraine in MS patients [13, 23]. Familial susceptibility, young age, female gender may predispose to both conditions or may be considered as additional risk factors.

The possibility that headache may occur as MS onset symptom remains an open question. Headache is not generally considered as a symptom of MS, but, except for the types symptomatic of central lesions, the occurrence in patients without any other specific symptoms or signs of the disease, showed by some studies [16, 27], should be supported by a careful neuroradiological study and clinical monitoring.

Headache may be considered among the side effects of IFN, worsening of pre-existing headaches or development of de novo headaches have been reported in the IFN-treated patients, although with variable frequencies (Table 2). Different mechanisms have been suggested [22], including the presence of other comorbidities such as psychiatric disorders. Preventive therapies [20] should be evaluated in selected patients during chronic MS treatments to ameliorate compliance.

Overall, these data show that MS patients have an increased risk of headache and suggest that headache should be investigated in the clinical work-up of these patients, mainly considering the impact on quality of life.

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## References

1. Adams DK, Sutherland JM, Fletcher WB (1950) Early clinical manifestations of disseminated sclerosis. Br Med J 2:431–436
2. McAlpine D, Compston ND (1952) Some aspect of the natural history of disseminated sclerosis. Q J Med 21:135–167
3. Abb L, Schaltebrand G (1956) Statistische Untersuchungen zum Problem der multiplen Sklerose. II. Mitteilung das Krankheitsbild der multiplen Sklerose. Dtsh Z Nervenheilkd 174:201–218
4. Bonduelle M, Albaranes R (1962) Étude statistique de 145 case de sclérose en plaque. Semin Hop Paris 68:3762–3773
5. Poser CM, Presthus J, Horsda O (1966) Clinical characteristics of autopsy-proved multiple sclerosis. Neurology 16:791–798
6. Kurtzke JF, Beebe GW, Nagler B, Auth TL, Kurland LT, Nefzger MD (1968) Studies on natural history of multiple sclerosis. Acta Neurol Scand 44:467–494

7. Watkins MS, Espir M (1969) Migraine and multiple sclerosis. J Neurol Neurosurg Psychiatry 32:35–37
8. Clifford DB, Trotter JL (1984) Pain in multiple sclerosis. Arch Neurol 41:1270–1272
9. Freedman MS, Gray TA (1989) Vascular headache: a presenting symptom of multiple sclerosis. Can J Neurol Sci 16:63–66
10. Rolak LA, Brown S (1990) Headaches and multiple sclerosis: a clinical study and review of the literature. J Neurol 237:300–302
11. Pollmann W, Feneberg W, Erasmus LP (2004) Pain in multiple sclerosis—a still underestimated problem. Nervenartz 75:135–140
12. D′Amico D, La Mantia L, Rigamonti A, Usai S, Mascoli N, Milanese C, Bussone G (2004) Prevalence of primary headaches in people with multiple sclerosis. Cephalalgia 24:980–984
13. Gee JR, Chang J, Dublin AB, Vijayan N (2005) The association of brainstem lesions with migraine-like headache: an imaging study of multiple sclerosis. Headache 45:670–677
14. Vacca G, Marano E, Brescia Morra V, Lanzillo R, de Vito M, Parente E, Orefice G (2007) Multiple sclerosis and headache co-morbidity. A case–control study. Neurol Sci 28:133–135
15. Villani V, Prosperini L, Ciuffoli A, Pizzolato R, Salvetti M, Pozzilli C, Sette G (2008) Primary headache and multiple sclerosis: preliminary results of a prospective study. Neurol Sci 29:S146–S148
16. Yetimalar Y, Secil Y, Inceoglu AK, Eren S, Basoglu M (2008) Unusual primary manifestations of multiple sclerosis. NZ Med J 121:47–59
17. Martinelli Boneschi F, Colombo B, Annovazzi P, Martinelli V, Bernasconi L, Solaro C, Comi G (2008) Lifetime and actual prevalence of pain and headache in multiple sclerosis. Multiple Scler 14:514–521
18. Nicoletti A, Patti F, Lo Fermo S, Liberto A, Castiglione A, Laisa P, Garifoli A, La Naia F, Maimone D, Sorbello V, Contrafatto D, Zappia M (2008) Headache and multiple sclerosis: a population-based case–control study in Catania, Sicily. Cephalalgia 28:1163–1169
19. Putzki N, Pfriem A, Limmroth V, Yaldizli O, Tettenborn B, Diener HC, Katsarava Z (2009) Prevalence of migraine, tension-type headache and trigeminal neuralgia in multiple sclerosis. Eur J Neurol 16:262–267
20. Brandles JL (2000) Migraine induced by interferon beta therapy for multiple sclerosis. Neurology 54(Suppl 3):A422 Abstract
21. Pollmann W, Erasmus LP, Feneberg W, Then Berg F, Straube A (2002) Interferon beta but not glatiramer acetate therapy aggravates headaches in MS. Neurology 59:636–639
22. La Mantia L, D′Amico D, Rigamonti A, Mascoli N, Bussone G, Milanese C (2006) Interferon treatment may trigger primary headaches in multiple sclerosis patients. Multiple Scler 12:1–5
23. Tortorella P, Rocca MA, Colombo B, Annovazzi P, Comi G, Filippi M (2006) Assessment of MRI abnormalities of the brain stem from patients with migraine and multiple sclerosis. J Neurol Sci 244:137–141
24. Galer BS, Lipton RB, Weinstein S, Bello L, Solomon S (1990) Apoplectic headache and oculomotor nerve palsy: an unusual presentation of multiple sclerosis. Neurology 40:1465–1466
25. Evans RW, Rolak LA (2001) Migraine versus multiple sclerosis. Headache 41:97–98
26. Then Berg F, Dose T, Forderreuther S, Straube A (2000) Symptomatic cluster headache. Expression of multiple sclerosis relapse with magnetic resonance tomography detection of pontomedullary lesion in the ipsilateral trigeminal nucleus area. Nervenarzt 71:1000–1002
27. Lebrun C, Bensa C, Debouverie H, De Seze J et al (2008) Unexpected multiple sclerosis: follow-up of 30 patients with MRI and clinical conversion profile. J Neurol Neurosurg Psychiatry 79:195–198
28. Nager BJ, Lanska DJ, Daroff RB (1989) Acute demyelination mimicking vascular migraine. Headache 29:423–424
29. Haas DC, Kent PF, Friedman DI (1993) Headache caused by a single lesion of multiple sclerosis in the periaqueductal gray area. Headache 33:452–455
30. Leandri M, Cruccu G, Gottlieb A (1999) Cluster headache-like pain in multiple sclerosis. Cephalalgia 19:732–734
31. Gentile S, Ferrero M, Vaula G, Rainero I, Pinessi L (2007) Cluster headache attacks and multiple sclerosis. J Headache Pain 8:245–247
32. Alstadhaug K, Breivik K, Rusic Z (2008) Recurrent headache due to MS plaque. Headache 48:453–454
33. De Santi L, Monti L, Menci E, Bellini M, Annunziata P (2009) Clinical radiologic heterogeneity of occipital neuralgiform pain as multiple sclerosis relapse. Headache 49:304–307
34. Liu FC, Fuh JL, Wang SJ (2008) Symptomatic trigeminal autonomic cephalalgia associated with allodynia in a patients with multiple sclerosis. J Chin Med Assess 71:583–586
35. Nelley LK, Goodin DS, Goodkin DE, Hauser SL (1996) Side effect profile of interferon beta-1b in MS: results of an open trial. Neurology 46:552–554
36. Filippini G, Munari L, Incorvaia B, Ebers GC, Polman C, D′Amico R, Rice GP (2003) Interferons in relapsing remitting multiple sclerosis: a systematic review. Lancet 361(9357):545–552

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INVITED LECTURE

# Neural substrate of depression during migraine

**Rami Burstein · M. Jakubowski**

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**Abstract** Migraine headache is triggered by and associated with a variety of hormonal, emotional, nutritional and physiological changes. The perception of migraine headache is formed when nociceptive signals originating in the meninges are conveyed to the somatosensory cortex through the trigeminal ganglion, medullary dorsal horn and thalamus. We propose that different migraine triggers activate a wide variety of brain areas that impinge on parasympathetic neurons innervating the meninges. According to this hypothesis, migraine triggers such as stress activate multiple hypothalamic, limbic and cortical areas, all of which contain neurons that project to the preganglionic parasympathetic neurons in the superior salivatory nucleus (SSN). The SSN, in turn, activates postganglionic parasympathetic neurons in the sphenopalatine ganglion, resulting in vasodilation and local release of inflammatory molecules that activate meningeal nociceptors. We propose that trigeminovascular projections from the medullary dorsal horn to selective areas in the midbrain, hypothalamus, amygdala and basal forebrain are functionally positioned to produce migraine symptoms such as irritability, loss of appetite, fatigue, depression and the quest for solitude. The network of bidirectional trafficking by which the trigeminovascular system can activate the same brain areas that have triggered its own activity in the first place provides an attractive mechanism of perpetual feedback that drives a migraine attack for many hours and even days.

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**Keywords** Headache · Nociception · Trigeminal · Stress · Sleep

## Introduction

Migraine is a recurring neurological disorder commonly described as unilateral throbbing headache, readily aggravated by routine activities. Similar to other pain pathways, the sensory discriminative aspect of migraine pain is believed to be mediated by activation and modulation of nociceptive trigeminothalamic tract by peripheral drivers and central modulators, respectively. In the case of the trigeminothalamic tract, the role of driver is played by meningeal nociceptors, whereas modulation is provided by inhibitory and facilitatory neurons in the brainstem. Evidence for the driving role of meningeal nociceptors comes from studies in which awake patients experienced headache in response to electrical stimulation of their dura [1, 2]. Evidence for descending modulation comes from studies that examined the effects of electrical stimulation of the periaqueductal gray (PAG) and rostral ventromedial medulla on nociceptive spinal neurons. Whereas electrical brainstem stimulation per se did not induce any activity in the spinal nociceptive neurons when they were quiet, it clearly increased or decreased their response magnitude to noxious and innocuous stimulation of their cutaneous and visceral receptive fields [3].

The initiation of migraine headache is commonly associated with a wide variety of circumstances, such as hormonal milieu, periods of stress, post-stress periods, skipping a meal, lack of sleep, olfactory stimulation and several types of aura [4, 5]. These associations raise the possibility that a migraine attack originates in brain areas that are not directly involved in nociception, but are wired

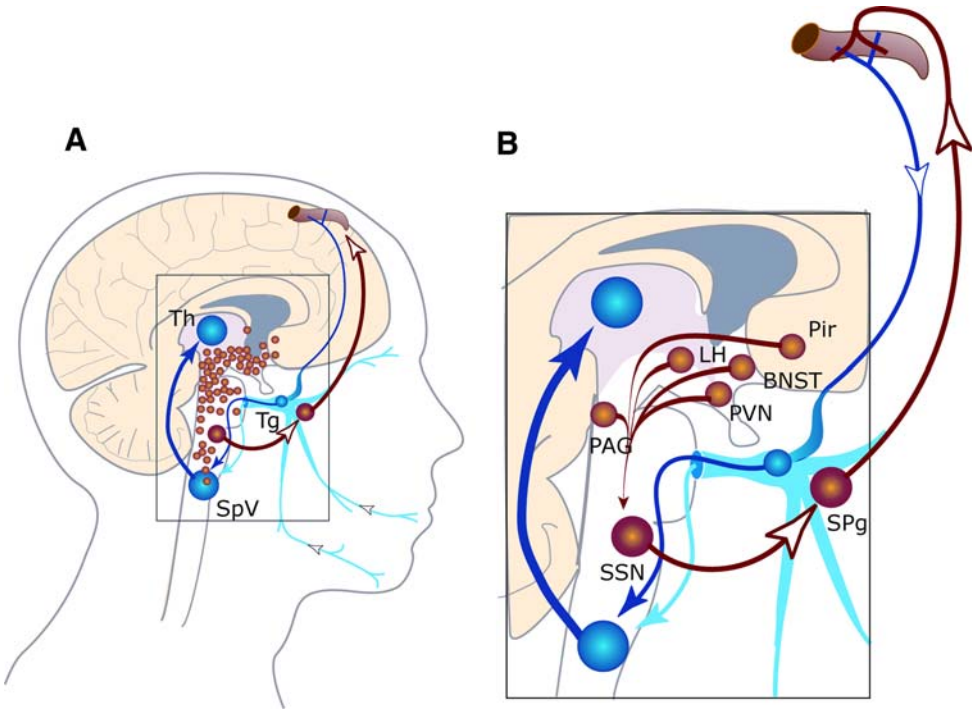


**Fig. 1** A proposed parasympathetic pathway for the activation of meningeal nociceptors. Preganglionic parasympathetic neurons in the superior salivatory nucleus (SSN) can trigger intracranial vasodilation and the release of nitric oxide in the meninges through postganglionic parasympathetic neurons in the sphenopalatine ganglion (SPG). **a** The SSN receives input from over 50 limbic and hypothalamic brain areas (*red dots*) whose activity may be influenced by common migraine triggers. **b** Examples of SSN afferents proposed to be involved in migraine triggering by olfactory stimuli (Pir), food and sleep deprivation (LH), stress or post stress (PVN, BNST, PAG). *BNST* bed nucleus stria terminalis, *LH* lateral hypothalamus, *PAG* periaqueductal gray, *Pir* piriform cortex, *PVN* paraventricular hypothalamic nucleus

to activate the trigeminovascular pathway. The trigeminovascular pathway consists of first-order nociceptors in the trigeminal ganglion that innervate the meninges; second-order trigeminothalamic tract neurons that receive sensory inputs from the meninges, periorbital skin and neck muscles; third-order thalamocortical neurons that process incoming pain signals from the trigeminal nerve, including the meninges; and cortical neurons located in the first somatosensory cortex.

## Activation of the trigeminovascular pathway by the limbic system and hypothalamus

The observation that visual aura precedes the onset of headache by several minutes promoted extensive research on the neural substrate by which cortical spreading depression can result in activation of meningeal nociceptors. Evidence suggests that in the wake of cortical spreading, depression the blood brain barrier becomes more permeable [6, 7], allowing potassium and hydrogen ions to diffuse from the surface of the cortex to the pia where they activate C-fiber meningeal nociceptors [8]. This activation appears to involve direct depolarization by potassium ions, and action of hydrogen ions through the vallinoid receptor (Caterina et al. 1997) or the acid-sensitive ion channel receptor (Waldmann et al. 1997). Consequently, the activated meningeal nociceptors release calcitonin-gene-related peptide [9] from their peripheral branches, resulting in neurogenic inflammation in the dura [10].

In contrast to the ongoing effort, to understand how aura triggers activity in meningeal nociceptors, little attention was given to the mechanisms by which brain areas involved in regulation of stress could activate meningeal nociceptors and trigger the headache. Is there a common pathway that activates meningeal nociceptors for a variety of migraine triggers? We are proposing that such a pathway involves pre- and postganglionic parasympathetic neuron in the superior salivatory nucleus (SSN) and sphenopalatine ganglion (SPG), respectively. According to our hypothesis, migraine triggers either activate or originate in a number of brain areas whose projections converge on the SSN. The SSN, in turn, stimulates the release of acetyl choline, vasopressin intestinal peptide and nitric oxide from meningeal terminals of SPG neurons, resulting (directly or indirectly) in a cascade of events that include the dilation of intracranial blood vessels, plasma protein

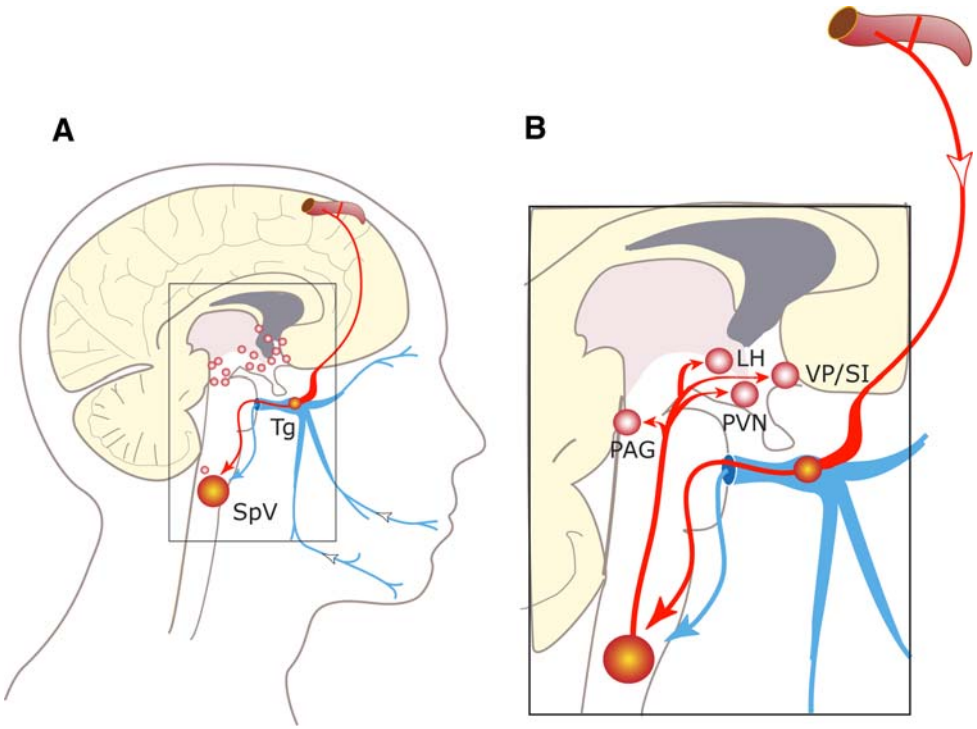


**Fig. 2** Proposed mechanism for the initiation of symptoms commonly associated with migraine headache by ascending trigeminovascular pathways to the brainstem, hypothalamus and basal ganglia. **a** Trigeminovascular neurons in the spinal trigeminal nucleus (SpV) project to multiple limbic and hypothalamic brain areas (*red dots*) whose activity my underlie common migraine symptoms. **b** Examples of SpV projections proposed to be involved in stress (PVN), decreased motivational state (VP/SI), pursuit of solitude (PAG), sleepiness, irritability and loss of appetite (LH). *LH* lateral hypothalamus, *PAG* periaqueductal gray, *PVN* paraventricular hypothalamic nucleus, *VP/SI* ventral pallidum/substantia innominata

extravasation, and local release of inflammatory molecules that activate adjacent terminals of meningeal nociceptors (Fig. 1).

Several lines of evidence support this parasympathetic hypothesis: (1) meningeal blood vessels are densely innervated by parasympathetic fibers [11–13]; (2) preganglionic parasympathetic neurons in the SSN increase their activity after activation of meningeal nociceptors [14]; (3) ongoing activity in meningeal nociceptors appears to depend on enhanced activity in the SPG [15]; (4) parasympathetic tone is enhanced during migraine, as evidenced by lacrimation, teary eyes, nasal congestion [5]; (5) blockade of the SPG provides partial or complete relief of migraine pain [16–25].

The SSN receives extensive input from more than 50 brain areas distributed throughout the forebrain, diencephalon, midbrain, pons and medulla [26]. SSN-projecting neurons located in some of these brain areas are theoretically positioned to mediate the onset of a migraine by means of their involvement in emotional responses (Fig. 1a). The bed nucleus of stria terminalis (BNST), the paraventricular hypothalamic nucleus (PVN) and the PAG are all involved in the circuitry that regulates "stress response". BNST neurons, which regulate hypothalamic-pituitary-adrenal axis, appear to mediate long-lasting behavioral responses during sustained stress, which persist long after the termination of stress [27, 28]; such neurons may be involved in stress-induced migraine and also in migraine triggered after the termination of stress. Parvocellular PVN neurons that project to sympathetic and parasympathetic preganglionic neurons in the brainstem and spinal cord promote the autonomic part of the stress response [29, 30], which includes localized cerebrovascular vasodilation in the early phase of the migraine attack [31]. Ventrolateral PAG neurons involved in passive emotional coping with inescapable stressors such as repeated defeat in social encounters [32, 33] may mediate onset of increase migraine frequency associated with a long period of social stress such as divorce.

## Activation of the hypothalamus and limbic system by the trigeminovascular pathway

The most frequently reported symptoms associated with migraine are depression, stress, irritability, fatigue, sleepiness, exaggerated emotional responses, nausea and loss of appetite. To elicit these symptoms, pain signals that originate in the trigeminovascular pathway during migraine must reach and alter the activity of hypothalamic and limbic structures that integrate sensory, physiological and cognitive signals that drive behavioral, affective and autonomic responses. Brain areas involved in the execution of such responses include the parabrachial complex, PAG, hypothalamus, amygdala, septum, nucleus accumbens, bed nucleus of the stria terminalis and basal ganglia [34–46]. Many of these brain areas receive direct inputs from laminae I–II and V neurons located in the ventrolateral area of

the upper cervical and medullary dorsal horn (Fig. 2)—an area containing the majority of second-order trigeminovascular neurons [47–56].

We propose that these ascending pathways are functionally positioned to produce irritability, loss of appetite, sleepiness, fatigue, chill, stress, depression, emotional arousal, decreased motivation, the quest for solitude and lethargy during migraine (Fig. 2b). For example, loss of appetite, sleepiness and irritability during migraine may be mediated by trigeminovascular projections to the lateral hypothalamus; in this area, neurons expressing melanin-concentrating hormone or hypocretin regulate food and water intake, sleep and arousal [36, 37, 57] through widespread projections to the cerebral cortex, brainstem and spinal cord [58–62]. Migraine-associated stress may be mediated by trigeminovascular projections to the paraventricular nucleus of the hypothalamus; this nucleus contains neurons expressing corticotrophin-releasing hormone and oxytocin which regulate stress responses [63]. Emotional arousal and decreased motivation during migraine may be mediated by trigeminovascular projections to forebrain nuclei such as the ventral pallidum and substantia innominata; these areas can alter endocrine, autonomic and somatomotor functions to match different emotional and motivational states [64].

The pursuit of solitude during migraine may be mediated by the ventrolateral PAG; this area receives more input from trigeminal neurons locate in C1-3 and nucleus caudalis than from the entire spinal cord [32, 54, 55]. The input to the ventrolateral PAG originates mainly in visceral and deep somatic tissues [65, 66]. Trigeminovascular projections to the ventrolateral PAG can activate neurons that mediate responses to deep, inescapable pain, such migraine pain [32, 67].

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## References

1. Penfield W, McNaughton F (1940) Dural headache and innervation of the dura mater. Arch Neurol Psychiat 44:43–75
2. Ray BS, Wolff HG (1940) Experimental studies on headache. Pain-sensitive structures of the head and their significance in headache. Arch Surg 41:813–856
3. Porreca F, Ossipov MH, Gebhart GF (2002) Chronic pain and medullary descending facilitation. Trends Neurosci 25(6):319–325
4. Zagami AS, Rasmussen BK (2000) Symptomology of migraine without aura. In: Olesen J, Tfelt-hansen P, Welch MA (eds) The headaches. Raven Press, New York, pp 337–343
5. Liveing E (1873) On megrim, sick headache. Arts & Boeve Publishers, Nijmegen
6. Gursoy-Ozdemir Y et al (2004) Cortical spreading depression activates and upregulates MMP-9. J Clin Invest 113(10):1447–1455
7. Moskowitz MA, Macfarlane R (1993) Neurovascular and molecular mechanisms in migraine headaches. Cerebrovasc Brain Metab Rev 5(3):159–177
8. Moskowitz MA, Cutrer FM (1993) SUMATRIPTAN: a receptor-targeted treatment for migraine [Review] [44 refs]. Annu Rev Med 44:145–154
9. Ebersberger A et al (1999) Release of substance P, calcitonin gene-related peptide and prostaglandin E2 from rat dura mater encephali following electrical and chemical stimulation in vitro. Neuroscience 89(3):901–907
10. Goadsby PJ, Edvinsson L (1993) The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. Ann Neurol 33(1):48–56
11. Suzuki N, Hardebo JE (1993) The cerebrovascular parasympathetic innervation. Cerebrovasc Brain Metab Rev 5(1):33–46
12. Larsson LI et al (1976) Immunohistochemical localization of a vasodilatory polypeptide (VIP) in cerebrovascular nerves. Brain Res 113(2):400–404
13. Nozaki K et al (1993) Possible origins and distribution of immunoreactive nitric oxide synthase-containing nerve fibers in cerebral arteries. J Cereb Blood Flow Metab 13(1):70–79
14. Knight YE et al (2005) Patterns of fos expression in the rostral medulla and caudal pons evoked by noxious craniovascular stimulation and periaqueductal gray stimulation in the cat. Brain Res 1045(1–2):1–11
15. Bolay H et al (2002) Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. Nat Med 8(2):136–142
16. Yarnitsky D et al (2003) 2003 Wolff Award: possible parasympathetic contributions to peripheral and central sensitization during migraine. Headache 43(7):704–714
17. Sluder G (1908) The role of the sphenopalatine ganglion in nasal headaches. N Y State J Med 27:8–13
18. Waldman SD (1990) The role of neural blockade in the management of common pain syndromes. In: Weiner RS (ed) Innovations in pain management. Deutch press, Orlando, pp 4–14
19. Waldman SD (1993) Sphenopalatine ganglion block—80 years later. Reg Anesth 18(5):274–276
20. Diamond S, Dalessio DJ (1982) The practicing physicians approach to headaches, 3rd edn. Williams & Wilkins, Baltimore
21. Dalessio DJ (1980) The major neuralgias, postinfections neuritis, intractable pain, and atypical facial pain. In: Delessio DJ (ed) Wolff's headache. Oxford Press, New York, pp 247–248
22. Kudrow L (1980) Cluster headache: mechanism and management. Oxford Press, London, pp 114–116
23. Kudrow L, Kudrow DB, Sandweiss JH (1995) Rapid and sustained relief of migraine attacks with intranasal lidocaine: preliminary findings. Headache 35(2):79–82
24. Reutens DC et al (1991) Is intravenous lidocaine clinically effective in acute migraine? Cephalalgia 11(6):245–247
25. Maizels M et al (1996) Intranasal lidocaine for treatment of migraine: a randomized, double- blind, controlled trial [see comments]. JAMA 276(4):319–321
26. Spencer SE et al (1990) CNS projections to the pterygopalatine parasympathetic preganglionic neurons in the rat: a retrograde transneuronal viral cell body labeling study. Brain Res 534(1–2):149–169
27. Forray MI, Gysling K (2004) Role of noradrenergic projections to the bed nucleus of the stria terminalis in the regulation of the hypothalamic-pituitary-adrenal axis. Brain Res Brain Res Rev 47(1–3):145–160

28. Walker DL, Toufexis DJ, Davis M (2003) Role of the bed nucleus of the stria terminalis versus the amygdala in fear, stress, and anxiety. Eur J Pharmacol 463(1–3):199–216
29. Swanson LW, Sawchenko PE (1980) Paraventricular nucleus: a site for the integration of neuroendocrine and autonomic mechanisms. Neuroendocrinology 31(6):410–417
30. Coote JH (2005) A role for the paraventricular nucleus of the hypothalamus in the autonomic control of heart and kidney. Exp Physiol 90(2):169–173
31. Olesen J (1998) Regional cerebral blood flow and oxygen metabolism during migraine with and without aura. Cephalalgia 18(1):2–4
32. Keay KA, Bandler R (2001) Parallel circuits mediating distinct emotional coping reactions to different types of stress. Neurosci Biobehav Rev 25(7–8):669–678
33. Bandler R et al (2000) Central circuits mediating patterned autonomic activity during active vs. passive emotional coping. Brain Res Bull 53(1):95–104
34. Bernardis LL, Bellinger LL (1993) The lateral hypothalamic area revisited: neuroanatomy, body weight regulation, neuroendocrinology and metabolism. Neurosci Biobehav Rev 17(2):141–193
35. Bernardis LL, Bellinger LL (1998) The dorsomedial hypothalamic nucleus revisited: 1998 update. Proc Soc Exp Biol Med 218(4):284–306
36. Lin JS et al (1989) A critical role of the posterior hypothalamus in the mechanisms of wakefulness determined by microinjection of muscimol in freely moving cats. Brain Res 479(2):225–240
37. Peyron C et al (1998) Neurons containing hypocretin (orexin) project to multiple neuronal systems. J Neurosci 18(23):9996–10015
38. Panksepp J (1971) Aggression elicited by electrical stimulation of the hypothalamus in albino rats. Physiol Behav 6(4):321–329
39. Kruk MR et al (1983) Discriminant analysis of the localization of aggression-inducing electrode placements in the hypothalamus of male rats. Brain Res 260(1):61–79
40. Norgren R (1970) Gustatory responses in the hypothalamus. Brain Res 21(1):63–77
41. Roeling TA et al (1993) Behavioural responses of bicucculline methiodide injections into the ventral hypothalamus of freely moving, socially interacting rats. Brain Res 615(1):121–127
42. Saper CB (1995) Central autonomic system. In: Paxinos G (ed) The rat nervous system. Academic Press, San Diego, pp 107–136
43. Sherin JE et al (1996) Activation of ventrolateral preoptic neurons during sleep. Science 271(5246):216–219
44. Simerly RB (1995) Anatomical substrates of hypothalamic integration. In: Paxinos G (ed) The rat nervous system. Academic Press, San Diego, pp 353–376 of 1136
45. Swanson LW (1987) The hypothalamus. In: Bjorklund A, Hokfelt T, Swanson LW (eds) Integrated systems of the CNS, part I. Elsevier, Amsterdam, pp 1–124
46. Scammell TE, Price KJ, Sagar SM (1993) Hyperthermia induces c-fos expression in the preoptic area. Brain Res 618(2):303–307
47. Burstein R, Giesler GJ Jr (1989) Retrograde labeling of neurons in the spinal cord that project directly to nucleus accumbens or the septal nuclei in the rat. Brain Res 497:149–154
48. Burstein R, Cliffer KD, Giesler GJ Jr (1990) Cells of origin of the spinohypothalamic tract in the rat. J Comp Neurol 291(3):329–344
49. Burstein R, Potrebic S (1993) Retrograde labeling of neurons in the spinal cord that project directly to the amygdala or the orbital cortex in the rat. J Comp Neurol 335(4):469–485
50. Malick A, Burstein R (1998) Cells of origin of the trigeminohypothalamic tract in the rat. J Comp Neurol 400:125–144
51. Malick A, Strassman RM, Burstein R (2000) Trigeminohypothalamic and reticulohypothalamic tract neurons in the upper cervical spinal cord and caudal medulla of the rat. J Neurophysiol 84(4):2078–2112
52. Bernard JF et al (1995) Organization of the efferent projections from the spinal cervical enlargement to the parabrachial area and periaqueductal gray: a PHA-L study in the rat. J Comp Neurol 353(4):480–505
53. Bester H et al (1995) Spino (trigemino) parabrachiohypothalamic pathway: electrophysiological evidence for an involvement in pain processes. J Neurophysiol 73(2):568–585
54. Keay KA, Bandler R (1992) Anatomical evidence for segregated input from the upper cervical spinal cord to functionally distinct regions of the periaqueductal gray region of the cat. Neurosci Lett 139(2):143–148
55. Vanderhorst VG et al (1996) Distinct cell groups in the lumbosacral cord of the cat project to different areas in the periaqueductal gray. J Comp Neurol 376(3):361–385
56. Strassman AM, Mineta Y, Vos BP (1994) Distribution of fos-like immunoreactivity in the medullary and upper cervical dorsal horn produced by stimulation of dural blood vessels in the rat. J Neurosci 14(6):3725–3735
57. Chemelli RM et al (1999) Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. Cell 98(4):437–451
58. van den Pol AN (1999) Hypothalamic hypocretin (Orexin): robust innervation of the spinal cord. J Neurosci 19(8):3171–3182
59. Bittencourt JC et al (1992) The melanin-concentrating hormone system of the rat brain: an immuno- and hybridization histochemical characterization. J Comp Neurol 319(2):218–245
60. Bittencourt JC, Elias CF (1993) Diencephalic origins of melanin-concentrating hormone immunoreactive projections to medial septum/diagonal band complex and spinal cord using two retrograde fluorescent tracers. Ann N Y Acad Sci 680:462–465
61. Sakurai T et al (1998) Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell 92(4):573–585
62. Elmquist JK, Elias CF, Saper CB (1999) From lesions to leptin: hypothalamic control of food intake and body weight. Neuron 22(2):221–232
63. Armstrong WE (1995) Hypothalamic supraoptic and paraventricular nuclei. In: Paxinos G (ed) The rat nervous system. Academic Press, San Diego, pp 377–390
64. Heimer L et al (1997) Substantia innominata: a notion which impedes clinical-anatomical correlations in neuropsychiatric disorders. Neuroscience 76(4):957–1006
65. Keay KA et al (1994) Convergence of deep somatic and visceral nociceptive information onto a discrete ventrolateral midbrain periaqueductal gray region. Neuroscience 61(4):727–732
66. Clement CI et al (2000) Spinal sources of noxious visceral and noxious deep somatic afferent drive onto the ventrolateral periaqueductal gray of the rat. J Comp Neurol 425(3):323–344
67. Depaulis A, Keay KA, Bandler R (1994) Quiescence and hyporeactivity evoked by activation of cell bodies in the ventrolateral midbrain periaqueductal gray of the rat. Exp Brain Res 99(1):75–83

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TREATMENT

# Migraine prophylaxis: key points for the practising clinician

**F. Moschiano · D. D'Amico · Gennaro Bussone**

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**Abstract** Migraine is a significant burden on individuals and society. Patients with most severe forms require preventive treatments, whose aim is to reduce the frequency and severity of attacks and consequently the overall impact of migraine. Although various medications are available for migraine prophylaxis, only a minority of migraineurs receive these drugs. This brief paper summarizes the most important indications for starting migraine prophylaxis, and provides an overview of the salient characteristics of available preventive drugs, to guide the choice of the most appropriate medication for a given patient.

**Keywords** Migraine · Prophylaxis · Preventive drugs · Guidelines

## Introduction

Migraine is a significant burden on individuals and society due to its high frequency and the severity of the pain and associated symptoms [1], which result in significant disability during attacks (with reduced productivity at work and impaired family and social life) [2–5], and diminished quality of life even outside attacks [6–8].

Both acute treatment and prophylactic treatments are used to manage migraine. The principal aims of prophylaxis are to reduce the frequency and severity of attacks and consequently to reduce the overall impact of migraine. Although various prophylactic medications are available [9, 10], only a minority of migraineurs receive these drugs [11, 12].

The aims of this brief paper are to summarize the most important indications for starting migraine prophylaxis, and to provide an overview of the salient characteristics of available prophylactics to guide the choice of the most appropriate drug for a given patient.

## When should prophylaxis be prescribed?

In the past, the most common, if not the only criterion for starting migraine prophylaxis was attack frequency. However, recent guidelines [9, 10], and expert reviews [13–18] have now identified a series of additional patient circumstances in which prophylaxis is advisable. The main indicator for deciding to start prophylactic treatment is now considered to be the impact of the condition on the patient. Impact should be evaluated in terms of functional disability and quality of life. Attack frequency (as mean number of attacks per month) remains a crucial factor in assessing impact. Other key factors are: effectiveness of acute therapy in the individual or presence of concomitant conditions that prevent their use; risk of medication overuse, or evolution to chronic headache forms; special circumstances, such as attacks with risk of permanent neurological injury; and patient views on taking daily medication for an extended period.

These guidelines indicated that, before deciding to prescribe prophylaxis, a comprehensive evaluation of the patient is necessary; however, practical criteria to be followed by the treating physician are not given. More

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specific suggestions have been provided by expert panels that have tried to consider the most relevant factors indicating prophylaxis with thresholds [18, 19]. In a survey of 14 headache specialists (neurologists and general practitioners) from various countries, the main factors considered when prescribing prophylaxis were headache frequency and symptomatic drug consumption [18]. The survey's authors suggested that prophylaxis should be prescribed to migraine patients reporting five or more attacks per month, who use acute medications 3 or more days/week (12 or more days/month), who have significant comorbidities that preclude the use of effective acute treatment, and when a medication can be used to treat both the migraine and the comorbidity (e.g., hypertension, depression, epilepsy). They recommended that prophylaxis should be considered in patients with increasing migraine frequency (at least 3–4 attacks/month), increasing use of acute medications (2 or more days/week or 8 or more days/month), or who experience between-attack dysfunction. Other factor recognized as influencing the decision to start prophylaxis were patient preference, disability level, and pregnancy status [18].

In the AMPP study [19], an expert panel of neurologists and primary care physicians concluded that prophylaxis should be offered to migraine subjects reporting either 6 or more headache days/month, 4 or more headache days with at least some impairment, or 3 or more headache days with severe impairment or requiring bed rest. Prophylaxis should be considered in migraineurs with 4 or 5 migraine days/month with normal functioning, 3 migraine days with some impairment, or 2 migraine days with severe impairment.

## Characteristics of available drugs and relevance to clinical practice

### Evidence-based efficacy

Evidence of efficacy, as assessed by controlled clinical trials, is the most important requisite for a preventive medication. For this, clinicians can rely on international guidelines [9, 10], which provide a list of drugs, classified according to standardized rating systems based on the quality of the published evidence. Criteria for evaluating trials consider important aspects such as the presence of a prospective baseline period, the quality of the statistical analyses, evidence for significant reduction in headache frequency between baseline and treatment period, in patients treated with the active drug versus those receiving placebo, and percentage and severity of adverse events.

Overall, there is general agreement that propranolol, valproic acid, and topiramate are first line treatments for migraine prophylaxis, based on their efficacy in clinical trial of adequate quality and clinical experience in the use of these medications in several countries. Other recommended compounds are: flunarizine, amitriptyline, timolol, metoprolol, atenolol, nadolol, bisoprolol, gabapentin, and methysergide. Weaker or insufficient evidence exists justifying the used of pizotifen, NSAIDS, ACE-inhibitors, sartans, selective serotonin re-uptake inhibitors, and MAO-inhibitors.

### Other methodological issues

When evaluating drug trials clinicians should pay attention to various methodological aspects that suggest the likely relevance of the drug in clinical practice. First, it is important to determine whether several endpoints were used to assess headache frequency reduction. In addition to mean number of attacks before and after treatment, the mean number of migraine days and the responder rate (percentage of patients migraine frequency by decreased 50% or more after treatment) should normally be reported in a trial. The last endpoint is clinically meaningful, in view of the wide variation in attack duration between migraineurs, and also in a single patient. The mean number of migraine days provides an intuitive measure of likely efficacy for the clinician and the patient.

Another methodological issue to be aware of is whether the published results pertain to all participants, i.e., whether the analysis was on the intent-to-treat (ITT) population, and not only on the patients who completed the study. Analyses performed only on completers are likely to be biased by favoring the active drug, as patients experiencing adverse events from the active drug or no early benefit may be early drop-outs (and not be included among the completers), while those experiencing clinical benefit early during the treatment period are more likely to complete the trial.

### Effects on coexisting conditions

The presence of other conditions coexisting with migraine in a patient may influence the choice of a preventive drug. Thus, several preventive drugs can be useful to control other conditions: e.g., propranolol for arterial hypertension; amitriptyline for both migraine and tension-type headaches; topiramate and valproate for a migraineur who also experiences seizures.

It should be noted, however, that some preventive drugs can exacerbate a coexisting condition. Examples: compounds with a high risk of increasing body weight (such as flunarizine, valproate, or amitriptyline) should not be given to obese patients; flunarizine may aggravate depression; amitriptyline and pizotifen may worsen glaucoma or urinary retention; beta-blockers can worsen asthma and diabetes; topiramate can be safely used in all the above

noted concomitant diseases, but can enhance the risk of renal calculi in predisposed subjects.

### Effects on impact of migraine and on acute drug consumption

The utility of a preventive drug is enhanced if it reduces migraine impact. Data from open studies in which different preventive compounds were administrated to migraine patients [20], and also from controlled trials in which topiramate was administered for migraine prophylaxis [21–23], indicate that prophylaxis can lead to a significant reduction in functional disability (measured by the MIDAS questionnaire), and improvement in physical and emotional dimensions of quality of life (as assessed by SF-36 and MSQ surveys).

For patients with "chronic migraine" the negative functional impact of the condition is quite marked (more so than with episodic migraine) and these patients are among the most difficult to treat [24–27]. Increasing headache frequency and increasing acute medication consumption have been identified as risk factors for progression from episodic migraine to "chronic daily headache" or "chronic migraine" [28, 29]. In a 1-year-follow up study in which 14% of the evaluated patients developed "chronic headache" odds ratios for progression to a chronic form were 20.1 (95% CI 5.7–71.5) for patients with 10–14 headache days/month, and 19.4 (95% CI 8.7–43.2) for patients with medication overuse [29].

Analysis of pooled data from three controlled trials in which patients received topiramate or placebo for 6 months, showed that the number of days with usage of acute medication was significantly lower in those on topiramate than in those on placebo ($3.3 \pm 3.7$ vs. $4.3 \pm 3.6$, $P < 0.001$) [30].

### Long administration

Three months is generally regarded as an optimal trial period for a prophylactic medication for migraine and most published trials have been concerned with 3 month treatment periods. However, clinical experience is that many patients require longer treatment periods in order to achieve good results. Only a few studies have tested medication efficacy over longer periods, or investigated the persistence of therapeutic effect after drug discontinuation.

A rather old open-label study [31] evaluated efficacy in 64 migraine patients followed for 18 months after discontinuation of successful prophylaxis with flunarizine, propranolol, or metoprolol. A quarter of this group experienced a long-lasting frequency reduction of at least 50%, while 75% of improved only initially. Another open-label study was designed to follow 117 patients for 3 years after treatment with divalproex in a previous controlled study [32]. Less than 50% of patients continued to take divalproex for more than a year, and only 33% of patients completed the study. Reasons for withdrawal included insufficient effectiveness (16%), drug intolerance (21%), and other (31%).

Two studies in which topiramate was administered for migraine prophylaxis for up to 14 months were published recently [23, 33]. A sample of 567 patients received an 8-month open-label extension after receiving topiramate for 6 months in two large placebo-controlled trials [33]. Patients on topiramate in the double-blind phase had a total treatment period 14 months and experienced a significant reduction in headache frequency, with further frequency reduction during the open-label phase. The frequency of topiramate-associated adverse events was lower in the open-label phase than the double-blind phase in these patients (for paresthesia the reduction was from 47.8 to 17.4%; for difficulty with memory the reduction was from 9.8 to 5.1%). The same trend was found for discontinuation due to adverse events: 22.2% on the double-blind phase and 8.6% in the open-label phase. A subsequent study [23] reversed the treatment schedule: patients were treated with open-label topiramate for 6 months and then randomized to topiramate versus placebo in a double-blind phase for a further 6 months. Prolonged prophylaxis was again found to afford sustained improvement (reduction in migraine frequency, significant reductions in acute medication intake, and improvement in disability and headache impact), with no evidence of higher rates of adverse events. Furthermore, no "rebound" effect as observed after discontinuation of topiramate although partial relapse occurred in patients receiving placebo in the second phase of the trial. The clinical lesson of these trials is that 6–14 months of prophylaxis with topiramate can lead to sustained clinical benefit.

## The patient's perspective

Patient preference, as well as patient understanding and acceptance of therapy, should be key elements in any long-term management plan for migraine [34, 35]. They are discussed in another article in this issue *(D'amico and Tepper, Key Points In Migraine Prophylaxis: The Patient's Perspective).*

## Concluding remarks

The main points discussed in this short overview are as follows:

1. Successful migraine prophylaxis remains a considerable clinical challenge.

2. Despite the demonstration that long-term preventive therapy with several compounds can reduce the burden of migraine, prophylaxis is largely underused.
3. Candidates for prophylaxis should be selected on the basis of a comprehensive evaluation.
4. The decision to start prophylaxis should be based mainly on headache frequency and headache impact on functioning.
5. The efficacy of acute treatment in the individual patient, and the risk of acute medication overuse are other important factors to be considered in the decision to start prophylaxis.
6. International guidelines list several compounds that have proved effective in controlled clinical trials, and which can be viewed as first-choice and second-choice drugs.
7. In evaluating the clinical relevance of published trials, a number of criteria should be applied: did the study have several meaningful endpoints (not only reduction in number of attacks but also reduction in number of migraine days, and responder rates)?; was the analysis clinically and methodologically sound (e.g., were all patients evaluated (ITT)—drop-outs as well as completers?).
8. The efficacy of a given medication may be enhanced by other characteristics. The following should be born in mind: long-term treatment may be necessary to obtain benefit, with possibility of longer term improvement after the medication is withdrawn; positive effects on disease impact; prevention of progression to daily/near-daily headaches; prevention of acute medication overuse; control of coexisting conditions; no negative effect on existing conditions.
9. First line treatment options are propranolol, valproic acid, flunarizine, and topiramate. Topiramate is the most extensively studied, with trial that are methodological sound and have multiple endpoints.
10. Good patient–physician communication is vital to obtain patient acceptance of prophylaxis, and adherence to long-term therapy.

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## References

1. Headache Classification Subcommittee of the International Headache Society (2004) The international classification of headache disorders: 2nd edition. Cephalalgia 24(Suppl 1):1–160
2. Bussone G, Usai S, Grazzi L, Rigamonti A, Solari A, D'Amico D (2004) Disability and quality of life in different primary headaches: results from Italian studies. Neurol Sci 25(Suppl 3):S105–S107
3. Lipton RB, Bigal ME, Kolodner K, Stewart WF, Liberman JN, Steiner TJ (2003) The family impact of migraine: population-based studies in the USA and UK. Cephalalgia 23(6):429–440
4. Dueland AN, Leira R, Burke TA et al (2004) The impact of migraine on work, family, and leisure among young women—a multinational study. Curr Med Res Opin 20:1595–1604
5. Steiner TJ, Scher AI, Stewart WF et al (2003) The prevalence and disability burden of adult migraine in England and their relationships to age, gender and ethnicity. Cephalalgia 23:519–527
6. Osterhaus JT, Townsend RJ, Gandek B et al (1994) Measuring the functional status and well-being of patients with migraine headache. Headache 34:337–343
7. Dahlof CGH, Dimenas E (1995) Migraine patients experience poorer subjective well-being/quality of life even between attacks. Cephalalgia 15:31–36
8. Terwindt GM, Ferrari MD, Tijhuis M et al (2000) The impact of migraine on quality of life in the general population. Neurology 55:624–629
9. Silberstein SD, for the US Headache Consortium (2000) Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 55:754–762
10. Members of the task force, Evers S, Afra J, Frese A et al (2006) EFNS guideline on the drug treatment of migraine—report of an EFNS task force. Eur J Neurol 13:560–572
11. Diamond S, Bigal ME, Silberstein S et al (2007) Patterns of diagnosis and acute and preventive treatment for migraine in the United States: results from the American Migraine Prevalence and Prevention Study. Headache 47:355–363
12. Lucas C, Géraud G, Valade D et al (2006) Recognition and therapeutic management of migraine in 2004, in France: results of FRAMIG 3, a French nationwide population-based survey. Headache 46:715–725
13. D'Amico D, Lanteri-Minet M (2006) Migraine preventive therapy: selection of appropriate patients and general principles of management. Expert Rev Neurother 6:1147–1157
14. Diamond ML, Wenzel RG, Nissan GR (2006) Optimizing migraine therapy: evidence-based and patient-centered care. Expert Rev Neurother 6:911–919
15. Dowson AJ, Sender J, Lipscombe S et al (2003) Establishing principles for migraine management in primary care. Int J Clin Pract 57:493–507
16. Silberstein SD, Goadsby PJ (2002) Migraine: preventive treatment. Cephalalgia 22:491–512
17. Loder E, Biondi D (2005) General principles of migraine management: the changing role of prevention. Headache 45(Suppl 1):S33–S47
18. Tepper SJ, D'Amico D, Baos V, Blakeborough P, Dowson AJ (2004) Guidelines for prescribing prophylactic medications for migraine: a survey among headache specialist physicians in different countries. Headache Care 1(4):267–272
19. Diamond S, Bigal ME, Silberstein S, Loder E, Reed M, Lipton RB (2007) Patterns of diagnosis and acute and preventive treatment for migraine in the United States: results from the American Migraine Prevalence and Prevention study. Headache 47(3): 355–363
20. D'Amico D, Solari A, Usai S et al. For the Progetto Cefalee Lombardia Group (2006) Improvement in quality of life and activity limitations in migraine patients after prophylaxis. A prospective longitudinal multicentre study. Cephalalgia 26:691–696
21. Dahlof C, Loder E, Diamond M et al (2007) The impact of migraine prevention on daily activities: a longitudinal and responder analysis from three topiramate placebo-controlled clinical trials. Health Qual Life Outcomes 5(1):56

22. Brandes JL, Kudrow DB, Rothrock JF et al (2006) Assessing the ability of topiramate to improve the daily activities of patients with migraine. Mayo Clin Proc 81(10):1311–1319
23. Diener HC, Agosti R, Allais G, Bergmans P, Bussone G, Davies B, Ertas M, Lanteri-Minet M, Reuter U, Del Río MS, Schoenen J, Schwalen S, van Oene J, TOPMAT-MIG-303 Investigators Group (2007) Cessation versus continuation of 6-month migraine preventive therapy with topiramate (PROMPT): a randomised, double-blind, placebo-controlled trial. Lancet Neurol 6(12): 1054–1062
24. Meletiche DM, Lofland JH, Young WB (2001) Quality-of-life differences between patients with episodic and transformed migraine. Headache 41:573–578
25. Bigal ME, Rapoport AM, Lipton RB, Tepper SJ, Sheftell FD (2003) Assessment of migraine disability using the migraine disability assessment (MIDAS) questionnaire: a comparison of chronic migraine with episodic migraine. Headache 43:336–342
26. D'Amico D, Grazzi L, Usai S, Rigamonti A, Curone M, Bussone G (2005) Disability pattern in chronic migraine with medication overuse: a comparison with migraine without aura. Headache 45(5):553–560
27. D'Amico D, Leone M, Grazzi L et al (2008) When should "chronic migraine" patients be considered "refractory" to pharmacological prophylaxis? Neurol Sci 29(Suppl 1):S55–S58
28. Scher AI, Stewart WF, Ricci JA et al (2003) Factors associated with the onset remission of chronic daily headache in a population-based study. Pain 106:81–89
29. Katsarava Z, Schneeweiss S, Kurth T et al (2004) Incidence and predictors for chronicity of headache in patients with episodic migraine. Neurology 62:788–790
30. Limmroth V et al (2007) Topiramate in patients with episodic migraine: reducing the risk for chronic forms of headache. Headache 47(1):13–21
31. Wober C et al (1991) Long-term results of migraine prophylaxis with flunarizine and beta blockers. Cephalalgia 11(6):251–256
32. Silberstein SD, Collins SD (1999) Safety of divalproex sodium in migraine prophylaxis: an open-label, long-term study. Headache 39(9):633–643
33. Rapoport A, Mauskop A, Diener HC, Schwalen S, Pfeil J (2006) Long-term migraine prevention with topiramate: open-label extension of pivotal trials. Headache 46(7):1151–1160
34. Manzoni CG, Torelli P (2007) The patient–physician relationship in the approach to therapeutic management. Neurol Sci 28:S130–S133
35. D'Amico D, Tepper SJ (2008) Prophylaxis of migraine: general principles and patient acceptance. Neuropsychiatr Dis Treat 4(6):1155–1167

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TREATMENT

# Key points in migraine prophylaxis: patient perspective

**Domenico D'Amico · S. J. Tepper**

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**Abstract** Migraine is a chronic neurological condition with heterogeneous presentation. It is associated with significant pain, disability, and diminished quality of life in a large proportion of patients. Patients with severe and/or frequent migraines require prophylaxis, which implies daily administration of anti-migraine compounds for several months, with potential adverse events or contraindications. This paper reviews the main factors influencing patient acceptance of anti-migraine prophylaxis, providing practical suggestions to maximize patient agreement with, and adherence to, preventive treatment.

**Keywords** Migraine · Prophylaxis · Acceptance · Adherence

## Introduction

Migraine prevalence and incidence tends to peak in middle life [1–3], when an individual is likely to be more actively engaged in work, social and family duties. Migraine is very disabling, causing severe functional impairment during attacks, as well as decreased quality of life [3–6]. Migraine heterogeneity in clinical features and impact implies that different patients will have different treatment needs [7].

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Migraine management includes non-pharmacological approaches, acute treatment, and prevention or prophylaxis. Patients with disabling and/or frequent migraine forms require prophylaxis [8–10]. Medications used for migraine prophylaxis have potential and often important adverse events or contraindications, and may interfere with concurrent conditions and treatments, inducing patients to reject prevention, or leading to poor patient adherence.

This paper reviews factors influencing patient acceptance of anti-migraine prophylaxis, providing practical suggestions to enhance a patient's willingness to accept pharmacological prevention.

## Main factors influencing patients' acceptance of prophylaxis

### Daily dosing

Patients might reject daily drug ingestion, independent from attack occurrence. Physicians should communicate that, although episodic in its manifestations, migraine is chronic neurological condition, with susceptibility to triggers, which can be partially corrected by the use of preventive medications that modulate the underlying "neurochemical instability" [11].

### Long therapy duration

Patients might not accept daily prophylaxis. Usually, prophylaxis should be used for a period of at least 3 months, although recent evidence, as well as clinical experience, suggest the possibility of increased efficacy with use of preventive drugs for longer periods (up to 6–14 months) [10, 12]. Education is crucial, as the effects of prevention

require regular and continuous administration for relatively long therapeutic cycles.

### Goals and expectations

Patients may expect that prophylaxis will eradicate headaches or that they can be neither cured nor relieved by medications. This means explaining that reduction in frequency is the primary goal, with spill over benefits on intensity, duration, and disability [12–14].

Patients should be educated that complete disappearance of attacks cannot be expected after prophylaxis, that acute attacks will still occur even with successful prevention, and that data from published literature indicate about 45% of migraineurs receiving available preventive drugs experience a frequency reduction of ≥50%, with around 20% of them with a frequency decrease of ≥75% [15–19]. Clinicians should emphasize that prophylaxis can also be useful in reducing migraine-related impact [8, 13, 14]. Patients should be encouraged to keep a headache diary of frequency, severity, duration, and degree of functional disability during their migraines. Communication about efficacy of ongoing treatment can be enhanced by use of specific questionnaires, such as the Migraine Disability Assessment score (MIDAS) [13, 20], and the Headache Impact test (HIT6) [21], to assess impact of migraine on functioning and well-being. These well-accepted paper tools are easy to use, and help assess the clinical situation from the patient point of view from first consult to follow-up visits.

According to a recent study, efficacy is the most important factor for patient preference in prevention (72%) [22]. Most of the surveyed patients chose those preventive treatments with higher efficacy rates, even with side effects.

### Adverse events

Concern for side effects during migraine prophylaxis very commonly expressed by patients when receiving a prevention prescription and may discourage them from accepting prophylaxis or may negatively influence patient adherence, with irregular dosing, dosage self-reduction, or drug discontinuation following trivial symptoms not treatment-related.

A comprehensive history is necessary, to include: evaluation of individual life-style, concerns about particular adverse events, and history of side effects from previous treatments. Clinicians should choose among various compounds with active participation of the patient.

Patients should be advised about most common adverse events of prescribed drugs and even of uncommon effects which could be clinically relevant. If possible, focus should be given to the benign nature of most effects, the possibility of resolution over time, or by reducing daily dosage.

The following scenarios can be regarded as practical examples:

- Avoid compounds with high risk of increasing weight (such as flunarizine, valproate, or amitriptyline) in obese patients or those concerned with weight gain.
- Avoid beta blockers, which cause exercise intolerance, in athletes.
- Avoid drugs which may cause CNS difficulty (such as topiramate) in those with cognitive employment, such as teachers,
- Avoid drugs causing excessive sedation or somnolence (such as amitriptyline) in drivers or machine operators.
- Inform patients that symptoms such as paresthesias during topiramate treatment, mild somnolence with flunarizine, or some nausea with sodium valproate, should be regarded as substantially benign, often self-limiting or gradually vanishing adverse events. Patients should also be told to contact their physician if they experience serious side effects such as visual disturbances, depression, or asthenia while on topiramate, flunarizine, or sodium valproate, respectively.

A recent survey found only 6% of enrolled patients rated lack of adverse events as the most important aspect of prevention when asked to rank a list of aspects which also included efficacy, speed of onset, dose frequency, out-of-pocket cost, and treatment type (prescription/vitamin) [22]. In another study, the second most highly ranked factor in terms of importance was that the prescribing clinician takes time to explain possible adverse events of proposed medications. Patients will accept effective prevention with a high side effect rate. Possible effects on weight and likelihood to cause sedation were indicated as important factors for rejection (especially in women) [23].

## Concluding remarks

Clinicians should be aware that treatment strategies for migraine patients require patient understanding and acceptance. This is particularly true when a long-term treatment plan, including prophylaxis, is prescribed.

While patients' preferences for acute migraine treatment have been extensively studied [24–30], only three studies have been published on patients' preference for prophylaxis) [22, 23, 31]. Further studies are warranted to explore possible factors influencing patient acceptance of prevention.

Prophylaxis requires a comprehensive evaluation of different aspects of a patient's migraine and life-style, acute therapy response, and migraine-related impact, to guide therapeutic decisions, as well as to assess outcomes.

Clinicians must direct efforts to help patients accept prophylaxis, taking into account:

- Differences in goals and treatment between acute therapy (attack relief), and prophylaxis (reduction in attack frequency and impact) should be explained, to help patient understanding that preventive drugs must be taken daily, and for long periods.
- The fact that the information given by the patient (particularly on intolerable side effects and on concomitant conditions which might influence treatment) has been taken into account to select the most appropriate prophylaxis must be communicated.
- Active involvement of the individual patient in assessment of prophylaxis outcomes, through use of a headache diary and administration of specific disability/impact tools, will likely increase patient treatment adherence and, therefore, patient satisfaction.
- Communication between patient and physician in the therapeutic management of primary headaches is crucial [10, 23, 32].

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## References


1. Stewart WF, Sheder AL, Simon D et al (1994) Migraine prevalence. A review of population-based studies. Neurology 44(Suppl 4):S17–S23
2. Roncolato M, Fabbri L, Recchia G et al (2000) An epidemiological study to assess migraine prevalence in a sample of Italian population presenting to their GPs. Eur Neurol 43:102–106
3. Lipton RB, Bigal ME, Diamond M, AMPP Advisory Group et al (2007) Migraine prevalence, disease burden, and the need for preventive therapy. Neurology 68:343–349
4. Lipton RB, Goadsby PJ, Sawyer JPC et al (2000) Migraine: diagnosis and assessment of disability. Rev Contemp Pharmacother 11:63–73
5. Bussone G, Usai S, Grazzi L, Rigamonti A, Solari A, D'Amico D (2004) Disability and quality of life in different primary headaches: results from Italian studies. Neurol Sci 25(Suppl 3): S105–S107
6. Terwindt GM, Ferrari MD, Tijhuis M et al (2000) The impact of migraine on quality of life in the general population. Neurology 55:624–629
7. Stewart WF, Shechter A, Lipton RB (1994) Migraine heterogeneity. Disability, pain intensity, and attack frequency and duration. Neurology 44(6 Suppl 4):S24–S33
8. Ramadan NM, Silberstein SD, Freitag FG et al (2000) Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. Neurology (serial on line) http://www.neurology.org
9. Members of the task force, Evers S, Afra J, Frese A et al (2006) EFNS guideline on the drug treatment of migraine—report of an EFNS task force. Eur J Neurol 13:560–572
10. D'Amico D, Tepper SJ (2008) Prophylaxis of migraine: general principles and patient acceptance. Neuropsychiatr Dis Treat 4:1–13
11. Goadsby PJ, Lipton RB, Ferrari MD (2002) Migraine-current understanding and treatment. N Engl J Med 346:257–270
12. Diener HC, Agosti R, Allais G, For the TOPMAT-MIG-303 Investigators Group et al (2007) Cessation versus continuation of 6-month migraine preventive therapy with topiramate (PROMPT): a randomised, double-blind, placebo-controlled trial. Lancet Neurol 6:1054–1062
13. D'Amico D, Solari A, Usai S, For the Progetto Cefalee Lombardia Group et al (2006) Improvement in quality of life and activity limitations in migraine patients after prophylaxis. A prospective longitudinal multicentre study. Cephalalgia 26:691–696
14. Dahlof C, Loder E, Diamond M et al (2007) The impact of migraine prevention on daily activities: a longitudinal and responder analysis from three topiramate placebo-controlled clinical trials. Health Qual Life Outcomes 5(1):56
15. Klapper J (1997) Divalproex sodium in migraine prophylaxis: a dose-controlled study. Cephalalgia 17:103–113
16. Mathew NT, Rapoport A, Saper J et al (2001) Efficacy of gabapentin in migraine prophylaxis. Headache 41:119–128
17. Brandes JL, Saper JR, Diamond M, For the MIGR-002 Study Group et al (2004) Topiramate for migraine prevention: a randomized controlled trial. JAMA 291(8):965–973
18. Silberstein SD, Neto W, Schmitt J, The MIGR-001 Study Group et al (2004) Topiramate in migraine prevention: results of a large controlled trial. Arch Neurol 61:490–495
19. Diener HC, Tfelt Hansen P, Dahlof C, For the MIGR-003 Study Group et al (2004) Topiramate in migraine prophylaxis-results from a placebo-controlled trial with propranolol as an active control. J Neurol 251:943–950
20. Stewart WF, Lipton RB, Whyte J et al (1999) An international study to assess reliability of the Migraine Disability Assessment (MIDAS) score. Neurology 53:988–994
21. Kosinski M, Bayliss MS, Bjorner JB et al (2003) A six-item short-form survey for measuring headache impact: the HIT-6. Qual Life Res 12:963–974
22. Peres MF, Silberstein S, Moreira F et al (2007) Patients' preference for migraine preventive therapy. Headache 47:540–545
23. Rozen TD (2006) Migraine prevention: what patients want from medication and their physicians (a headache specialty clinic perspective). Headache 46:750–753
24. Salonen R, Ashford EA, Gibbs M, Hassani H (1999) Patient preference for oral sumatriptan 25 mg, 50 mg, or 100 mg in the acute treatment of migraine: a double-blind, randomized, crossover study. Sumatriptan Tablets S2CM11 Study Group. Int J Clin Pract Suppl 105:16–24
25. Davies GM, Santanello N, Lipton RB (2000) Determinants of patient satisfaction with migraine therapy. Cephalalgia 20:554–560
26. Sheftell FD, Feleppa M, Tepper SJ, Volcy M, Rapoport AM, Bigal ME (2004) Patterns of use of triptans and reasons for switching them in a tertiary care migraine population. Headache 44:661–668
27. Dowson AJ, Tepper SJ, Vaos V, Baudet F, D'Amico D, Kilminster S (2004) Identifying patients who require a change in their current acute migraine treatment: the Migraine Assessment of Current Therapy (Migraine-ACT) questionnaire. Curr Med Res Opin 20:1125–1135
28. Goadsby PJ, Dodick DW, Ferrari MD et al (2004) TRIPSTAR: prioritizing oral triptan treatment attributes in migraine management. Acta Neuro Scand 110:137–143
29. Lainez MJ, Evers S, Kinge E, Allais G, Allen C, Rao NA, Massaad R, Lis K (2006) Preference for rizatriptan 10-mg wafer vs. eletriptan 40-mg tablet for acute treatment of migraine. Cephalalgia 26:246–256

30. Diez FI, Straube A, Zanchin G (2007) Patient preference in migraine therapy. A randomized, open-label, crossover clinical trial of acute treatment of migraine with oral almotriptan and rizatriptan. J Neurol 254:242–249
31. Kol CM, Dekker F, Neven AK et al (2008) Acceptance or rejection of prophylactic medicine in patients with migraine: a cross-sectional study. Br J Gen Pract 58:98–101
32. Manzoni CG, Torelli P (2007) The patient–physician relationship in the approach to therapeutic management. Neurol Sci 28:S130–S133

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TREATMENT

# Costs of hypothalamic stimulation in chronic drug-resistant cluster headache: preliminary data

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**Abstract** In about 20% of chronic cluster headache (CH) cases, drugs may become ineffective. Under these circumstances, steroids and triptans are frequently employed leading to fearful side effects in one and high costs in the other. The direct costs of drug-resistant chronic CH are mainly due to frequent medical consultations and frequent use of expensive drugs. In recent years, hypothalamic stimulation has been employed to treat drug-resistant chronic CH patients suffering multiple daily attacks and long-term results from different centres show a 60% overall benefit. Nine years since the introduction of this technique, we attempt a preliminary analysis of the direct costs of hypothalamic stimulation based on patients treated at our centre. We estimated the following direct costs as follows: cost of neurosurgery plus cost of equipment (electrode, connection and impulse generator = 25,000 euro), cost of hospital admissions in long-term follow-up (2,000 euro per admission), cost of single sumatriptan injection (25 euro). Number of daily sumatriptan injections in the year before and for each year after hypothalamic implantation was obtained from headache diaries. To estimate the saving due to the reduction in sumatriptan consumption following hypothalamic stimulation, we calculated the following for each year of follow-up after surgery: number of sumatriptan injections in the year before surgery minus number of sumatriptan injections in each year, updated to December 2008. In our 19 implanted patients, the costs of neurosurgery plus cost of equipment were 475,000 euro; the costs of hospital admissions during follow up were 250,000 euro. Reduction in sumatriptan consumption resulted in a total saving of 3,573,125 euro. Hence, in our 19 patients, the sumatriptan saving (3,573,125 euros) minus the direct costs due to operation and follow up hospitalisations (475,000 + 250,000) euro is equal to 2,848,125 euros. These preliminary results indicate that hypothalamic stimulation is associated with marked reduction of direct costs in the management of complete drug-resistant chronic CH.

**Keywords** Hypothalamic stimulation · Cluster headache · Intractable · Costs

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## Introduction

Cluster headache (CH) is a primary headache syndrome characterized by strictly unilateral head pain accompanied by ipsilateral oculofacial autonomic phenomena [1]. An obsolete name for the condition is suicide headache, reflecting the fact that the pain, reported as excruciating or worse than that experienced at childbirth, is one of the most severe known. The attacks last for 15–180 min, occur up to eight times daily, and render the patient agitated [1]. The ipsilateral autonomic manifestations include conjunctival injection, lacrimation, miosis, ptosis, eyelid oedema, rhinorrhea, nasal blockage, and forehead or facial sweating [1]. There are two main forms of CH: episodic and chronic. Episodic CH is characterized by cluster periods during which the attacks typically occur daily and alternate with more or less extended attack-free periods [1]. In chronic CH, there is no notable remission and the attacks may continue unabated for years,

resulting in severe debilitation [1]. Approximately 20% of CH patients have the chronic form [2] and need continuous medical care because of pain persistence. Although no definitive cure is available, clinical experience is that drug treatments are able to control or prevent the attacks in approximately 80% of patients with chronic CH. In the remaining 20% of chronic cases, drugs are ineffective. Loss of drug efficacy may develop during the course of the condition, often after years of successful pharmacologic control. Patients then resort to various drugs (e.g., analgesics, triptans, nonsteroidal anti-inflammatory drug, opioids, ergot-derivatives, steroids) in increasingly desperate attempts to relieve their daily pain episodes.

Steroids and triptans are most frequently used by chronic drug-resistant CH patients [3]. Steroids often achieve full control of the attacks but in some patients they only reduce the frequency from seven to eight daily to one to two daily. In the latter case, patients need sumatriptan injections to block ongoing attacks when they occur [4]. Prolonged use (years) of steroids may have fearful and high cost consequences including chronic intestinal bleeding, bone demineralization leading to fractures and aseptic necrosis of the femoral head, fluid retention leading to heart failure, hypertension, bulimia and marked weight increase, severe myopathy with loss of ability to walk, and glaucoma. There also may be agitation, insomnia, and even frank psychosis. In these patients, use of sumatriptan injections daily for years [3, 5–7] may facilitate the onset of myocardial ischaemia and increase blood pressure [8]. Furthermore, sumatriptan injections are expensive: completely drug-resistant CH patients suffering multiple daily attacks notwithstanding prophylaxis (even oral steroids), need 4–8 injections per day [5]. In Italy, the cost of one injection is about 25 euro, hence 1 day treatment costs (mean 6 injections per day) is about 150 euro.

Patients with chronic CH also require frequent visits to a headache specialist to monitor their condition, prescribe new medications, and assess the effects of repeated drug use. Hospital admissions may be required for detoxification or "heavy-duty" treatments such as intravenous steroids or ergotamines. Patients with chronic CH often lose their jobs; family and social life is gravely disrupted, and quality of life is poor [9]. As a result of these stresses, severe anxiety-depressive syndromes may develop, which themselves may require medication. The direct and indirect costs of chronic drug-resistant CH are therefore high.

In recent years, neurostimulation methods have been introduced to treat chronic CH [5, 10–17]. The method most consonant with what is known of the pathophysiology of CH, and which has so far produced the best results, is hypothalamic stimulation [5, 10–14]. The idea for hypothalamic stimulation arose because PET studies had revealed activation of the ipsilateral posterior inferior hypothalamic gray matter during CH attacks [18], and voxel-based morphometric MRI had documented alteration of the same area, [19] strongly suggesting that the generator of the pain attacks was located in this region [18, 20, 21]. Just as electrode stimulation is effective for intractable movement disorders, it was supposed that stereotactic stimulation of the hypothalamus might interfere with the supposed hypothalamic CH generator, and relieve intractable cluster headache [10]. The procedure has been employed in over 50 patients: marked improvement has been obtained in about 60% of these [for a review see Ref. 22]. Candidates for implantation and stimulation are those experiencing multiple daily attacks, and patients only received hypothalamic implant after prolonged pre-implant follow-up during which all drugs, alone and in combination, were tried without benefit [23].

Nine years since the introduction of this technique, the present paper attempts a preliminary analysis of the costs of hypothalamic stimulation based on patients treated at our centre.

## Patients and methods

Nineteen patients (15 men; mean age at operation 42 years; mean duration of chronic CH 3 years, range 1–10; 5–8 attacks/daily) with chronic CH diagnosed according to International Headache Society criteria, were selected for hypothalamic stimulation [1, 5]. Addition selection criteria—in view of the invasive nature of hypothalamic implant and stimulation—were multiple daily attacks and complete drug-resistance (all known drugs tried without benefit including oral steroids) [23, 24]. Median follow-up is 5.6 years (range 3.3–8.8 years). Patients were required to keep a headache diary in which they noted number of attacks per day, and number of sumatriptan phials injected subcutaneously per day.

We estimated the following direct costs as follows:

1. Cost of neurosurgery plus cost of Medtronic electrode = 25,000 euro
2. Cost of follow up admissions = 2,000 euro per admission
3. Cost of single sumatriptan injection = 25 euro

From diary data, we next calculated mean daily sumatriptan use in the year before and for each year after hypothalamic implantation. We then calculated the following for each year of follow-up after surgery:

Number of sumatriptan injections in the year before surgery minus number of sumatriptan injections in each of the years after implantation. These data are presented in Fig. 1, updated to December 2008.

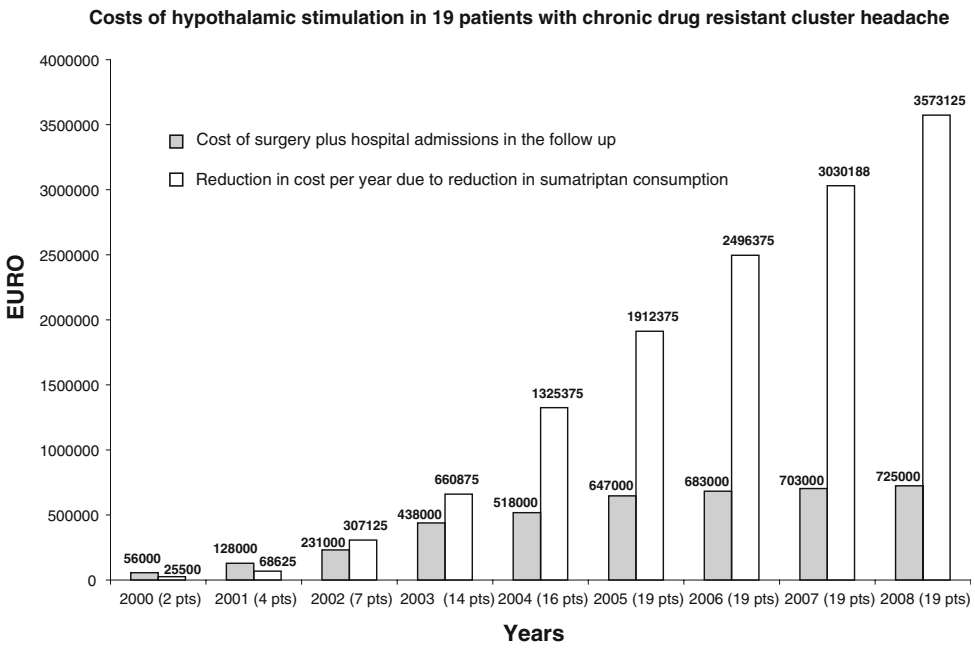


**Fig. 1** Cumulative annual costs of hypothalamic implant (surgery, electrode and hospitalisation) are indicated as *grey bars* with corresponding figures above them. Cumulative annual savings in sumatriptan use compared to sumatriptan use in the year prior to surgery are shown as *colourless bars*, with actual figures above. Data refer to 19 patients treated from 2000 to 2008

## Results

From July 2000 to December 2008, 19 chronic drug-resistant CH patients received hypothalamic implant and stimulation. All had multiple daily attacks and had tried all known pharmacological treatments for the condition without notable benefit, as recommended in our published guidelines [23, 24]. Many of these patients had been forced to take steroids continuously over the long term. The steroids only partially controlled the headaches and brought with them severe side effects, which in some cases were irreversible [5].

Figure 1 shows the direct costs per year calculated as described above, and include costs of additional (follow-up) hospitalisations after implantation. At the end of 2008, the total cost (all 19 patients) of the implantations (electrodes plus surgery) was 475,000 euro, and the total cost of all hospitalisations was 250,000 euro. After implantation, following reduction in headache frequency in many patients [5], the reduction in sumatriptan consumption resulted in a total saving of 3,573,125 euro. Hence, in our 19 patients, after hypothalamic implantation, the sumatriptan saving (3,573,125 euro) minus the direct costs due to operation and follow-up hospitalisations (475,000 + 250,000) euro was 2,848,125 euro.

## Discussion

The costs of treating chronic drug-resistant CH have, as far as we are aware, not been estimated previously. The present study also appears to be the first attempt to assess the costs of hypothalamic stimulation in drug-resistant chronic CH. Most of our patients had such severe several times daily headaches that they were no longer able to work, further increasing the costs of the illness which were not, however, estimated in the present study. Our data show cumulative cost savings due to reduced sumatriptan over a median of almost 6 years of follow-up and suggest that hypothalamic stimulation can reduce treatment costs for this highly disabling condition.

The estimation was made possible by the fact that our patients kept headache diaries, not only prior to their neurosurgery, but in the years following their operation. Clearly, without data from headache diaries it would be extremely difficult to estimate drug costs. Furthermore if diaries were not compiled regularly, the tendency would be to underestimate the number of sumatriptan injections, seriously overestimating the cost savings. To ensure that diaries were kept diligently, the treating neurologist checked that diaries were being compiled periodically throughout follow-up.

The study considered three sources of direct treatment costs: (1) cost of implant plus surgery, (2) cost of hospitalisation (for implantation and successive follow-up), and (3) difference between cost of sumatriptan use in each year after implantation and the cost of sumatriptan in the year before implantation. Patients suffered 4–8 headache attacks per day before implantation [5].

Assuming that the yearly number of sumatriptan injections would have remained constant at pre-implant levels (6 sumatriptan injections per day) if hypothalamic stimulation had not been applied, the total saving due to hypothalamic stimulation over the period 2000–2008 is

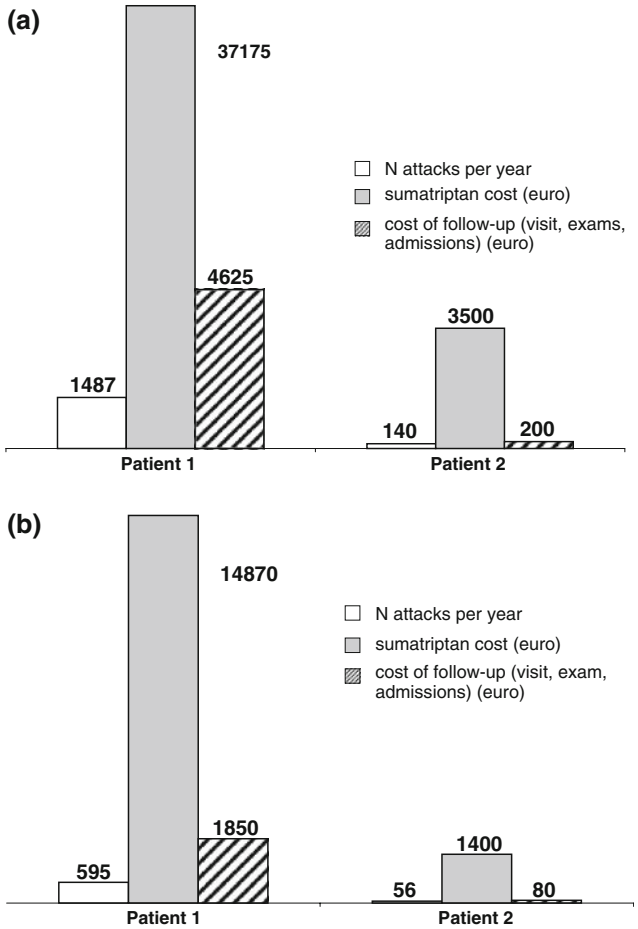


**Fig. 2** **a** Comparison of management costs for two patients with chronic CH prior to hypothalamic implant. In patient 1, the attacks occur several times daily and are only reduced by steroids so that several times daily sumatriptan injections and frequent visits to the doctor are required. In patient 2, lithium reduces the frequency to 1–3 week and the number of sumatriptan injections required is correspondingly reduced. Few visits to the doctor are necessary. **b** Management costs for the same two patients as in **a** after hypothalamic implant supposing a 60% reduction in attack frequency. The annual cost saving in patient 1 is 14,870 euro for fewer sumatriptan injections plus 1,850 euro for fewer visits to the doctor. Thus, the total saving is 16,720 euro per year. In patient 2, the saving estimated in the same way is 1,400 euro plus 80 euro for a total 1,480 euro per year

2,848,125 euro. This indicates that hypothalamic stimulation is associated with a marked reduction in the costs of managing drug-resistant [24] chronic CH.

In purely economic terms, therefore, hypothalamic stimulation appears useful in the management of this condition. However, the situation in individual patients is not always so favourable [5, 10–16, 22]. To illustrate this, we examine two of our patients separately, both of whom have been followed for several years. In patient 1 (Fig. 2), the attacks are several times daily, only partly controlled with steroids and hence requiring several times daily sumatriptan injections and also frequent visits to the headache specialist. Patient 2 took lithium that reduced the attacks to about 1–3 per week so sumatriptan injections were required 1–3 times a week. This patient did not require frequent checks by the treating physician. Assuming that hypothalamic stimulation reduced attack frequency by 60% in both patients [22], in patient 1, the annual cost saving related to reduction sumatriptan injections and visits to the doctor was 16,720 euro (difference between Fig. 2a and b). In patient 2, the saving is only 1,480 euro (difference between Fig. 2a and b). This hypothetic comparison shows that, in patient 1, the costs of implantation are recovered completely in the first 2 years after implant. In contrast, in patient 2, the cost of implant requires 15–20 years to be recovered. Thus, hypothalamic stimulation is not, from a strictly economic point of view, advantageous in chronic CH [1] patients with low attack frequencies [25]. Although the decision to perform hypothalamic implant in a given patient is not and cannot be made on purely economic grounds, knowledge of the likely cost savings of the operation can inform the patient and lead to a more balanced decision.

The present findings are consistent with previously published proposals by our group [23, 24, 26], which urge that patients undergoing neurostimulation procedures should be closely followed at specialist centres since the treatments are still experimental. During this follow-up patients should be made aware that assiduous compilation of a headache diary is essential [26]. The IHS guidelines on CH prophylaxis also stress this point, emphasizing that reduction in headache frequency is the primary endpoint of such treatment [25]. It is only due to conscientious and regular recording of headache frequency by the patient that it is possible to objectively evaluate frequency reduction and also the reduction in sumatriptan consumption, thereby permitting cost comparisons. We note, finally, that sumatriptan injections seem to be one of the most important single direct cost items in the long-term management of chronic drug-resistant CH.

**Conflict of interest statement** The authors declare that they have no conflict of interest related to the publication of this manuscript.

## References

1. Headache Classification Committee of The International Headache Society (2004) The International Classification of Headache Disorders (second edition). Cephalalgia 24:1–195
2. Manzoni GC, Micieli G, Granella F, Tassorelli C, Zanferrari C, Cavallini A (1991) Cluster headache-course over ten years in 189 patients. Cephalalgia 11:169–174
3. Leone M, Franzini A, Proietti Cecchini A, Mea E, Broggi G, Bussone G (2009) Cluster headache: pharmacological treatment and neurostimulation. Nat Clin Pract Neurol 5:153–162
4. The Sumatriptan Cluster Headache Study Group (1991) Treatment of acute cluster headache with sumatriptan. N Engl J Med 325:322–326

5. Leone M, Franzini A, Broggi G, Bussone G (2006) Hypothalamic stimulation for intractable cluster headache: long-term experience. Neurology 67:150–152
6. Ekbom K et al (1995) Cluster headache attacks treated for up to three months with subcutaneous sumatriptan (6 mg). Sumatriptan Cluster Headache Long-term Study Group. Cephalalgia 15:230–236
7. Göbel H (1998) Acute therapy for cluster headache with sumatriptan: findings of a one-year long-term study. Neurology 51:908–911
8. Dodick DW et al (2004) Cardiovascular tolerability and safety of triptans: a review of clinical data. Headache 44(Suppl 1):S20–S30
9. D'Amico D, Rigamonti A, Solari A, Leone M, Usai S, Grazzi L, Bussone G (2002) Health-related quality of life in patients with cluster headache during active periods. Cephalalgia 22(10):818–821
10. Leone M, Franzini A, Bussone G (2001) Stereotactic stimulation of posterior hypothalamic gray matter for intractable cluster headache. NEJM 345(19):1428–1429
11. Schoenen J, Di Clemente L, Vandenheede M et al (2005) Hypothalamic stimulation in chronic cluster headache: a pilot study of efficacy and mode of action. Brain 128:940–947
12. Starr PA, Barbaro NM, Raskin NH, Ostrem JL (2007) Chronic stimulation of the posterior hypothalamic region for cluster headache: technique and 1-year results in four patients. J Neurosurg 106:999–1005
13. Bartsch T, Pinsker MO, Rasche D et al (2008) Hypothalamic deep brain stimulation for cluster headache–experience from a new multicase series. Cephalalgia 28(3):285–295
14. Owen SLF, Green AL, Davies P et al (2007) Connectivity of an effective hypothalamic surgical target for cluster headache. J Clin Neurosci 14(10):955–960
15. Magis D, Allena M, Bolla M, De Pasqua V, Remacle JM, Schoenen J (2007) Occipital nerve stimulation for drug-resistant chronic cluster headache: a prospective pilot study. Lancet Neurol 6:314–321
16. Burns B, Watkins L, Goadsby PJ (2007) Treatment of medically intractable cluster headache by occipital nerve stimulation: long-term follow-up of eight patients. Lancet 369(9567):1099–1106
17. Schwedt TJ, Dodick DW, Hentz J, Trentman TL, Zimmerman RS (2007) Occipital nerve stimulation for chronic headache—long-term safety and efficacy. Cephalalgia 27:153–157
18. May A, Bahra A, Buchel C, Frackowiak RS, Goadsby PJ (1998) Hypothalamic activation in cluster headache attacks. Lancet 352:275–278
19. May A, Ashburner J, Buchel C, McGonigle DJ, Friston KJ, Frackowiak RS, Goadsby PJ (1999) Correlation between structural and functional changes in brain in idiopathic headache syndrome. Nat Med 7:836–838
20. Goadsby PJ (2002) Pathophysiology of cluster headache: a trigeminal autonomic cephalgia. Lancet Neurol 1:251–257
21. May A (2005) Cluster headache: pathogenesis, diagnosis, and management. Lancet 366:843–855
22. Leone M, Proietti Cecchini A, Franzini A, Broggi G, Cortelli P, Montagna P, May A, Juergens T, Cordella R, Carella F, Bussone G (2008) Lessons from 8 years' experience of hypothalamic stimulation in cluster headache. Cephalalgia 28:789–797
23. Leone M, May A, Franzini A et al (2004) Deep brain stimulation for intractable chronic cluster headache: proposals for patient selection. Cephalalgia 24(11):934–937
24. Leone M, Proietti A, Mea E, D'Amico D, Tullo V, Grazzi L, Bussone G (2008) Therapeutic neurostimulation in chronic headaches: problems of patient selection. Neurol Sci 29:S59–S61
25. Leone M, Franzini A, Proietti Cecchini A, Broggi G, Bussone G (2007) Stimulation of occipital nerve for drug-resistant chronic cluster headache. Lancet Neurol 6(4):289–291
26. Lipton RB, Micieli G, Russell D, Solomon S, Tfelt-Hansen P, Waldenlind E (1995) Guidelines for controlled trials of drugs in cluster headache. Cephalalgia 15:455–462

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# Antimigraine drugs: new frontiers

**A. Rapoport**

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**Abstract** There are many acute care and preventive medications for the treatment of migraine. However, patients may often find that their headaches are not under optimal control. There are several targets that have been looked at and studied for the production of new, more effective medications. There are also effective devices for therapy of migraine. A list of targets will be put forth and a small number of them will be described in greater detail in this paper.

**Keywords** Migraine · Migraine treatment · Botulinum toxin type A · CGRP antagonists · Dihydroergotamine · Ketorolac · Sumatriptan

## Introduction

Migraine is a chronic and at times disabling disorder, usually consisting of attacks of significant headache, various associated symptoms (i.e. nausea, vomiting, sonophobia, photophobia and worsening with exertion) and sometimes visual or other types of auras. It affects about 12% of the population of the US and other Western countries. There are several categories of acute care medications including over the counter substances and prescription medications. They include simple analgesics, combination analgesics, NSAIDs, prescription analgesics, ergots and triptans.

In Europe and Canada, the first triptan was launched in 1991. In the US, it was first available in 1993 and today there are seven triptans available with a variety of formulations including tablets, injections, orally disintegrating tablets and nasal sprays. Although triptans are usually considered as the first-line treatment for acute care of migraine attacks, some patients cannot afford them, over one-third of patients do not respond ideally to triptans and over half are willing to try other treatments than the one they are currently taking.

There are only five preventive medications approved by the FDA and only four of them are available in the US at this time, two beta blockers and two antiepileptic medications. However, none of them works in more than 50% of patients and they all have significant possible adverse events.

There are multiple targets that form the basis for possible new acute care and preventive treatments for migraine. This paper will list many categories of them and concentrate on some new drugs which may become available within the next few years.

## Categories of future acute care and preventive medication for migraine

There are many future targets and some are being investigated as possible new therapies and others have already led to the creation of drugs that are currently in clinical trials [1]. What follows is a listing of future targets:

1. Calcium channel modulators
2. Sodium channel blockers (lacosamide, a slow sodium channel blocker)
3. Glutamate blockers
4. Novel antiepileptics (SV2A blockers, e.g. levetiracetam)
5. GABA enhancers and analogs (valproate)
6. $AT_2$ (angiotensin 2 inhibitors)

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7. Alpha-2 agonists
8. 5-$HT_{2A}$ antagonists
9. 5-$HT_7$ antagonists
10. Acetylcholine receptor modulators
11. BDNF modulators (brain-derived neurotrophic factor)
12. Orexin-melatonin pathway modulators
13. Dopamine antagonists delivered by oral inhalation (prochlorperazine and loxapine)
14. Sigma receptor agonists (dextromethorphan and others)
15. Non AMPA-kainate glutamate receptor modulators
16. Potassium current modulators
17. Chloride channel enhancers
18. Connexin hemi-channel modulators (tight junction antagonists, e.g. tonabersat)
19. NOS inhibitors (nitric oxide synthase)
20. Arachidonic cascade modulators (COX-2 and cysteinyl leukotriene antagonists)
21. Astrocytic calcium wave inhibitors
22. Existing and new 5-$HT_{1B/D/F}$ agonists
23. CGRP antagonists (olcegepant and telcagepant)
24. Glutamate modulators (memantine and tezampanel)
25. Anti-inflammatory drugs [NSAIDs: ketorolac nasal spray (ROX-828) and diclofenac (PRO-153)]
26. COX-3 inhibitors (dipyrone in Brazil)
27. Peripheral cannabinoid agonists ($CB_1$ —dronabinol)
28. $TRPV_1$ antagonists (+civamide-like drugs)
29. NSAIDs
30. Prostanoid antagonists
31. Others.

## CGRP receptor antagonists

Calcitonin gene-related peptide, closely related structurally to calcitonin and amylin, has been intensely studied over the last 20 years as an agent possibly related to migraine pathophysiology. CGRP is involved in sensory neurotransmission and can be found in most sensory nerves, especially those trigeminovascular afferents in the meninges involved in migraine [2]. It is one of the most potent vasodilators known. CGRP levels measured in the jugular venous system are elevated after migraine and cluster headache attacks, and are normalized by therapy with sumatriptan. For years, it was thought that blocking its dilating effect might help to treat migraine and its antagonism held promise to be a novel strategy to relieve migraine headache. It is now known to effectively block migraine pain without overt vasoconstriction. If and when they gain approval in the US by the FDA and in other countries, CGRP receptor antagonists would be the first non-serotonergic, non-vasoconstricting, migraine specific medication.

CGRP has been shown to have several sites of action including blood vessels, mast cells in the meninges and as a facilitator of pain transmission the brain stem [3]. CGRP receptors have been found in trigeminal ganglion, in the brain stem in neurons of the trigeminal nucleus caudalis and in smooth muscle of the meningeal vasculature [6]. CGRP can be blocked by a fragment of the peptide containing amino acids 8-37 (CGRP 8-37). The first effective CGRP receptor blocker was BIBN4096 (olcegepant). It was reported that intravenous administration helped a significant number of patients versus placebo, without constricting blood vessels in preclinical studies [4]. Telcagepant, previously termed MK-0974, was the first reported oral formulation of a CGRP receptor antagonist. It has been reported to work well in migraine in a phase IIB study published in Neurology and recently in a phase III study published in *Lancet* [5, 6]. Preclinical data suggest that telcagepant is not a vasoconstrictor and clinical studies show it to be as effective as rizatriptan and zolmitriptan and as tolerable as placebo. It is predicted that this drug could be launched in 2010, possibly to be followed by one or two competitors sometime afterwards.

In the recently published article, telcagepant 300 mg was found to be as effective as zolmitriptan with fewer adverse events [6]. This was a randomized, parallel-treatment, placebo and active-controlled, double-blind, trial performed at 81 sites in Europe and the USA of adults with migraine diagnosed by International Headache Society criteria. Patients treated moderate or severe migraine attacks with either oral telcagepant 150 or 300 mg, zolmitriptan 5 mg, or placebo. There were five co-primary endpoints: pain freedom, pain relief and absence of nausea, photophobia and phonophobia, at 2 h after treatment.

According to Dr. Ho's article, "1,380 patients were randomly assigned to receive telcagepant 150 mg ($n = 333$), 300 mg ($n = 354$), zolmitriptan 5 mg ($n = 345$) or placebo ($n = 348$). Telcagepant 300 mg was more effective than placebo for pain freedom (95 [27%] of 353 patients vs. 33 [10%] of 343 [$P < 0.0001$]), pain relief (194 [55%] of 353 vs. 95 [28%] of 343 [$P < 0.0001$]), and absence of phonophobia (204 [58%] of 353 vs. 126 [37%] of 342 [$P < 0.0001$]), photophobia (180 [51%] of 353 vs. 99 [29%] of 342 [$P < 0.0001$]), and nausea (229 [65%] of 352 vs. 189 [55%] of 342 [$P = 0.0061$]). The efficacy of telcagepant 300 mg and zolmitriptan 5 mg were much the same, and both were more effective than telcagepant 150 mg. Adverse events were recorded for 31% taking telcagepant 150 mg, 37% taking telcagepant 300 mg, 51% taking zolmitriptan 5 mg, and 32% taking placebo." The measurement of 2–24 h sustained pain freedom was slightly better numerically for telcagepant 300 mg versus zolmitriptan 5 mg, but there was no statistical difference.

A potential benefit of telcagepant and other CGRP receptor antagonists is the lack of vasoconstriction in animal models. This suggests that they may be able to be given to patients with vascular disease, but that was not studied in this trial as zolmitriptan is contraindicated in patients with vascular disease and will have to be studied in the future.

## Transdermal patches

Recently, sumatriptan became the first of the seven triptans to become generic in several countries, which has led to the development of generic formulations of available products and to the design of some novel products containing the generic formulation, including needle-less injection, sublingual, intranasal and patch forms. One of the most interesting products in development, which may address the unmet need of the nauseated migraineur and/or the patient who does not absorb oral medication optimally during a migraine attack, is a sumatriptan patch. NP101, from NuPathe, is an iontophoretic patch that delivers sumatriptan transdermally. It utilizes a small electric current to drive sumatriptan across the skin delivering 6 or 12 mA/h and maintaining sumatriptan plasma levels above the target level of $\geq$10 ng/ml for greater than 7 h [7]. There is a linear relationship between the applied current and drug delivery. As a result, drug delivery is precisely controlled at desired levels, providing consistent therapeutic drug levels. In pK studies, the patch delivered sumatriptan more consistently than either the 100 mg oral tablet or 20 mg nasal preparation. This finding supports the hypothesis that parenteral administration (subcutaneous or transdermal) provides more predictable delivery by bypassing absorption through the GI tract.

At the intended plasma concentrations delivered by the patch, which were in between those of the 20 mg nasal spray and 100 mg oral tablet, the patches were well tolerated. No subject reported atypical pain and pressure sensations or other common triptan adverse events after application of NP101 patches. The most common adverse event for NP101 was application site-related pruritus, which was generally mild and resolved without treatment. No subject withdrew from the study due to local skin irritation. The data suggest that transdermal iontophoretic delivery of sumatriptan with NP101 may offer significant clinical utility for migraine patients, including circumventing underlying migraine-associated GI disturbances including nausea and gastric stasis. The patch also provides consistent, predictable delivery of desired drug levels over a 4 h period. This offers the potential to avoid atypical pain, pressure and other sensations commonly associated with current triptan formulations.

## Oral inhalers

Three drugs are being tested as inhalers: DHE, prochlorperazine and loxapine. The last two are dopamine antagonists, a class of drugs that has been shown to treat migraine acutely when given intravenously. DHE (dihydroergotamine mesylate) has been available in various forms for over 50 years and still remains the mainstay of treatment at major headache centers in the US when patients require hospitalization or comes to the emergency room after having already developed central sensitization. It is usually given several times per day intravenously. It is also used orally in Europe as a preventive and intranasally in the US and Canada as an acute care medication. The intravenous preparation is often very effective, but cannot be used at home and often causes the patient to become more nauseated or even vomit, in spite of pretreatment with an antiemetic. Oral inhalation seems to provide similar efficacy with the ease of home use and fewer adverse events.

Studies were performed with a specially designed device called the Tempo Inhaler (MAP Pharma), to deliver DHE deep into the lung after breath actuation [8].

A phase I study of four doses of orally inhaled DHE delivered by the specially designed inhaler versus 1 mg of IV DHE ($n = 18$) was performed. There was a rapid systemic absorption of DHE with a $t_{max}$ of 12 min with a 0.88 mg respirable dose (vs. a 6 min $t_{max}$ with the IV preparation). The systemic levels attained were slightly lower than with IV DHE, with the ratio of AUC 0-infinity of inhaled versus IV approximately 0.77. The Tempo® inhaler is a proprietary, novel, breath-actuated device that is expected to deliver most of the drug to the deep lung, thereby minimizing oropharyngeal deposition. Phase II data suggest an onset of action comparable to IV administration of DHE, with relief that is both rapid and sustained [9]. Phase II results demonstrate that 32% of patients achieve pain relief as early as 10 min ($P = 0.019$) at 0.5 mg dose. This is somewhat lower that the usual dose IV.

DHE delivered by this inhaler was well tolerated in phase II studies with no serious adverse events. There was decreased nausea and no clinically significant changes observed in pulmonary function tests, clinical lab findings, heart rate, blood pressure or respiratory rate. Phase III studies are ongoing and have been designed to confirm that the onset of action is 10 min versus placebo, that there is sustained pain relief and freedom over 24 and 48 h, with good safety and tolerability.

## Nasal sprays

There are three nasal sprays currently in use for the acute treatment of migraine in the US, including two triptans,

sumatriptan and zolmitriptan and DHE. Intranasal ketorolac has been studied in a convenient, single dose device in a formulation specifically designed for episodic use. It provides a *p*K profile equivalent to that of ketorolac administered intramuscularly. Ketorolac is a racemic NSAID, which inhibits the cyclooxygenase system (COX 1 and COX 2), and hence prostaglandin synthesis, with potent analgesic and moderate anti-inflammatory activity. It is highly water soluble and can be delivered in an amount suitable for intranasal administration (100 μl).

In a phase I, single dose, five-way crossover, randomized study, absorption of ketorolac started immediately, and median $t_{max}$ ranged from 0.50 to 0.75 h postdose, irrespective of the dose of ketorolac [10]. There was a terminal phase half-life of approximately 5–6 h. Very similar profiles were observed for the IM doses.

Ketorolac has no active metabolites and is metabolized in the liver by glucuronidation and parahydroxylation. Further studies compared the pharmacokinetics of intranasal versus intramuscular dosing. ROX-828, from Roxro, is a nasal spray formulation of ketorolac composed of 30 mg + 12 mg lidocaine, which reduces nasal irritation. The *p*K profile is equal to or better than ketorolac given intramuscularly. The preparation utilizes a single dose device with two available sprays. The plasma concentration curves show that this intranasal formulation achieves peak blood levels faster than IM injections.

A phase II trial, done in Germany and Finland, consisted of a double-blind, placebo- controlled, randomized, single dose study using 30 mg of ketorolac.

The primary endpoint was 2 h pain freedom. The *n* was ROX-828 = 68 and placebo = 73. The primary end point just missed significance (if 3 outlier patients were removed, the primary endpoint was significant at 2 h). Pain relief was significant at 1, 1.5, 2, 3 and 4 h. An intranasal dose of 30 mg produced plasma level roughly equivalent to 20 mg intramuscularly. Further studies are planned, possibly with a higher dose.

## Gap junction blocker (preventive)

Tonabersat is a novel benzoyl-aminobenzopyran anticonvulsant and antimigraine medication developed by SmithKline Beecham. It binds selectively with high affinity to a unique stereoselective site on neurons and glia. It has no affinity for any other previously established antiepilepsy or antimigraine site. Tonabersat inhibits cortical spreading depression number and duration. Unpublished studies with carabersat (a close structural analog) in a rat hippocampal slice model, demonstrated that the action of the class is related to the inhibition of neuronal-glial gap junctions. There was also inhibition of electrical coupling of GABAergic inter-neurons. Tonabersat is 2–3 times more potent than carabersat. Recent rat trigeminal ganglion research in vivo indicated that the effect of tonabersat on gap junctions (hemi-channel communication) is mediated by *connexin 26*.

Early studies were done for acute treatment of migraine and only showed a trend for efficacy. A trial investigated the efficacy of SB-220453 in the glyceryltrinitrate (GTN) human experimental migraine model [11]. The study reported, "15 patients with migraine without aura entered a randomized, double-blind, crossover study with 40 mg or placebo followed by a 20-min GTN infusion. Four subjects had a hypotensive episode after SB-220453 plus GTN but none after GTN alone. The reaction was unexpected, since animal models and previous human studies had shown no vascular or sympatholytic activity with SB-220453. The study was terminated prematurely because of this interaction. SB-220453 had no significant pre-emptive anti-migraine activity compared with placebo in this human model of migraine."

Tonabersat was then studied as a preventive migraine agent. According to the Minster Pharmaceuticals website, "Tonabersat completed a phase IIA clinical trial in prophylaxis (prevention) of migraine in 2007. Positive data from this study include a significant increase in subjects classed as 'responders'—defined as a 50% or greater reduction in migraine attacks at the end of the 3 months of treatment—on tonabersat compared with those on placebo. The figures were 62% for tonabersat compared with 45% for placebo ($P < 0.05$)."

A double-blind, controlled, randomized clinical trial of migraine with and without aura was performed in patients on no preventive migraine medication. The doses were 20–40 mg, given once daily, for 3 months. The reduction in migraine days was 3.7 days for placebo and 4.4 days for tonabersat, which was not significant. Adverse events were generally mild and the drug was well tolerated. Fifty-one percent of placebo patients and 61% of tonabersat patients had treatment-emergent AEs. Treatment-related adverse events were 15% for placebo and 39% for tonabersat. Adverse events leading to withdrawal were two for tonabersat (nausea and dizziness) and one for placebo (dizziness and memory impairment). There were no laboratory abnormalities. Apparently, a phase IIB trial did not meet its primary endpoint as announced by Minster Pharmaceuticals in early February 2009. The future development of this migraine medication is unclear.

## Neurotoxin therapy: botulinum toxin injections (preventive)

Although the exact mechanism of action of botulinum toxin type A injections as a treatment for headache are not

known, it is thought that that the antinociceptive action is probably independent of its anti-cholinergic effects at the neuromuscular junction. It is no longer believed that the relaxation or induced weakness of muscles contributes to the therapeutic effect. Instead inhibition of peripheral sensitization, leading to the inhibition of central sensitization through the blocking of glutamate, substance P and CGRP peripherally, is thought to lead to the therapeutic effect. There have been many positive open trials and a few double-blind, controlled studies with conflicting reports of efficacy. In a chronic migraine trail, in which the primary endpoint was not reached, efficacy was shown only in a subgroup not taking preventive medication [12].

A recent study to compare the effectiveness of treatment of transformed migraine between botulinum toxin type A and topiramate demonstrated that both groups had significantly fewer headaches compared with baseline 6 months after the start of therapy. At 9 months, the two treatments were equivalent. More patients in the topiramate group dropped out of the study due to adverse events [13]. Another recent study compared botulinum toxin type A with divalproex in episodic and chronic migraine. The data demonstrate that both treatments showed a significant reduction in disability with fewer adverse events in the botulinum toxin type A treated group [14].

Two large, double-blind, placebo-controlled, randomized phase III trials were performed in patients with chronic migraine according to the IHS definition who were not on preventive medication. Although the results have not been released or published, a press release was issued by Allergan in September 2008 about the results [15].

The primary endpoint for the first trial was change from baseline in the number of headache episodes at the end of 3 months. In the second trial, the primary endpoint was the change in number of headache days in a 28-day period at the end of 3 months. In the second phase III study, the primary endpoint and secondary endpoint showed statistically significant benefit of botulinum toxin type A treatment over placebo injections. Patients treated with botulinum toxin type A demonstrated a greater decrease in both number of headache days ($P < 0.001$) (primary endpoint) and number of headache episodes ($P = 0.003$) (secondary endpoint). However, the first phase III study did not meet its primary endpoint. It is thought that if the FDA suggested endpoint had been used (decrease in number of headache days), the first study would also have been significant. It is suspected that Allergan will file for an indication for treatment of chronic migraine with botulinum toxin type A sometime in 2009, based on these two phase III studies.

## Conclusion

There are many new acute care and preventive therapies being investigated for the treatment of migraine. A few of them, which should be available in the near future, have been presented here. I am cautiously optimistic that some of them will make it to the clinic and will be effective additions to the headache specialist's armamentarium.

**Conflict of interest statement** A. Rapoport is on the Advisory Boards of NuPathe, MAP and Roxro. A. Rapoport is an author of the Phase IIB study on telcagepant.

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## References

1. Ramadan NM, Buchanan TM (2006) New and future migraine therapy. Pharmacol Ther 112:199–212
2. Goadsby PJ, Edvinsson L (1993) The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. Ann Neurol 33: 48–56
3. Levy D, Burstein R, Strassman AM (2005) Calcitonin gene-related peptide does not excite or sensitize meningeal nociceptors: implications for the pathophysiology of migraine. Ann Neurol 58:698–705
4. Olesen J, Diener HC, Husstedt IW et al (2004) Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine. N Engl J Med 350:1104–1110
5. Ho TW, Mannix LK, Fan X et al (2008) Randomized controlled trial of an oral CGRP receptor antagonist, MK-0974, in acute treatment of migraine. Neurology 70:1304–1312
6. Ho TW, Ferrari MD, Dodick DW et al (2008) Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial. Lancet 372:2089–2090
7. Pierce M, Marbury T, O'Neill C et al (2008) A novel patch formulation of sumatriptan succinate utilizing SmartRelief™ transdermal technology. Data presented at the 50th annual scientific meeting of the American Headache Society 28 June 2008
8. Armer T, Shrewsbury S, Newman S et al (2007) Aerosol delivery of ergotamine tartrate via a breath-synchronized plume-control inhaler in humans. Curr Med Res Opin 23:3177–3187
9. Shrewsbury S, Cook R, Taylor G et al (2008) Safety and pharmacokinetics of dihydroergotamine mesylate administered via a novel (TEMPO®) Inhaler. Headache 48:355–367
10. McAleer SD, Majid O, Venables E et al (2007) Pharmacokinetics and safety of ketorolac following single intranasal and intramuscular administration in healthy volunteers. J Clin Pharmacol 47:13–18
11. Tvedskov JF, Iversen HK, Olesen J (2004) A double-blind study of SB-220453 (Tonerbasat) in the glyceryltrinitrate (GTN) model of migraine. Cephalalgia 24:875–882
12. Dodick DW, Mauskop A, Elkind AH et al (2005) Botulinum toxin type A for the prophylaxis of chronic daily headache: subgroup analysis of patients not receiving other prophylactic

medications: a randomized double-blind, placebo-controlled study. Headache 45:315–324
13. Mathew NT (2008) A double-blind comparison of botulinum toxin type A (BoNTA) and topiramate for the prophylactic treatment of transformed migraine headaches: a pilot study. Presented at the 12th congress of the European Federation of the European Societies: 23–26 Aug 2008, Madrid, Spain
14. Blumenfeld AM, Schim JD, Chippendale TJ (2008) Botulinum toxin type A and divalproex sodium for prophylactic treatment of episodic or chronic migraine. Headache 48:210–220
15. Allergan announces positive top-line results from phase III BOTOX headache program—Released 11 Sept 2008 0900 a.m. Eastern Daylight Time

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# Migraine prevalence in eating disorders and pathophysiological correlations

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**Abstract** The eating disorders (ED): anorexia nervosa (AN) and Bulimia nervosa (BN) are severe psychiatric and somatic conditions occurring mainly in young woman. Although the etiology is largely unknown, same evidences suggest that biological and psychological factors play a relevant role in the pathogenesis, along with monoamine, indole and same hypothalamic hormonal dysfunctions. Migraine is characterized by similar metabolic and psychological anomalies suggesting that a possible relationship exists between the two pathological conditions. In order to understand the possible relationship between migraine and ED, we have investigated the prevalence of migraine and the other primary headaches in a large group of AN and BN patients. In addition, we have studied the role of tyrosine metabolism in the same group of AN and BN young woman sufferers. In particular, we measured plasma levels of elusive amines: tyramine (Tyr) and octopamine (Oct) and catecholamines: noradrenalin (NE), dopamine (DA). The results of this study show that the prevalence of migraine in the woman affected be EA is very high (>75%). The levels of Tyr and DA were higher and levels of NE were lower in the ED patients with respect to the control subject. These biochemical findings suggest that abnormalities of limbic and hypothalamic circuitries play a role in the pathogenesis of ED. The very high prevalence of migraine in our group of ED sufferers and the biochemical profile of migraine, similar to that ED patients have shown in this study, suggest that migraine may constitute a risk factor for the occurrence of ED in the young females. This hypothesis is supported by the onset of migraine attacks that initiated, in the majority of the patients, before the occurrence of ED symptoms.

**Keywords** Eating disorders · Migraine · Noradrenalin · Dopamine · Trace amines

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## Introduction

Eating disorders (ED) such as anorexia nervosa (AN) and bulimia nervosa (BN) are the severe psychiatric and somatic pathological conditions that occur mainly in young woman [1]. The etiology of ED is poorly understood, although psychological and biological factors may play a significant role in the physiopathology of this disorder [2]. Among psychological factors depression, low self-esteem, insecure attachment, obsessive trait, anxiety, etc. seem be identified, thus far, with a reasonable degree of evidence. Longitudinal studies have found that same of the symptoms linked to these risk factors clearly precede the onset of the illness. Among biological factors, abnormalities of serotonin (5-HT), noradrenalin (NE) and dopamine metabolism have been reported in anorexic animal models and same human studies [3, 4]. The anomalous eating behavior, the

absence of menses and the sexual appetite that characterize the ED disease suggest that anomalies in these neurotransmitters are localized in the limbic, hypothalamic and dopaminergic circuitries [5].

Intriguingly, migraine presents similar catecholamine dysfunctions as ED [6]. In addition, the high levels of trace amines such as tyramine (Tyr) and octopamine (Oct), in plasma and platelets, recently found in migraine patients, suggest that anomalies of hypothalamic and limbic areas contribute to migraine physiopathology, as trace amine associated receptors are localized in the brain areas [7]. Indeed, many of the symptoms of ED patients are attributed to the anomalies of the same brain regions [8]. However, while these findings suggest migraine and ED may, to same degree, share similar underlying physiopathological aspects, no information is available to possible prevalence of migraine among ED patients and it is unknown whether anomalies in the metabolism of trace amines play a role in the pathogenesis of ED. To ascertain this hypothesis we, here, evaluate plasma levels of NE, DA, Tyr and Oct in a large group of ED sufferers. We also assess the prevalence of migraine and the other primary headaches in the same patient sample.

## Methods

NE, DA Tyr and Oct were measured in plasma of 109 patients affected by anorexia ($n = 89$, 71.2%) or bulimia nervosa ($n = 36$, 28.8%) and 27 healthy control subjects matched for age and sex with the patients. The diagnosis of each type of ED syndrome was, in accordance with the DSM-IV criteria [9], made utilizing the body mass index (BMI) (below 17.5 for anorexia, under 17.5 for bulimia). Forty-eight patients were free from pharmacological treatment (44%); 61 (56%) patients were under antidepressant therapies (Table 1). In the subject, peripheral venous blood (25 ml) was drown by the same operator from the antecubital vein, following overnight fasting, at 9 a.m. at supine position and collected in fr/10 volume citric acid/citrate dextrose as anticoagulant for estimation of the biochemical markers. Platelet poor plasma (PPP) was obtained as described elsewhere [10] An aliquot of perchloric acid was added to PPP (total volume 4 ml) for the deproteinization. After brief centrifugation (14,000 rpm for 5 min), the supernatant was passed through an ultrafilter membrane. The levels of NE, DA, Tyr and Otc were evaluated using an HPLC coulometric method.

Statistical analysis was conducted by SPSS version 13. Sample distribution was evaluated using Kolmogorov–Smirnov test. Groups with Gaussian distribution were compared by Welch $t$ test, while groups displaying non-parametric distribution were compared by Mann–Whitney test.

A neurologist expert in the diagnosis and treatment of primary headaches interviewed all ED patients. Migraine and the other primary headaches present among ED sufferers were diagnosed in agreement of HIS diagnostic criteria 2004 second edition [11].

## Results

### Biochemical results

NE was detected in plasma of 103 out of 125 patients and in all controls subjects, DA in 74/107 patients and 13/26 controls, Tyr in 106/107 patients and 25/27 controls, and

**Table 1** Characteristics of the population studied

| | ED, $n = 109$ | AN, $n = 76$ (69.7%) | BN, $n = 33$ (30.0%) | C, $n = 27$ |
|---|---|---|---|---|
| Gender | All females | | | |
| Age (years) | | | | |
| Mean ± SD | 26.56 ± 8.498 | 26.18 ± 8.128 | 26.06 ± 8.778 | 27.73 ± 6.247 |
| Range | 16–58 | 16–58 | 17–56 | 20–53 |
| BMI ± SD | 17.29 ± 4.816 | 14.93 ± 2.488 | 22.53 ± 4.130 | |
| Patient treated | 61 (55.96%) | 42 (54.7%) | 19 (58.1%) | |
| Antidepressive[a]1 | 54 | 38 | 16 | |
| Antipsychotic[b]2 | 16 | 9 | 7 | |
| Benzodiazepine[c]3 | 37 | 26 | 11 | |
| Patient without pharmaceutical therapy | 48 (44.04%) | 34 (45.3%) | 14 (41.9%) | 27 |

*ED* eating disorders patient, *AN* anorexia nervosa, *BN* Bulimia nervosa, *C* control subjects

[a] 1 and stabilizant (SSRI 20 mg/day, valproic acid 400–600 mg/day)

[b] 2 (densapro 5–10 mg/day)

[c] 3 (bromazepan 3–6 mg/day)

Oct in 62/107 patients and 19/26 controls. In comparison with the control subjects, the plasma levels of DA and Tyr were significantly higher in ED patients ($P = 0.05$, $P < 0.001$), whereas the plasma levels of NE were lower in the patient group ($P < 0.04$). The levels of Oct were in the same range in both subject groups (Table 2).

Upon comparison of the NE, DA, Tyr and Oct levels in the anorexic to those of bulimic patients and of the each group of those of the control subjects, we found that DA and NE plasma levels were in the same range in the two patient groups. In contrast, Tyr plasma levels were significantly higher in bulimic patient group when compared with levels found in both the anorexic and control group ($P = 0.02$, $P = 0.03$, respectively). The Oct plasma levels were more elevated in anorexic group that those of the bulimic group ($P = 0.03$) and the Oct levels of the bulimic group were significantly lower to that of control subjects ($P = 0.05$) (Table 3).

Prevalence of primary headaches among ED patients

One hundred and nine patients affected by either anorexia ($n = 76$, 70%) and/or bulimia nervosa ($n = 33$, 30%), afferent to ED Center of Eating Disorders, were enrolled in the study. All subjects were female, age of them ranged between 18 and 32 years (mean age range = 25). The diagnosis of migraine with and without aura of migraine or other primary headaches was made in accordance with HIS criteria [11] utilizing a questionnaire that included questions about the presence of migraine in parental first-degree relatives of the patients and characteristics of the headache attacks, i.e. frequency and duration. Ninety-one ED patients complained of primary headaches (84.4%). Eight-one ED patients satisfied HIS criteria for the diagnosis of migraine (89%), of which 16 (55%) present migraine without aura (MwwA), tree (2.8%) present migraine with aura (MwA), five (4.6%) with probable MwwA, eight (7.3%) with possible MwwA, and five (4.6%) present a chronic migraine. Six (6.6%) ED patients were affected by tension-type headache, four (4,4%) patients present non-classifiable headache. Twelve ED patients not suffering from migraine (11%), but have a first-degree relative affected by MWWA. In 16, two patients (68.1%) the migraine attacks begun a prior to the onset of ED symptoms, in 15 patients (16.5%) the attacks initiated at the same time, and in the minority (14 patients, 15%) migraine appeared after the onset of ED symptoms (Table 4). The frequency of the attacks in ED patients affected by migraine ranged between 1 and 15 attacks/month and the duration between 8 and 72 h or more. No statistical differences in the frequency and duration of migraine attacks were found between the anorexic and bulimic patients.

**Table 2** Plasma levels of tyramine, octopamine, noradrenalin, dopamine, in ED patients and control subjects

| | ED ($n = 109$) M/SD | C ($n = 27$) M/SD | *P* |
|---|---|---|---|
| Tyramine | 0.855/0.615 | 0.686/0.342 | 0.05** |
| Octopamine | 1.178/1.736 | 1.293/1.354 | NS* |
| Noradrenaline | 104.264/115.509 | 153.181/73.197 | 0.039** |
| Dopamine | 14.0037/17.018 | 2.877/4.119 | 0.001* |

*M* mean, *SD* standard deviation, ED eating disorders patient, *C* control subjects

* Mann–Whitney two-tailed unpaired test

Values are expressed as ng/mL

## Discussion

The results of this study indicate that a possible relationship exists between ED and migraine. The prevalence of migraine in woman affected by ED is very high (74.5%) in comparison with that of the general population (12–15%)

**Table 3** Plasma levels of tyramine, octopamine, noradrenalin, dopamine in anorexia, bulimic patient and control subjects

| | AN (M/SD) | BN (M/SD) | C (M/SD) | *P* |
|---|---|---|---|---|
| Tyramine | 0.774/0.565 | 1.087/0.699 | 0.686/0.342 | AN versus ctrl: NS** |
| | | | | BN versus ctrl: 0.035* |
| | | | | AN versus BN: 0.026* |
| Octopamine | 1.345/1.904 | 0.7082/1.022 | 1.293/1.354 | AN versus ctrl: NS** |
| | | | | BN versus ctrl: 0.05** |
| | | | | AN versus BN: 0.03** |
| Noradrenalin | 105.412/122.756 | 101.189/95.345 | 153.181/73.197 | AN versus ctrl: <0.001* |
| | | | | BN versus ctrl: 0.028** |
| | | | | AN versus BN: NS* |
| Dopamine | 12.849/16.537 | 17.261/2.877 | 2.877/4.119 | AN versus ctrl: 0.006* |
| | | | | BN versus ctrl: <0.001* |
| | | | | AN versus BN: NS* |

Values are expressed as ng/mL

*M* mean, *SD* standard deviation, *AN* anorexia nervosa, *BN* Bulimia nervosa, *C* control subjects

* Mann–Whitney two-tailed unpaired test

** *t* test

**Table 4** Prevalence of headache patients among ED sufferers

| | | | |
|---|---|---|---|
| Total patient | 109 | | |
| Patient with headache | 91 (84.4%) | | |
| Migraine | 81 (74.3%) | | |
| MwA3 | (2.8%) | | |
| MwwA | 60 (55%) | | |
| MwwAps | 8 (7.3%) | | |
| MwwApr | 5 (4.6%) | | |
| CM 5 (4.6%) | | | |
| Tension headache | 6 (5.5%) | | |
| ETH | 3 (2.8%) | | |
| CTH | 3 (2.8%) | | |
| Other headaches | 4 (3.7%) | | |
| Onset of headache | ED | AN | BN |
| Before ED | 62 (68.1%) | 46 (73.0%) | 16 (48.5%) |
| Corresponding to ED | 15 (16.5%) | 10 (15.9%) | 5 (15.1%) |
| After ED | 14 (15.4%) | 7 (11.1%) | 7 (25.0%) |
| Total patient | 91 | 76 | 33 |

*MwA* migraine with aura, *MwwA* migraine without aura, *MwwAps* migraine without aura possible, *MwwApr* migraine without aura probably, *CM* chronic migraine, *ETH* episodic tension headache, *CTH* chronic tension headache

[12] and in the majority of patients, the onset of migraine attacks began prior to or in the same time of the first ED symptoms. The results of biochemical study support this hypothesis. In comparison with control subjects, ED patients present significantly higher dopamine plasma levels, whereas noradrenalin, derived from its precursor dopamine, via the activation of dopamine $\beta$-hydroxylase enzyme activity [13], significantly lower plasma levels. The plasma levels of tyramine, product of tyrosine decarboxylase enzyme activity with tyrosine being the substrate [14], are significantly higher in ED versus controls, whereas those of the octopamine are apparently similar in both patient groups. However when these data, which includes both the anorexic and bulimic patent groups, are disaggregated, their profiles change. The anorexic patients show tyramine and octopamine plasma levels in the same range as those of controls. The only relevant data in this patient group is that the plasma levels of octopamine inversely correlate with BMI (Pearson test, $P < 0.04$) suggesting that the higher levels of octopamine are related with the severity of the anorexia. In contrast, in comparison with controls and anorexic subjects, tyramine is significantly higher, and octopamine is significantly lower in the bulimics. The interpretation of this anomaly of tyrosine levels in ED patients is uncertain; however, the large accumulation in plasma of dopamine and the low levels of noradrenalin strongly suggest that the activity of DBH is reduced in both anorexic and bulimic patients. The different profiles of tyramine and octopamine plasma levels may indicate that the possible shift from anorexia to bulimic state may be related with differences in the metabolism of trace amines. In fact, it is known that octopamine regulate the body mass through glucose and lipid metabolism [15, 16]. The low levels of octopamine in the bulimic group may favor a glucose and lipid synthesis with an increase of body mass in these patients.

The pathophysiology of anorexia and bulimia is not completely understood, however, the obsessive control of the feeding behavior and the change in body weight, a reduced sexual appetite and disappearance of menstrual cycle suggest that a dysfunction of the hypothalamus [8], limbic centers [17] and amygdala [18] may play an important role in the pathogenesis. BOLD NMR studies show that these CNS structures are activated in ED patients when adequately stimulated with different kind of foods [19]. Moreover, the recovery from the ED symptoms seems to be accompanied by the activation of the lateral and apical prefrontal cortex, part of the limbic structure [17]. The increase in dopamine and tyramine along with a decrease in octopamine in bulimic patients support this hypothesis since dopamine and elusive amine synthesis and their receptors (DA and TAARs) are localized in the limbic, amygdala and hypothalamic circuitries [20]. The activation of dopaminergic pathways, i.e., also reported in obsessive-compulsive syndromes, may play an important role in the fixation of the repetitive behavior repertoires that characterize ED patients [21] and in the abnormal feeling of satiety in the anorexic sufferers [3].

Migraine seems characterized by similar biochemical findings. Migraine patients show, in comparison to control subjects, higher dopamine and lower of noradrenaline levels in plasma and platelets [22]. In these patients an anomalous activity of DBH it has been demonstrated, along with a polymorphism in the gene that controls the function of this enzyme [23]. In addition, metabolism of elusive amines is also deranged in migraine patients [7]. This, together with the premonitory symptoms that precede the migraine attacks (nausea, depression, thirst, sexual excitement, anger, hyperosmia, etc.) suggest that a hypothalamic and limbic disfunction(s) play a role in pathogenesis of migraine [24, 25].

In conclusion, the data here shown indicate that ED is characterized by an anomalous tyrosine metabolism, with a very high circulating levels of dopamine and tyramine and low levels of noradrenalin and octopamine (the latter amine at least in bulimic group). These findings support the hypothesis that a metabolic derangement in the limbic, amygdala and hypothalamus centers plays an role in the etiology of ED. This biochemical profile is similar to that of migraine and prevalence of migraine is overwhelming among ED sufferers. All these evidences suggest that migraine may constitute a risk factor for the occurrence of ED.

**Conflict of interest statement** The authors declare that they have no conflict of interest related to the publication of this manuscript.

## References


1. Bravander T, Bryant-Waugh R, Herzog D et al (2007) Classification of child and adolescent eating disturbances. Workgroup for classification of eating disorders in children and adolescents (WCEDCA). Int J Eat Disord 40(Suppl):S117–S122
2. Management of Eating Disorders (2006) RTI-UNIC Evidence Based Practice Center, Research Triangle Park, NC. AHRQ Publication No. 06-E010 April
3. Avraham Y, Hao S, Mendelson S and Berry EM (2001) Tyrosine improve appetite, cognition, and exercise tolerance in activity anorexia. Medicine&Science in Sports and Exercise 2104–210
4. Gross HA, Raymond Lake C, Hebert MH, Ziegler MG, Kopin IJ (1979) Catecholamine metabolism in primary anorexia nervosa. J Clin Endocrinol Metab 49:805–809
5. Guido KF, Bailer FU, Shannan H, Wagner A, Kaye WH (2004) Neuroimaging studies in eating disorders. CNS Spectr 9(7):539–548
6. D'Andrea G, Perini F, Terrazzino S, Nordera GP (2004) Contributions of biochemistry to the pathogenesis of primary headaches. Neurol Sci 3 (Suppl 3):589–592
7. D'Andrea G, Granella F, Leone M, Perini F, Farruggio A, Bussone G (2006) Abnormal platelet trace amine profiles in migraine with and without aura. Cephalalgia 26(8):968–972
8. Stamatakis EA, Hetherington MM (2003) Neuroimaging in eating disorders. Nutr Neurosci 6(6):325–334
9. Diagnostic and Statistical Manual of Mental Disorders (1994) 4th edn text rev. American Psychiatric Press, Washington DC
10. D'Andrea G, Terrazzino S, Fortin D, Farruggio A, Rinaldi L, Leon A (2003) HPLC electrochemical detection of trace amines in human plasma and platelets and expression on mRNA transcripts of trace amines receptors in circulating leukocytes. Neurosci Lett 346:89–92
11. The International Classification of Headache Disorders, second edition. Cephalalgia 24(Suppl 1):1–160
12. Rasmussen KB (2006) Epidemiology of migraine. In: Olesen J, Goasby PJ, Ramadan MN, Tfelt-Hansen P, Welch KMA (eds) The headache, 3rd edn. Williams&Wilkins, Baltimore, pp 235–242
13. D'Andrea G, Nordera GP, Perini F, Allais G, Granella F (2007) Biochemistry of neuromodulation in primary headaches: focus on tyrosine metabolism. Neurol Sci 28:S1–S5
14. D'Andrea G, Terrazzino S, Fortin D, Cocco P, Balbi T (2003) Elusive amines and primary headaches: historical background and prospectives. Neurol Sci 24:S65–S67
15. D'Andrea G, Terrazzino S, Leon A, Fortin D, Perini F, Granella F, Bussone G (2004) Elevated levels of circulating trace amines in primary headaches. Neurology 62:1701–1705
16. Carpenè C, Galitzky J, Fontana E, Atgié C, Lafontan M, Berlan M (1999) Selective activation of $B_3$-adrenoceptors by octopamine: comparative studies in mammalian cells. Naunyn-Schmiedeberg's Arch Pharmacol 359:310–321
17. Visintin V, Morin N, Fontana E, Prevot D, Boucher J, Castan I, Valet P, Grujic D, Carpenè C (2001) Dual action of octopamine on glucose transport into adipocites: inhibition via $B_3$-adrenoceptor activation and stimulation via oxidation by amine oxidases. JPET 299:96–104
18. Uher R, Brammer MJ, Murphy T, Campbell CI, Ng VW, Williams S, Treasure J (2003) Recovery and chronicity in anorexia nervosa: brain activity associated with differential Outcomes. Biol Psychiatry 54:934–942
19. Seeger G, Braus DF, Ruf M, Golderberg U, Schmidt MH (2002) Body image distortion reveals amygdala activaton in patients with anorexia nervosa-a functional magnetic resonance imaging study. Neurosci Lett 326:25–28
20. Uher R, Murphy T, Brammer MJ, Dalgeish T, Phillips ML et al (2004) Medial prefrontal cortex activity associated with symptoms provocation in eating disorders. Am J Psychiatry 161:1238–1246
21. Borowsky B, Adham N, Jones KA et al (2001) Trace amines: identification of a family of mammalian G protein-coupled receptors. Proc Natl Acad Sci USA 98:933–941
22. Jordan J, Joice PR, Carter FA, Horn L et al (2008) Specific and non specific comorbidity in anorexia nervosa. Int J Eat Disord 41(19):47–56
23. D'Andrea G, Granella F, Perini F, Farruggio A, Leone M, Bussone G (2006) Platelet levels of dopamine are increased in migraine and cluster headache. Headache 46:585–591
24. Fernandez F, Lea RA, Colson NJ, Bellis C, Quinlan S, Griffiths CR (2006) Association between a 19 bp deletion polymorphism at the dopamine $\beta$-hydroxylase (DBH) locus and migraine with aura. J Neurol Sci 21:251(1–2):118–123
25. Demarquay G, Royet JP, Mick G, Ryvlin P (2008) Olfactory hypersensitivity in migraineurs: a H (2) (15) O-PET study. Cephalalgia 28(10):1069–1080

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# Migraine and psychiatric disorders: comorbidities, mechanisms, and clinical applications

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**Abstract** Migraine is often comorbid with psychiatric disorders such as major depression, bipolar disorder, and anxiety disorders. Although most of the research on psychiatric comorbidities and migraine is of an epidemiologic nature, a growing body of literature has investigated possible mechanisms underlying this relationship, such as medication overuse, serotonergic dysfunction, ovarian hormone fluctuations, and central sensitization. The present article overviews this growing literature and notes strategies for the clinical management of migraine patients with psychiatric comorbidities.

**Keywords** Migraine · Psychiatric comorbidity · Depression · Anxiety · Mechanisms

## Introduction

Recent reviews show a strong relationship between migraine and psychiatric disorders [1–5]. Psychiatric comorbidities may complicate diagnosis, impact quality of life, affect treatment adherence, and alter the course of migraine [6–10]. Comorbid psychiatric disorders are associated also with increased medical costs, reduced treatment satisfaction, poorer prognosis, and increased disability [11, 12]. The relationship between migraine and affective disorders, such as depression [13, 14] and panic disorder [15], appears to be bidirectional in nature, with one disorder increasing the risk for the other and vice versa, suggestive of a shared etiology.

The relationship between psychiatric disorders and migraine is complex and largely unclear, as most data on this topic are of an epidemiologic nature. A smaller body of literature has addressed underlying mechanisms, effects on migraine progression, and treatment. This paper overviews the comorbidity of psychiatric disorders and migraine (focusing specifically on mood and anxiety disorders), speculates on possible mechanisms, and briefly reviews strategies for clinical management.

## Comorbidity of psychiatric disorders and migraine

### Mood disorders

In population studies, migraine sufferers are between 2.2 and 4.0 times more likely to suffer from major depressive disorder (MDD) than non-migraineurs [4], and they are also at higher risk for suicide attempts (regardless of depression status) [16]. Depression appears to be more common in migraine patients than in other chronic pain conditions, occurring in 28% of migraineurs [17, 18]. Numerous studies have shown evidence of a bidirectional relationship between migraine and depression that is specific to migraine and not to other types of severe headache [5, 13, 14, 16]. Rates of depression are higher in migraine with aura than in migraine without aura, as are rates of suicide attempts [19–21].

Although limited research has focused on comorbidity between migraine and bipolar disorder, existing evidence suggests that migraine patients are approximately 3 times

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more likely to suffer from a bipolar spectrum disorder than are non-migraineurs; this relationship is also strongest for migraine with aura [16, 22, 23]. One recent study has even suggested that migraine in depressed patients may represent a bipolar spectrum trait, after finding that migraine patients with unipolar depression had clinical features similar to a group of bipolar II patients [24].

### Anxiety disorders

The prevalence of anxiety disorders in migraine sufferers is almost twice that of major depression (ranging from 51 to 58%) [5]. Compared to individuals without migraine, migraineurs are at 4–5 times greater risk for generalized anxiety disorder (GAD) [5, 16, 22, 23], 5 times greater risk for obsessive-compulsive disorder (OCD) [5], and 3–10 times more likely to suffer from panic disorder [1, 3, 5, 15, 16, 25]. Phobic disorders are also predictive of future migraine, as shown in a 13-year prospective study [25]. The onset of anxiety often precedes migraine, with the risk of depression increasing subsequently [16, 22, 23, 26]. Posttraumatic stress disorder (PTSD) is infrequently studied by comparison, although two studies have provided evidence that PTSD is more common in recurrent headache patients than in the general population [27] and is more common in chronic than episodic migraine [28]. A history of physical, emotional or sexual abuse is present in upwards of 1/3 of severe migraineurs [29] and is most common in chronic migraine [30] and migraineurs with affective comorbidities [29, 31].

Anxiety disorders were found to be the only type of psychiatric disorder that was predictive of the persistence of headache during an 8-year longitudinal study by Guidetti and colleagues [10]. Though limited by a small sample size, this study underscores the notion that anxiety disorders serve as negative prognostic factors for migraine. Coupled with evidence that migraine-related disability is higher for comorbid anxiety than for comorbid depression [12], these studies highlight the need to attend to comorbid anxiety in addition to comorbid depression [32].

### Chronic headache and medication overuse

Chronic daily headache, and particularly transformed migraine (i.e., episodic migraine that converts to chronic migraine), has been associated with higher rates of depressive and anxiety disorders than has episodic headache [33–35]. In one study, 90% of the 88 chronic daily headache patients studied had at least one comorbid psychiatric disorder, and 45% had comorbid mood and anxiety disorders [33]. Recent studies have shown consistently that comorbid psychiatric disorders are highly prevalent also in medication overuse headache [36–40], with the psychiatric disorder typically preceding onset of medication overuse. These findings suggest that medication overuse may underlie relationships between migraine and affective disorders in some individuals.

## Possible mechanisms

### Serotonergic dysfunction

The 5-HTTLPR polymorphism in the promoter region of the 5-HTT gene gives rise to long and short alleles, the latter which slows down synthesis of the serotonin transporter, may increase the risk for depression, and may influence sensitivity to stress and anxiety [41–45]. Polymorphisms in the 5-HT transporter have been associated also with migraine susceptibility [46–48] and attack frequency [49]. In addition, decreased plasma 5-HT between migraine attacks and increased concentrations of 5-HT during attacks have been observed consistently among migraineurs [50, 51], and selective serotonin agonists (triptans) are the abortive treatments of choice for migraine. A chronically low serotonergic disposition presumably predisposes one to cortical spreading depression, in turn increasing sensitivity of trigeminovascular pathways that underlie migraine pain. Because affective conditions such as depression and anxiety are also associated with reduced serotonergic availability and positive response to selective serotonin reuptake inhibitors (SSRIs), migraine and affective disorders may ultimately share a dysfunction in central 5-HT availability [50].

### Ovarian hormones

Ovarian hormones modulate numerous neurotransmitters in women [52], and both migraine and depression are strongly affected by monthly and lifelong fluctuations in such hormones. Migraine and affective disorders are 2–3 times more common in women than in men [53, 54], and this discrepancy becomes most apparent following puberty. Female migraineurs often suffer attacks associated with falling estrogen levels around menses. Many women also evidence mood disturbance coinciding with menses, the postpartum period, and the perimenopausal period. The late luteal phase of the menstrual cycle appears to be a particularly vulnerable time for migraine and affective problems, as estrogen levels decline precipitously and there is up-regulation of the sympathetic system and down-regulation of serotonergic and GABA-ergic systems [52].

Sensitization and HPA dysregulation

In a minority of individuals, migraine and affective disorders can progress to more chronic states that are refractory to treatment and show poor inter-episode recovery, suggesting that a process of sensitization may also underlie their comorbidity in chronic forms. These central sensitization syndromes may involve numerous sensory and emotional neural networks [7–9, 55]. Frequent migraine attacks have been shown to impair the periaqueductal gray (PAG) area [56], and repeated episodes of unipolar depression reduce hippocampal volume [57].

More specifically, dysregulation of the hypothalamic-pituitary adrenal (HPA) axis has been implicated [58, 59]. Early sensitization in response to significant stress, such as childhood maltreatment, may be operable in both affective disorders and migraine. It has also been hypothesized that proinflammatory mechanisms may be a link between affective disorders, migraine, and obesity [60], perhaps by altering tryptophan metabolism, reducing 5-HT synthesis, and activating the HPA axis [61].

## Clinical applications

All headache patients, but particularly those presenting to specialty clinics or with chronic and refractory headache syndromes, should be screened for depression and anxiety [32].

Numerous pharmacologic and psychological treatments exist for mood and anxiety disorders in headache patients [62, 63], the choice of which is based on factors such as severity, adverse effects, patient preference, treatment history, and adherence. At present there is no established algorithm to guide treatment decisions for comorbid migraine patients. Ideally, treatment of both conditions would be accomplished with a single agent, but this approach sometimes proves insufficient or complicates the clinical situation [26, 64]. Adjusting a single drug to meet the dosing requirements of two conditions is often difficult (e.g. the dose required for treating migraine may be insufficient to treat the affective disorder). Some medications may adversely affect the comorbid condition, as when a beta-blocker prescribed for migraine may worsen depression [65] or when a tricyclic antidepressant may induce mania in bipolar patients [66]. Despite controversy regarding the actual risk of serotonin syndrome in migraine patients treated with a triptan and another serotonergic agent [67], clinicians should be attentive to the possibility of this event in patients treated with multiple serotonergic agents.

The treatments of choice for acute episodes of major depression are the second-generation antidepressants, although there do not appear to be any striking differences in efficacy between the SSRIs, SNRIs, or SSNRIs in the initial (acute) stages of depression treatment [68, 69]. If the patient has not responded after 6–8 weeks of adequate treatment, modification of the treatment regimen is warranted. Continuation treatment, which aims to prevent the high risk of relapse in depressed patients, should be continued for 4–9 months after a first MDD episode [70]. In most anxiety disorders, SSRIs are the agents of choice, with the highest doses typically used for OCD [1], although benzodiazepines are sometimes used in a short-term or adjunctive manner. Unfortunately, neither the SSRIs nor benzodiazepines have shown consistently strong efficacy for migraine.

Behavioral and cognitive-behavioral therapies are also first-line treatments for mood and anxiety disorders [62], and they may be combined with pharmacotherapy to increase medication adherence, delay relapse, and increase maintenance of treatment gains [71]. These therapies help patients modify distorted thinking, increase access to pleasurable activities (with depression), reduce maladaptive avoidance behaviors (with anxiety), and improve problem-solving abilities. Because they are free from the side effects of pharmacotherapy and give patients a sense of control over their suffering, these therapies can be easily combined with pharmacologic treatments or adapted to behavioral headache interventions.

Clinical experience suggests that the severity and pattern of migraine should guide decisions about acute versus preventive pharmacologic management of migraine. In cases where depression or anxiety is mild, non-pharmacologic management of the affective condition may be sufficient, and the affective disorder may also respond to progressive improvements in migraine. In cases of moderate to severe affective distress, pharmacologic management of the affective disorder and/or more intensive psychotherapy is warranted. In instances of multiple medications, the clinician should be attentive to drug–drug interactions and use a "staggered" start.

## Conclusions

Those with migraine are at higher risk for mood and anxiety disorders than are individuals in the general population. The highest rates of psychiatric comorbidities are found in patients with chronic daily headache and medication overuse headache. In addition to medication overuse, mechanisms such as serotonergic dysfunction, ovarian hormone fluctuations, central sensitization, and HPA axis dysregulation have been implicated in the relationship between migraine and affective disorders.

Treatment options for the migraine sufferer with comorbid psychiatric illness are numerous, but at present there are no empirical guidelines for managing such

patients. Empirical research and clinical experience suggest that untreated mood or anxiety disorders can negatively affect migraine, and poorly treated migraine may also negatively impact underlying affective conditions. More research is needed to better elucidate underlying biologic mechanisms and to identify the most effective treatment strategies for these comorbid disorders.

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

## References


1. Baskin SM, Lipchik GL, Smitherman TA (2006) Mood and anxiety disorders in chronic headache. Headache 46(Suppl 3):S76–S87
2. Radat F, Swendsen J (2004) Psychiatric comorbidity in migraine: a review. Cephalalgia 25:165–178
3. Lake AE, Rains JC, Penzien DB, Lipchik GL (2005) Headache and psychiatric comorbidity: historical context, clinical implications, and research relevance. Headache 45:493–506
4. Hamelsky SW, Lipton RB (2006) Psychiatric comorbidity of migraine. Headache 46:1327–1333
5. Breslau N (1998) Psychiatric comorbidity in migraine. Cephalalgia 18(Suppl 22):56–61
6. Feinstein A (1970) The pre-therapeutic classification of comorbidity in chronic disease. J Chronic Dis 23:455–468
7. Bigal ME, Lipton RB (2006) Modifiable risk factors for migraine progression. Headache 46:1334–1343
8. Scher AI, Midgette LA, Lipton RB (2008) Risk factors for headache chronification. Headache 48:16–25
9. Smitherman TA, Penzien DB, Maizels M (2008) Anxiety disorders and migraine intractability and progression. Curr Pain Headache Rep 12:224–229
10. Guidetti V, Galli F, Fabrizi P, Giannantoni AS, Napoli L, Bruni O, Trillo S (1998) Headache and psychiatric comorbidity: clinical aspects and outcome in a 8-year follow-up study. Cephalalgia 18:455–462
11. Pesa J, Lage MJ (2004) The medical costs of migraine and comorbid anxiety and depression. Headache 44:562–570
12. Lanteri-Minet M, Radat F, Chautard MH, Lucas C (2005) Anxiety and depression associated with migraine: influence on migraine subjects' disability and quality of life, and acute migraine management. Pain 118:319–326
13. Breslau N, Schultz LR, Stewart WF, Lipton RB, Lucia VC, Welch KM (2000) Headache and major depression: is the association specific to migraine? Neurology 54:308–313
14. Breslau N, Lipton RB, Stewart WF, Schultz LR, Welch KM (2003) Comorbidity of migraine and depression. Neurology 60:1308–1312
15. Breslau N, Schultz LR, Stewart WF, Lipton R, Welch KM (2001) Headache types and panic disorder: directionality and specificity. Neurology 56:350–354
16. Breslau N, Davis GC, Andreski P (1991) Migraine, psychiatric disorders, and suicide attempts: an epidemiologic study of young adults. Psychiatry Res 137:11–23
17. McWilliams LA, Goodwin RD, Cox BJ (2004) Depression and anxiety associated with three pain conditions: results from a nationally representative sample. Pain 111:77–83
18. Patel NV, Bigal ME, Kolodner KB et al (2004) Prevalence and impact of migraine and probable migraine in a health plan. Neurology 63:1432–1438
19. Fasmer OB, Oedegaard KJ (2001) Clinical characteristics of patients with major affective disorders and comorbid migraine. World J Biol Psychiatry 2:149–155
20. Oedegaard KJ, Angst J, Neckelmann D, Fasmer OB (2005) Migraine aura without headache compared to migraine with aura in patients with affective disorders. J Headache Pain 6:378–386
21. Oedegaard KJ, Neckelmann D, Mykletun A et al (2006) Migraine with and without aura: association with depression and anxiety disorder in a population-based study. The Hunt Study. Cephalalgia 26:1–6
22. Merikangas KR, Angst J, Isler H (1990) Migraine and psychopathology. Arch Gen Psychiatry 47:849–853
23. Merikangas KR, Merikangas JR, Angst J (1993) Headache syndromes and psychiatric disorders: association and familial transmission. J Psychiatr Res 27:197–210
24. Oedegaard KJ, Fasmer OB (2005) Is migraine in unipolar depressed patients a bipolar spectrum trait? J Affect Disorders 84:233–242
25. Swartz KL, Pratt LA, Armenian HK, Lee LC, Eaton WW (2000) Mental disorders and the incidence of migraine headaches in a community sample: results from the Baltimore Epidemiologic Catchment area follow-up study. Arch Gen Psychiatry 57:945–950
26. Evans RW, Rosen N (2008) Migraine, psychiatric comorbidities and treatment. Headache 48:952–958
27. de Leeuw R, Schmidt JE, Carlson CR (2005) Traumatic stressors and post-traumatic stress disorder symptoms in headache patients. Headache 45:1365–1374
28. Peterlin BL, Tietgen G, Meng S, Lidicker J, Bigal M (2008) Posttraumatic stress disorder in episodic and chronic migraine. Headache 48:517–522
29. Tietgen GE, Brandes JL, Digre KB et al (2007) History of childhood maltreatment is associated with comorbid depression in women with migraine. Neurology 69:959–968
30. Peterlin BL, Ward TW, Lidicker J, Levin M (2007) A retrospective, comparative study on the frequency of abuse in migraine and chronic daily headache. Headache 47:397–401
31. Tietjen GE, Herial NA, Hardgrove J, Utley C, White L (2007) Migraine comorbidity constellations. Headache 47:857–865
32. Maizels M, Smitherman TA, Penzien DB (2006) A review of screening tools for psychiatric comorbidity in headache patients. Headache 46(Suppl 3):S98–S109
33. Verri AP, Proietti Cecchini A, Galli C, Granella F, Sandrini G, Nappi G (1998) Psychiatric comorbidity in chronic daily headache. Cephalalgia 18(Suppl 21):45–49
34. Zwart JA, Dyb G, Hagen K, Odegard KJ, Dahl AA, Bovim G, Stovner LJ (2003) Depression and anxiety disorders associated with headache frequency. The Nord-Trondelag Health Study. Eur J Neurol 10:147–152
35. Juang KD, Wang SJ, Fuh JL, Lu SR, Su TP (2000) Comorbidity of depressive and anxiety disorder in chronic daily headache and its subtypes. Headache 40:818–823
36. Atasoy HT, Atasoy N, Unal AE, Emre U, Sumer M (2005) Psychiatric comorbidity in medication overuse headache patients with preexisting headache type of episodic tension type headache. Eur J Pain 9:285–291
37. Radat F, Creac'h C, Swendsen JD et al (2005) Psychiatric comorbidity in the evolution from migraine to medication overuse headache. Cephalalgia 25:519–522
38. Radat F, Sakh D, Lutz G et al (1999) Psychiatric comorbidity is related to headache induced by chronic substance use in migraineurs. Headache 39:477–480
39. Lake AE (2006) Medication overuse headache: Biobehavioral issues and solutions. Headache 46(Suppl 3):S88–S97
40. Rothrock J, Lopez I, Zweilfer R et al (2007) Borderline personality disorder and migraine. Headache 47:22–26

41. Rot M, Mathew SJ, Charney DS (2009) Neurobiological mechanisms in major depressive disorder. CMAJ 180:305–313
42. Lotrich FE, Pollock BG (2004) Meta-analysis of serotonin transporter polymorphisms and affective disorders. Psychiatr Gen 14:121–129
43. Caspi A, Sugden K, Moffitt TE et al (2003) Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301:386–389
44. Lesch KP, Bengel D, Heils A et al (1996) Association of anxiety-related traits with polymorphisms in the serotonin transporter gene regulatory region. Science 274:1527–1531
45. Sen S, Burmeister M, Ghosh D (2004) Meta-analysis of the association between a serotonin transporter promoter polymorphism (5-HTTLPR) and anxiety-related personality traits. Am J Med Genet B Neuropsychiatr Genet 127:85–89
46. Juhasz G, Zsombok T, Laszik A, Gonda X, Sotonyi P, Faludi G, Bagdy G (2003) Association analysis of 5-HTTLPR variants, 5-HT2a receptor gene 102T/C polymorphism and migraine. J Neurogenet 17:231–240
47. Todt U, Freudenberg J, Goebel I et al (2006) Variation of the serotonin receptor gene SLC6A4 in the susceptibility to migraine with aura. Neurology 67:1707–1709
48. Marziniak M, Mossner R, Schmitt A, Lesch KP, Sommer C (2005) A functional serotonin transporter gene polymorphism is associated with migraine with aura. Neurology 64:157–159
49. Kotani K, Shimomura T, Shimomura F, Ikawa S, Nanba E (2002) A polymorphism in the serotonin transporter gene regulatory region and frequency of migraine attacks. Headache 42:893–895
50. Hamel E (2007) Serotonin and migraine: biology and clinical implications. Cephalalgia 27:1295–1300
51. Ferrari MD, Saxena PR (1993) On serotonin and migraine: a clinical and pharmacological review. Cephalalgia 13:151–165
52. Martin VT, Behbehani M (2006) Ovarian hormones and migraine headache: understanding mechanisms and pathogenesis-part I. Headache 46:3–23
53. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M (2001) Prevalence and burden of migraine in the United States: data from the American Migraine Study II. Headache 41:646–657
54. Kessler RC, McGonagle KA, Zhao S et al (1994) Lifetime and 12-month prevalence of DSM-III-R psychiatric disorder in the United States. Results from the National Comorbidity Survey. Arch Gen Psych 51:8–19
55. Monroe SM, Harkness KL (2005) Life stress, the "kindling" hypothesis, and the recurrence of depression: considerations from a life stress perspective. Psychol Rev 112:417–445
56. Welch KMA, Nagesh V, Aurora SK, Gelman N (2001) Periaqujeductal gray matter dysfunction in migraine: cause or the burden of illness? Headache 41:629–637
57. Videbech P, Ravnkilde B (2004) Hippocampal volume and depression: a meta-analysis of MRI studies. Am J Psychiatry 161:1957–1966
58. Barden N (2004) Implication of the hypothalamic–pituitary–adrenal axis in the physiopathology of depression. J Psychiatry Neurosci 29:185–193
59. Peres MF, Sanchez DR, Seabra ML et al (2001) Hypothalamic involvement in chronic migraine. J Neurol Neurosurg Psychiatry 71:747–751
60. Bigal ME, Lipton RB, Holland PR, Goadsby PJ (2007) Obesity, migraine and chronic migraine: possible mechanisms of interaction. Neurology 68:1851–1861
61. Miura H, Ozaki N, Sawada M et al (2008) A link between stress and depression: shifts in the balance between the kynurenine and serotonin pathways of tryptophan metabolism and the etiology and pathophysiology of depression. Stress 11:198–209
62. Lipchik GL, Smitherman TA, Penzien DB, Holroyd KA (2006) Basic principles and techniques of cognitive-behavioral therapies for comorbid psychiatric symptoms among headache patients. Headache 46(Suppl 3):S119–S132
63. Griffith JL, Razavi M (2006) Pharmacological management of mood and anxiety disorders in headache patients. Headache 46(Suppl 3):S133–S141
64. Silberstein S, Dodick D, Freitag F et al (2007) Pharmacological approaches to managing migraine and associated comorbidities: clinical considerations for monotherapy versus polytherapy. Headache 47:585–599
65. Huffman JC, Stern TA (2007) Neuropsychiatric consequences of cardiovascular medications. Dialogues Clin Neurosci 9:29–45
66. Belmaker RH (2004) Bipolar disorder. N Engl J Med 351:476–486
67. Shapiro RE, Tepper SJ (2007) The serotonin syndrome, triptans, and the potential for drug–drug interactions. Headache 47:266–269
68. Thase ME (1999) Long-term nature of depression. J Clin Psychiatry 60(Suppl 14):3–9
69. Qaseem A, Snow V, Denberg TD et al (2008) Using second-generation antidepressants to treat depressive disorders: a clinical practice guideline from the American College of Physicians. Ann Int Med 149:725–733
70. Prien RF, Kupfer DJ (1986) Continuation drug therapy for major depressive episodes: how long should it be maintained? Am J Psychiatry 143:18–23
71. Pampallona S, Bollini P, Tibaldki G et al (2004) Combined pharmacotherapy and psychological treatment for depression: a systematic review. Arch Gen Psychiatry 61:714–719

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# Local therapies in migraine

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**Abstract** Fixed-site" approach and "follow-the-pain" approach briefly considered the techniques of local therapy that now generate more interest and discussion on headaches and, in particular, of migraine. Far from being a full discussion, the work aims only to stimulate further thought and interest in local therapies which often are not sufficiently considered and that conversely are a possibility in the treatment of migraine.

**Keywords** Migraine · Local therapies · Botulinum toxin · Transcranial magnetical stimulation (TMS) · Great occipital nerve (GON)

## Introduction

The skull always represents an anatomical target full of meaning and values going beyond the tinged-related pathologies. Not surprising that migraine has always had amongst its possible remedies local treatments. Along with the origins of headache, main features of therapeutics have already been mentioned, often reflecting a magical determination with treatments discovered by empirical trial-and-error tests. Treatment could be magical, pharmacological or surgical. In the ancient Egypt the origin of all kinds of aches and pains was often attributed to peculiar pain-matter demons and there was only a very short and tentative explanation of headache. Later it was developed a certain rationalization with the "humoral theory of cephalalgia" which became the dominant explanation for the next three millennia [1]. Later attempts to discover the mechanisms of beneficial action were obfuscated by uncertainty as to the mechanisms that generate the primary headache disorders, and thus the identity of appropriate therapeutic targets. Even today, despite safer drug therapies, there are procedures in which a local action can give a comprehensive response to migraine. For example, acupuncture, which is not discussed here, based on its action from a local stimulus on a global response of the body. Amongst the local treatments for migraine that nowadays are supported by scientific evidences, the therapeutic use of botulinum toxin in migraine, the magnetic cortical stimulation, the local treatment of the great occipital nerve and, finally, other therapies supported by limited scientific evidences here will be remembered.

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## Botulinum toxin

Botulinum toxin type A (BT-a) has long been used to treat disorders associated with increased muscle tone and pain. Enzymatic blockade of neurotransmitter release such as substance P is believed to underlie a direct, clinically useful antinociceptive effect of BT-a [2]. Furthermore, peripheral exposure to BT-a blocks the release of glutamate and prevents the expression of FOS, a product of the immediate early gene, c-fos, with neuronal stimuli. Modulation of peripheral sensitization and, indirectly, central sensitization is believed to underlie the efficacy of BT-a in preventing migraine [3]. The ability of BTX-A to cause muscle paralysis by blocking acetylcholine release at the neuromuscular junction is well known. The toxin produces the effect by proceeding through a sequence of four steps: (a) binding to receptors on the plasma membrane, (b) penetration of plasma membrane by receptor-mediated

endocytosis, (c) penetration of the endosome membrane by pH-induced translocation and (d) intracellular expression of an enzymatic action that culminates in blockade of exocytosis [4]. BTX-A not only reduces acetylcholine release from the alpha motor neuron endings, but also decreases the activity of the muscle spindles by inhibiting the signals from gamma motor neurons and subsequent reduces the Ia afferent signals. In addition, the inhibitory effect on the central pain pathways such as trigeminal ganglion or trigeminal cervical complex in the brainstem has been implicated because suppression of the release of substance P from the dorsal root ganglion [5] or CGRP (calcitonine gene-related peptide) from the trigeminal ganglion [6] has been shown in animal studies. Focussed on an evidence-based manner, most of the initial open-labelled reports on BTX-A in tension-type headache and in migraine were positive. Most recently, these results were not unfortunately reproduced as well in controlled trials, suggesting that a wide-spread clinical use of BTX-A in headache is not recommended [7]. So the use of botulinum toxin type A (BT-a) as a preventive headache treatment is increasing but, as said, remains debated and controversial. Exactly why BTX-A is effective in relieving headache is not clear, but mechanisms of actions include direct effects at the neuromuscular junction and direct antinociceptive effects on nerves in the face, head and neck. To date, responses to BT-a in migraine patients in a evidence-based view give us more pessimistic picture showing non-consistent efficacy of BT-a in idiopathic headache disorders. BT-A is probably ineffective for the treatment of chronic tension-type headache. Factors that may affect the response of patients to BT-a include headache characteristics, disease duration, the use of concurrent preventive medications and the presence or absence of medication overuse. However, encouraging experiences arise from the response to BT-A treatment in a subgroup of patients suffering from chronic migraine with and without analgesic abuse [8]. In particular, it is likely that patients with chronic daily headache who are severely impaired and who are not receiving other prophylactic treatment are the appropriate group of patients with a benefit from BT-A [9]. The challenge for the future studies is to identify those patients who will best respond to the drug and to determine optimal injection sites, doses and frequency of treatment.

Selection of appropriate candidates for preventive therapy begins with accurate headache diagnosis and classification. Upon these rules, BTX-A therapy may be appropriate for: patients with disabling primary headaches, patients who have failed to respond adequately to conventional treatments, patients with unacceptable side effects (from existing treatments), patients in whom standard preventive treatments are contraindicated, patients in special populations or situations, patients misusing or abusing or overusing medications, patients with co-existing jaw, head or neck muscle spasm, patients who prefer this treatment [10]. There is no established or standardized methodology for the injection of BTX-A for migraine and tension-type headache. BTX-A is administered either at fixed injection sites, or at sites of pain or tenderness ("follow the pain"), or a combination of both [11]. The clinical dose of BTX-A commonly used for migraine therapy is between 25–200 units (Botox) and 100–500 units (Dysport); number of injected sites may vary from 10 to 25. However, the total dosage of toxin administered, the number of units per site of injection, dilution of toxin, and sites of injection varied widely between studies. Current data do not appear to indicate a dose–response benefit [12]. Therefore, there is need for further studies in order to identify the minimal effective dosage and optimal individualized dosing regimen. On the other hand, some data report a greater efficacy with repeated dosing. This may be because repeated injections had a step-like therapeutic effect: the consecutive therapeutic effect of each injection built on the effect previously achieved [13]. To date, injection with different techniques regarding anatomical sites, doses and concentrations of BT-A has been used. There are mainly two types of injection techniques for BT-A, named "fixed-site" approach and "follow-the-pain" approach and even in a combination of both methods has also been reported. Other factors such as volume per injection site, number of injection sites per area, the dilution of BT-A, and the injection technique vary across studies and are not uniform.

Results from clinical studies have proposed a patient population which may be more appropriate for BT-A application, which are listed in Table 1 [14].

The efficacy and safety profile of BTX-A suggest that it is an effective, well-tolerated prophylactic treatment in migraine patients with chronic daily headache who are not using other prophylactic headache treatments. The data also suggest that assessment of the frequency of headaches is a sensitive measure of efficacy in this patient population and future studies confirming these findings are needed. Optimal dosing and injection regimens are not yet known. Dosage ranges usually administrated are effective, and adverse side effects, which are often mild to moderate, are transient; however, they appear to be dose-dependent. A combination of fixed anterior injections with a follow-the-pain approach appears to be optimal, but further studies are necessary to determinate the most effective injection regimens. Another aspect is the frequency of treatment that seems to have a cumulative effect with subsequent injections [15].

Further evidence is needed to determine whether this agent can serve as a first-line therapy for patients with less refractory headaches, and to determine optimal injection sites, doses, and frequency of treatment.

**Table 1** Candidates for BT-A therapy for Headache

| |
|---|
| Patients with disabling primary headaches |
| Patients who have failed to respond adequately to conventional treatments |
| Patients with unacceptable side effects (from existing treatments) |
| Patients in whom standard preventive treatments are contraindicated |
| Patients in special populations or situations (the elderly, those at risk of unacceptable side effects from trial drugs or traditional treatments) |
| Patients misusing or abusing or overusing medications |
| Patients with coexisting jaw, head or neck muscle spasm |
| Patients who prefer this treatment |

## Transcranial magnetic stimulation

Enhanced excitability of the occipital cortex is proposed as the basis for the spontaneous or triggered onset of migraine aura [16]. There is mixed evidence of increased interictal occipital cortex neuronal excitability in migraneurs, including differences in the amplitude of visual or motor responses. However, studies of transcranial magnetic stimulation (TMS)-induced phosphene in migraneurs have produced conflicting results. Besides data suggesting a lowered threshold in migraneurs with aura, other evidences hypothesize a decreased excitability of the visual areas and also no differences [17–19]. More recently, studies of phosphene threshold using TMS and other electrophysiological techniques have suggested that effective migraine preventives reduce cortical hyperexcitability [20]. If some of these discrepancies could be due to methodological differences, either TMS device or patient population dependent, it must be taken into account the influence of temporal variables in the cortical excitability in migraine.

There is a growing interest towards the use of repetitive TMS (rTMS) as a potential therapeutic tool in migraine because of its ability to induce long-term plastic effects on cortical excitability [21].

## Great occipital nerve (GON)

Peripheral nerve blocks have long been used in headache treatment. The most widely used procedure for this purpose has been GON block. The GON is composed of sensory fibres that originate predominantly at the C2 level and its cutaneous distribution covers the posterior part of the head up to the vertex. The rationale of performing a GON block for the treatment of headache is based on the anatomical connections between trigeminal and upper cervical sensory fibres at the level of the trigeminal nucleus caudalis.

Amongst other techniques, manipulation, acupuncture and electrical stimulation of the GON must be taken in account. Taken together these works, although generally positive, were limited by the lack of a standardized treatment protocol or a retrospective design [22].

More recently, the use of electronic devices implanted subcutaneously at the base of the skull close to GON emerges, has proved effective in controlling headache pain through a central neuromodulation action [23].

## Other therapies

Spinal manipulation, cranial electrotherapy, pulsating electromagnetic fields are supported by limited evidences. Methodological limitations coupled with the small number and considerable heterogeneity of the randomized trials were not able to identify the true effectiveness of this therapies and to distinguish any improvements made by other variables. The action of physical treatment combination, useful in tension-type and cervicogenic headaches, has not shown real benefits in the treatment of migraine. However, additional better-designed trials are required before such treatments can be considered effective for headache disorders [24].

**Conflict of interest statement** The author declares that he has no conflict of interest related to the publication of this manuscript.

## References


1. Karenberg A, Leitz C (2001) Headache in magical and medical papyri of Ancient Egypt. Cephalalgia 21:911–916
2. Aoki KR (2003) Evidence for antinociceptive activity of botulinum toxin type A in pain management. Headache 43(Suppl 1):9–15
3. Silberstein SD, Aoki KR (2003) Botulinum toxin type A: myths, facts, and current research. Headache 43(suppl1):1
4. Simpson LL (1981) The origin, structure and pharmacological activity of botulinum toxin. Pharmacol Rev 33:155–188
5. Purkiss J, Welch MKA, Doward S, Foster K (2000) Capsaicin-stimulated release of substance P from cultured dorsal root ganglion neurons: involvement of two distinct mechanisms. Biochem Pharmacol 59:1403–1406
6. Durham PL, Cady R, Cady R (2004) regulation of calcitonin gene-related peptide secretion from trigeminal nerve cells by botulinum toxin type A: implications for migraine therapy. Headache 44:35–43
7. Schulte-Mattler WJ, Martinez-Castrillo JC (2006) Botulinum toxin therapy of migraine and tension-type headache. Eur J Neurol 13(Suppl 1):51–54
8. Dodick D, Mauskop Elkind AH et al (2005) Botulinum toxin ype A for the prophylaxis of chronic daily headache: subgroup analysis of patents not receiving other prophylactic medications: a randomized double-blind, placebo-controlled study. Headache 45:315–324
9. Freitag G, Freitag DO, Diamond S, Diamond M, Urban G (2007) Botulinum toxin type A in treatment of chronic migraine without medication overuse. Headache 48:201–209

10. Blumenfeld AM (2003) Botulinum toxin type A as an effective prophylactic treatment in primary headache disorders. Headache 43:853–860
11. Saper JR, Mathew NT, Loder EW, Degryse R, VanDenburgh AM (2007) A double-blind, randomized, placebo-controlled comparison of botulinum toxin type A injection sites and doses in the prevention of episodic migraine. Pain Med 8(6):478–485
12. Tepper S, Bigal M, Sheftell F, Rapoport A (2004) Botulinum neurotoxin type A in the preventive treatment of refractory headache. Headache 44:749–800
13. Schulte-Mattler WJ, Krack P (2004) Treatment of chronic tension-type headache with botulinum toxin A. Pain 109:110–114
14. Blumenfeld AM, Binder W, Silberstein SD, Blitzer A (2003) Procedures for administering botulinum toxin type A for migraine and tension-type headache. Headache 43:884–891
15. Goadsby P (2007) Emerging therapies for migraine. Nat Clin Pract Neurol 3(11):610–619
16. Welch KMA, D'Andrea G, Tepley N, Barkley G, Ramadan NM (1990) The concept of migraine as a state of central neuron hyperexcitability. Neurol Clin 8:817–828
17. Aurora S, Cao Y, Bowyer SM, Welch KM (1999) The occipital cortex is hyperexcitable in migraine: experimental evidence. Headache 39:469–476
18. Mulleners WM, Chronicle EP, Palmer JE, Koehler PJ, Vredeveld JW (2001) Visual cortex excitability in migraine with and without aur. Headache 41:565–572
19. Valli G, Capellari A, Zago S, Ciammola A, De Benedittis G (2001) Is migraine associated with hyperexcitability of the occipital cortex? A transcranial magnetic stimulation controlled study. Neurology 56:1066–1069
20. Young W, Shaw J, Bloom M, Gebeline-Myers C (2008) Correlation of increase in phoshene threshold with reduction of migraine grequency: observation of leviracetam-treated subjects. Headache 12:1490–1498
21. Fumal A, Coppola G, Bohotin V, Gerardy PY, Seidel L, Donneau AF et al (2006) Induction of long-lasting changes of visual cortex excitability by five daily sessions of repetitive rTMS in healty volunteers and migraine patients. Cephalalgia 26:143–149
22. Ashkenazi A, Levin M (2007) Greater occipital nerve block for migraine and other headaches it is useful? Curr Pain Headache Rep 11(3):231–235
23. Matharu MS, Bartsch T, Ward N, Frackowiak RS, Weiner R, Goadsby P (2004) Central neuromodulation in chronic migraine patients with suboccipital stimulators: a PET study. Brain 127:220–230
24. Bronfort G, Nilsson N, Haas RL, Goldsmith CH, Assendelft WJ, Bouter LM (2009) Non-invasive physical treatments for chronic/recurrent headache. Cochrane Libr 3(1):1–70

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# Functional-MRI evaluation of pain processing in chronic migraine with medication overuse

**Luisa Chiapparini · L. Grazzi · S. Ferraro · M. L. Mandelli · S. Usai · F. Andrasik · M. G. Bruzzone · G. Bussone**

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**Abstract** Withdrawal is the first step for treating patients with chronic migraine and medication overuse. Recent studies confirmed common elements in personality between these patients and subjects addicted; some neuroimaging researches showed that abnormalities revealed are related to a specific cerebral pattern and that they can return to the normal state after withdrawal. Aim of the study was to submit a group of patients suffering from chronic migraine and medication overuse (the diagnosis was made according to Silberstein-Lipton criteria) to a withdrawal, to evaluate by f-MRI the presence of specific cerebral patterns before treatment and their possible changes after withdrawal. f-MRI seems to be a useful technique to obtain information on particular neuronal changes of the pain network involved in this type of patients. The activated areas are congruent with some data of the literature and the data emerged are discussed according to preceding reports.

**Keywords** Chronic migraine · Medication overuse · Withdrawal · Functional-MRI

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## Introduction

Chronic migraine (CM) with medication overuse is a frequent and disabling health problem. In migraine population, the 10% of migraine sufferers develop CM [1]. CM is characterized by an insidious increase of headache frequency and intensity, inefficacy of alternative abortive or preventive medications in controlling headaches and development of drug dependency or addiction [2].

Recurrent migraine attacks seem to be linked to structural changes in the central nervous system. Several studies showed that silent brain damages [3, 4] and increased iron concentration in deep nuclei involved in central pain processing [5] are more frequent in migraneurs when compared with control subjects.

Besides structural changes, functional changes of the CNS, manifested through central sensitization with alteration in nociceptive thresholds (allodynia and hyperalgesia), are reported [6] in migraneurs. Central sensitisation seems to be a mechanism of headache chronification and chronicity maintaining [7]. Functional abnormalities are reported by a neuroimaging work by Fumal et al. [8]: in a study by PET the authors showed that bilateral thalami, bilateral insula, ventral striatum and right posterior parietal lobule (areas recognized as involved in pain processing) were significantly less metabolically active in chronic migraine with medication overuse than in healthy subjects. Their work is in line with some imaging studies performed in other pain disorders: bilateral blood flow changes have been described in ventral posterior lateral thalamus, posterior parietal cortex, insula, ventral striatum and anterior cingulate cortex in chronic neuropathic pain [9–11]. All these studies seem to support an important role of the pain matrix in migraine; although has to be established which kind of role: a causative role? A result of the prolonged pain processing at central level?

### Pain processing

Studies based on PET and f-MRI have investigated changes in brain activity in response to various experimental stimuli inducing pain. This has led to the characterization of a specific network of brain areas forming a "pain matrix" involved in different dimensions of pain perception.

Functional imaging of pain processing in healthy subjects has predominantly used phasic or tonic noxious heat, tonic cold, and noxious chemical or electrical stimulation of the skin; few studies have been published (for a review see [12]) concerning cerebral activation in response to painful mechanical stimulation used to induce deep pain. Furthermore, it has been suggested that tonic pain may be psychologically more similar to chronic pain than phasic pain [13].

### Purpose of the study

On the basis of preceding reports, we hypothesized that in patients suffering from chronic migraine with medication overuse, specific cerebral patterns might be found in brain areas belonging to the pain network respect to healthy controls.

To verify this hypothesis, we performed f-MRI in a group of chronic migraine patients longstanding medication overuse and we compared the results with a group of healthy volunteers.

## Materials and methods

### Participants

Thirteen female patients suffering from chronic migraine and medication overuse, (chronic migraine group—CM group), were recruited from the Headache Center of the Neurological Institute in Milan for being submitted to a inpatient withdrawal program.

The frequency of headache was 20.8 ± 6.5 days per month and analgesic intake was 26.1 ± 13.7 pills per month, as revealed from the patients headache daily card. The patients were overusing analgesics in the last 3 ± 1.4 years and all of them were using triptans and NSAIDS daily, only in two cases they were using butalbital combined to NSAIDS daily. Ten patients were been previously treated in other headache centers for migraine prophylaxis by using flunarizine, neuromodulators, antidepressants, beta-blockers for several months without any significant improvement of headache condition and without doing any kind of detoxication. Only two patients never tried any kind of pharmacological treatment for prophylaxis.

Eleven female control subjects (mean age 37 ± 7 years) (C group) were also recruited. The subjects had no history or signs of neurological disease, and of cognitive disturbance. They did not take any analgesic medication at the time of testing and reported no pre existing pain.

All subjects had normal MRI scan.

The study protocol was approved by the Human Research Ethic Committee of the Neurological Institute Carlo Besta in Milan. Written informed consent was obtained from all participants.

### Procedure

The study was conducted over two sessions during the same day. In an initial psychophysical testing session, mechanical pressure stimuli were applied over the first metacarpo-phalangeal joints of the forefinger and middle finger of the left hand, with a plexiglass tensiometer instrument built in our lab via a 0.2 $mm^2$ punctate probe. This kind of stimulation has been shown to be adequate to activate A- and C-fiber nociceptors [19]. All subjects were instructed to code the sensory intensity of perceived pain on a visual analogue scale (VAS) 0–10 scale, in which 0 denoted "no pain" and 10 denoted "the maximum imaginable intensity of pain". A detection threshold (innocuous stimuli) was defined as the highest stimulus intensity required for the subject to report a sensation of pressure rated 0. Moreover, the weight needed to provoke pain rated 2 [weak pain (WP)], rated 4 [moderate pain (MP)] and rated 6 [(strong pain (SP)] on VAS was determined. It was explained that the estimate concerned the sensory intensity of pain and not unpleasantness [20].

In a subsequent session, f-MRI data were performed using a 1.5T Siemens Magnetom Avanto MR scanner (Erlangen, Germany).

We performed two runs in the f-MRI section. In both runs subjects were exposed to the intensity levels of the stimuli as assessed during the previous psychophysical test.

The first run was performed to evocate sensory encoding of pain (P run), while the second to evocate sensory encoding of pain and cognitive pain intensity evaluation (PE run) in order to register a feedback to estimate the felt pain for each subject.

### Statistical analysis

For each subject f-MRI data were first realigned and resliced to correct for subject movement, then normalized to the MNI stereotactic space, smoothed with a 8 mm FWHM Gaussian Kernel. Finally data were statistically analyzed with SPM5 software (Wellcome Department of Cognitive Neurology, London, UK) (Matlab).

We performed contrasts to examine regions showing increased activity during painful stimuli compared to their baseline. We identified regions showing increased activity in each group with a double statistical threshold: only clusters with a voxel-wise intensity threshold of $p < 0.05$ (FDR correction) and a spatial extent of $p < 0.05$ uncorrected were considered to be significant. Moreover, we assessed the differences between the two groups (C group > CM group and CM group > C group) with a voxel-wise intensity threshold of $p < 0.001$ uncorrected and a spatial extent threshold of $p < 0.05$ (uncorrected).

In order to control for Type I error, we restricted the voxel-wise analysis to a set of prespecified ROIs in medial and lateral pain system of the pain matrix. For bilateral SI, SII, hIP1 and hIP2 ROIs were generated with the cytoarchitectonic probabilistic map presented in SPM Anatomy Toolbox, while for bilateral IC, IPL and ACC, ROIs were generated with the standard WFU Pickatlas Tool (Version 2.4) [21, 22] because those areas were not available as probabilistic areas in SPM Anatomy toolbox.

## Results

### Psychophysical results

Pain sensitivity thresholds following mechanical stimulation were determined for the CM group and the C group during the psychophysical session (Fig. 1). Analysis of variance with repeated measures of the weight used to evocate WP, MP and SP showed no effect for group membership [$F(2,19) = 1.63$; n.s.], a significant effect of threshold level [$F(4,17) = 29.488$ $p < 0.05$] and the absence of any interaction between the group and the threshold level [$F(4,17) = 0.68$, n.s]. Moreover, pain ratings of the stimuli administered during the PE run of the f-MRI session were recorded: a $t$ test showed no effect for group membership (mean CM group = 3.74; mean C group = 3.64; $p = 0.7573$ n.s.).

### Functional-magnetic resonance imaging results

#### *Whole brain analysis*

Analysis of f-MRI data revealed a common network for both groups of pain (P run) and pain with cognitive evaluation (PE run) related activity, showing increased activity in both medial and lateral pain system. These regions were the aMCC, IC, STG, IFG and PPC with different degree of lateralization. The analysis between groups revealed increased activity in the lateral pain system in particular in right postcentral gyrus, right inferior parietal lobule and bilateral supramarginal gyrus in the C group compared to CM group. No increase activity was found in the CM group when compared with the C group.

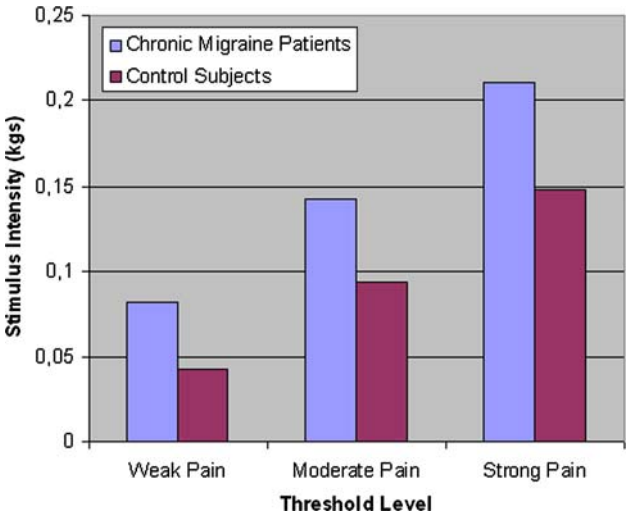


**Fig. 1** Mean pain sensitivity threshold

ROIs analysis were conducted to better investigate the predefined regions of the pain matrix over the contrast C group > CM group. We analyzed with a restrictive threshold ($p < 0.05$ FWE) the areas of the pain matrix that showed different activations between the two groups in the whole brain analysis: cluster of activations survived in the right hIP1, hIP2 and IPL. Moreover, we investigated the remaining areas of the pain matrix, that did not show any differences between the two groups, with a threshold of $p < 0.001$ uncorrected: in this case we did not find any differences in IC, ACC/aMCC or in SII.

## Discussion

Our data give new insight into the neural correlates that process the conscious perception of normal tonic mechanically induced cutaneous pain in healthy volunteers and in chronic migraine patients with medication overuse.

The major finding is the different activation of the right inferior parietal cortex between healthy subjects and chronic in migraine patients with medication overuse, in particular a decreased activation was found in the right supramarginal gyrus and in the right inferior and superior parietal cortex in chronic migraine subjects and this gets well with study confirming hypoactivation in some areas of the pain matrix in chronic migraine patients overusing medications [8].

Moreover, these data are consistent with the hypothesis that the pain matrix is significantly activated and that this activation produces a changed metabolism in some cortical areas in particular right posterior parietal cortex.

These change predominate in the right-sided posterior parietal cortex, which has been attributed the possible role

of the right hemisphere in the emotional aspects of pain and behavior.

Some of these mechanisms are involved in other chronic pain conditions as for example neuropathic chronic pain.

The idea of a common mechanism in chronic pain conditions is confirmed by PET studies showing bilateral blood flow changes in posterior parietal cortex in chronic neuropathic pain [8].

The difference we have found in the inferior parietal cortex seems to be framed in the possible role of the inferior parietal cortex in orientation and attention toward painful sensory stimuli.

Kulkarni et al. [23] in a PET study, designed to demonstrate division between sensory discriminative and affective response, found that attention to the location of the painful stimuli induces a significant change in inferior parietal cortex. Moreover, we found non-activation of SI, SII in both groups. Some functional imaging study failed to show activation in S1 [24, 25] during acute pain.

New common perspectives for the pathophysiology of chronic migraine with medication overuse might arise from brain imaging. Substance overuse and abuse in addiction to drug dependency and chronic neuropathic pain have multiple causes and demonstrate a shared pathophysiological base among these disorders.

Neuroimaging approaches might also highlight the differences among patients with medication overuse and patients with chronic headaches without overuse and patients with chronic neuropathic pain to reveal the disregulated neuroanatomic circuits associated with these syndromes.

It remains to be clarified if this type of change represents a primary regional pathologic aspect or a result of a pathologic process elsewhere in the brain that secondarily alters function in the regions probed by our f-MRI paradigm remains to be further elucidated.

**Conflict of interest statement** The authors declare that they have no conflict of interest related to the publication of this manuscript.

## References


1. Katsarava Z, Limmroth V, Finke M, Diener HC, Fritsche G (2003) Rate and predictors for relapses in medication overuse headache: a one year prospective study. Neurology 60:1682–1684
2. Biondi M (2006) Is migraine a neuropathic pain syndrome. Curr Pain Headache Rep 10:167–178
3. Kruit MC, van Buchem MA, Hofman PA, Bakkers JT, Terwindt GM, Ferrari MD, Launer LJ (2004) Migraine as a risk factor for subclinical brain lesions. JAMA 291:427–434
4. Kruit MC, Launer LJ, Ferrari MD, van Buchem MA (2005) Infarcts in the posterior circulation territory in migraine. The population-based MRI CAMERA study. Brain 128:2068–2077
5. Kruit MC, Launer LJ, Overbosch J, van Buchem MA, Ferrari MD (2009) Iron accumulation in deep brain nuclei in migraine: a population-based magnetic resonance imaging study. Cephalalgia 29:351–359
6. Kitaj MB, Klink M (2005) Pain thresholds in daily transformed migraine versus episodic migraine headache patients. Headache 45:992–998
7. Filatova E, Latysheva N, Kurenkov A (2008) Evidence of persistent central sensitization in chronic headaches: a multi-method study. J Headache Pain 9:295–300
8. Fumal A, Laureys S, Di Clemente L, Boly M, Bohotin V, Vandenheede M, Coppola G, Salmon E, Kupers R, Schoenen J (2006) Orbitofrontal cortex involvement in chronic analgesic-overuse headache evolving from episodic migraine. Brain 129:543–550
9. Talbot JD, Marrett S, Evans AC, Meyer E, Bushnell MC, Duncan GH (1991) Multiple representations of pain in human cerebral cortex. Science 251:1355–1358
10. Hsieh JC, Belfrage M, Stone-Elander S, Hansson P, Ingvar M (1995) Central representation of chronic ongoing neuropathic pain studied by positron emission tomography. Pain 63:225–236
11. Iadarola MJ, Max MB, Berman KF, Byas-Smith MG, Coghill RC, Gracely RH, Bennett GJ (1995) Unilateral decrease in thalamic activity observed with positron emission tomography in patients with chronic neuropathic pain. Pain 63:55–64
12. Apkarian V, Bushnell M et al (2005) Human brain mechanism of pain perception and regulation in health and disease. Eur J Pain 9:463–484
13. Sternbach R (1976) The need for an animal model of chronic pain. Pain 2:2–4
14. Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh Inventory. Neuropsychologia 9:97–113
15. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961) An inventory for measuring depression. Arch Gen Psychiatry 4:561–571
16. Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA (1983) Manual for the state-trait anxiety inventory (form Y). Mind Garden, Palo Alto
17. Stewart WF, Lipton RB, Whyte J, Dowson A, Kolodner A, Liberman J (1999) An International study to assess reliability of the Migraine Disability Assessment (MIDAS) score. Neurology 53:988–994
18. D'Amico D, Mosconi P, Genco S, Usai S, Prudenzano AM, Grazzi L, Leone M, Puca FM, Bussone G (2001) The Migraine Disability Assessment (MIDAS) questionnaire: translation and reliability of the Italian version. Cephalalgia 21:947–952
19. Ziegler EA, Magerl W, Meyer RA, Treede RD (1999) Secondary hyperalgesia to punctate mechanical stimuli. Central sensitization to A-fibre nociceptor input. Brain 122:2245–2257
20. Price D (2000) Psychological and neural mechanism of the affective dimension of pain. Science 288:1769–1772
21. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH (2003) An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage 19:1233–1239
22. Maldjian JA, Laurienti PJ, Burdette JH (2004) Precentral gyrus discrepancy in electronic versions of the Talairach atlas. Neuroimage 21:450–455
23. Kulkarni B, Bentley DE, Elliott R, Youell P, Watson A, Derbyshire SW, Frackowiak RS, Friston KJ, Jones AK (2005) Attention to pain localization and unpleasantness discriminates the functions of the medial and lateral pain systems. Eur J Neurosci 21:3133–3142
24. Jones AKP, Brown WD, Friston KJ (1991) Cortical and subcortical localization of response to pain in man using positron emission tomography. Proc R Soc Lond Biol 244:39–44
25. Bornhövd K, Quante M, Glauche V, Bromm B, Weiller C, Büchel C (2002) Painful stimuli evoke different stimulus-response functions in the amygdala, prefrontal, insula and somatosensory cortex: a single-trial fMRI study. Brain 125:1326–1336

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# Cluster headache and TACs: rationale for central and peripheral neuromodulation

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**Abstract** Cluster headache, the most severe of primary headache conditions for functional and social impairment it provokes, has been recently the object of a great amount of clinical, physiopathological, surgical and functional neuroradiological studies aimed to uncover the real mechanisms which underlie its disabling manifestations. Refinement of methodological and systematic features of multidisciplinary researches in this field has been allowing for more and more precise delineations of the role of both peripheral and central nervous system's contribution in pathophysiology of the disease. Aim of this manuscript is the report of the present knowledge in the role of the different surgical options in the treatment of drug-resistant cluster headache and Short-lasting Unilateral neuralgiform headache attacks with Conjunctival injection and Tearing (SUNCT), which take into account their different hypothesized pathological mechanisms and which comprise central nervous system's approach (Deep Brain Stimulation [DBS] and peripheral approach, namely Occipital Nerve Stimulation (ONS) and Vagal Nerve Stimulation (VNS).

**Keywords** Trigeminal autonomic cephalalgias · Deep-Brain Stimulation · Peripheral Nerve Stimulation

## Introduction

Diagnostic criteria for Trigeminal Autonomic Cephalalgias (TACs) are essentially clinical-based and are currently defined by the second edition of the International Headache Classification [ICHD-1, 2]. They comprise Cluster Headache, Paroxysmal Hemicrania, and SUNCT. Apart from strict characterization of pain's type, they all share the clinical features of headache and prominent cranial parasympathetic autonomic features, which comprise conjunctival injection and lacrimation (which suffice for definition of SUNCT) and other diagnostic features as nasal congestion, rhinorrhoea, forehead and facial sweating, miosis, ptosis, and eyelid oedema (which are more typical of Cluster Headache and Paroxysmal Hemicrania, though they could also be detected in SUNCT). They predominantly affect one side of the face, at least as far as initial manifestations are concerned.

The most relevant clinical features of CH attacks are their excruciating, stabbing, knife-like, and circadian-like characters. Diagnosis for Paroxysmal Hemicrania also require absolute response to therapeutical doses of Indomethacine. SUNCT pain attacks are typically short-lasting (5–240 s in length) and very frequent in the course of the day (3–200 in 24 h).

Cluster Headache can be further subdivided into two subtypes: episodic and chronic. In the episodic subtype, pain attacks usually occur in a cluster-like pattern, with clinical episodes lasting from 7 days to even 1 year, separated by pain-free intervals of at least one month. In chronic cluster headache pain attacks recur for a time period longer than one year without remission, or otherwise remission periods do not exceed one month.

Apart from Paroxysmal Hemicrania (which responds to Indomethacine administration), primary therapeutical management of Cluster Headache and SUNCT comprise drug therapy with different agents of several pharmacological classes, and including calcium-channel blockers (verapamil, nifedipine), beta-channel blockers (propranolol), cell membrane-stabilizers (sodium valproate, tiagabine,

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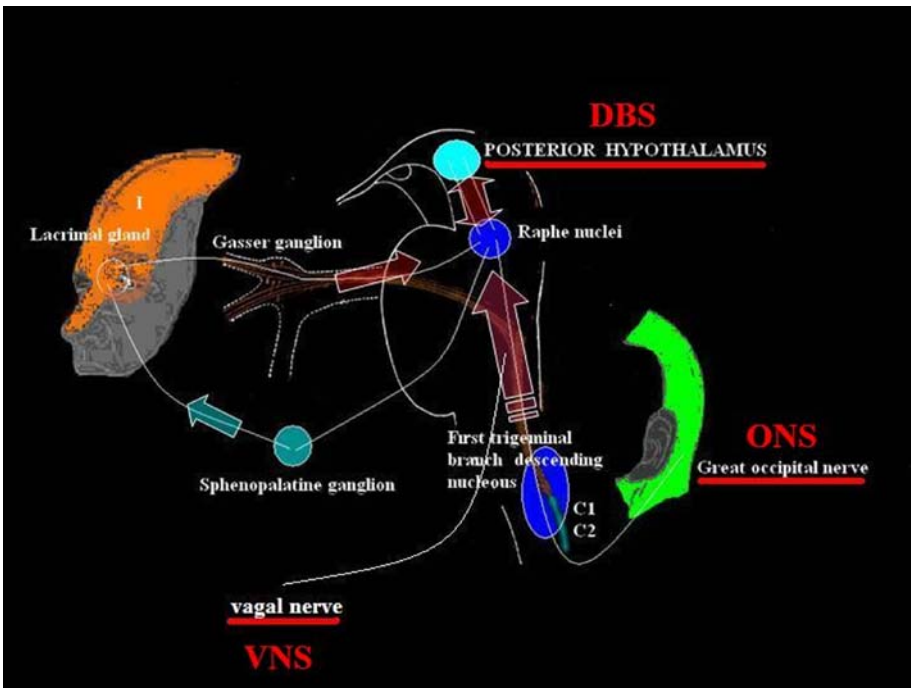


**Fig. 1** Schematic drawing of the neuronal pathways potentially influenced by central and peripheral stimulation in TACs. Note the central position of the raphe nuclei and the three "gates" for Neuromodulation (in *red*)

topiramate, lithium, levetiracetam), monoamine reuptake inhibitor agents (amitriptiline, bupropion, paroxetine, trazodone), opioids (methadone, hydromorphone, morphin), steroids and abortive drugs (sumatriptan, zolmitriptan, rizatriptan, almotriptan, meperidine, dihydroergotamine).

Pharmacotherapy is always adapted to the clinical needs and characteristics of the single patient, and the above-mentioned agents are variably combined among each other, their dosages and posology being modified according to the time-course and evolution of the disease.

Nevertheless, about 10–20% of patients with chronic CH continue to present daily attacks that are severely disabling despite optimum medical therapy [2]. Such refractory patients' population is nowadays considered for surgical procedures. Rationales for such invasive therapeutical options are provided by increasing amount of data addressing the role of specific peripheral and central nervous system's pathways and circuits in the pathophysiology and phenomenology of these life-threatening diseases.

## Considerations for surgical treatment

Selection criteria for surgical approaches to trigeminal autonomic cephalalgias invariably comprise:

- absence of functional improvement after adequate dosages of prophylactic and abortive drugs;
- patient's choice;
- normal neuroradiological examinations (including brain MR, CT and magnetic resonance angiography);
- absence of general medical conditions contraindicating surgical treatment.

Initial surgical management of refractory TACs has dealt with *peripheral* components of central nervous system potentially involved in the genesis of pain attacks. It comprised resection of the greater superficial nerve and of intermedius nerve, sphenopalatine ganglion block by local anesthesic or radiofrequency lesion, posterior fossa trigeminal sensory rhizotomy or percutaneous radio-frequency trigeminal gangliorhizolysis [3–11]. In particular, Taha et al. [11] reported the long-term effectiveness of percutaneous stereotactic radiofrequency rhizotomy in some patients with chronic cluster headache, though pointing out that patients with severe pain localized in the temple, ear and cheek regions may not be adequately benefit from such procedure, which mainly involves the "trigemino-vascular" system. Jarras et al. [10] reported that trigeminal nerve section could constitute an "effective treatment with acceptable morbidity for a carefully selected group of patients". Although potentially applicable and effective in some of the patients included in this reported series, these destructive procedures are irreversible in nature and could harbour major complications such as keratitis and anaesthesia dolorosa.

Peripheral interventional procedures on greater petrosal nerve and sphenopalatine ganglion underlie awareness of the involvement of vegetative system in the genesis of TACs, though they did not address the potential role of the autonomic-related structures of central nervous system.

*Central* nervous system-directed surgical approaches emerged in strict correlation to neuroimaging functional data, revealing metabolic abnormality in these structures in patients affected from Cluster Headache. May et al. [12] reported activation in ipsilateral posteroinferior hypothalamus during CH attacks, thus uncovering the role of diencephalon and related CNS regions in the genesis of this kind of painful syndrome. Deep-Brain-Stimulation has since then performed in Posterior Hypothalamus in a number of patients [13, 14] and in several Institutions, and it has shown to be an effective and safe procedure in the management of drug-refractory Cluster Headache. We also reported its efficacy in a patient with SUNCT, with which CH share autonomic-related manifestations, and in two out of five patients with Multiple Sclerosis-related trigeminal neuralgia [15].

Involvement in diencephalic structures in the genesis of TACs subsequently paved the way to further investigations aimed to estabilish the role of some of the brainstem regions which appear to contract functional relationships with posteroinferior hypothalamus in the generation of facial pain.

While physiological nociceptive perception shows a distinct topographic distribution, (with anterior head portions being innervated by trigeminal branches and posterior regions being innervated by the greater occipital nerve and posterior branches of the upper cervical nerves), such somatotopy may be not respected during headache attacks; it is not unusual for a patient with typical CH at onset to present an irradiation of pain into the occipital regions at later stages of the disease. Several lines of evidence have demonstrated the existence of a functional overlap between trigeminal nucleus caudalis and nuclei of spinal cord's dorsal horn of the first two cervical segments [16, 17]. The practical consideration deriving from this findings is that electrical stimulation of C2 C3 afferent fibers (the "occipital nerve complex") could modulate the trigeminal nucleus caudalis due to the anatomical relationships of C1, C2 and C3 sensory pathways to the trigeminal bulbo-pontine nucleus and the posterior hypothalamus [18, 19].

Taking into account such neurophysiological remarks, occipital nerve stimulation (ONS) has been in fact used not only for the treatment of occipital neuralgia, but also for CH, as well as for other facial painful syndromes and has showed to be effective in several patients [20–23]. Due to its less invasive nature and, subsequently, to the relatively minor surgical complications with respect to DBS, its employment is gaining crescent acceptance as primary surgical treatment of CH. At our Institution we primarily perform bilateral occipital electrodes placement connected to a dual-channel internal pulse generator (Kinetra Medtronic Inc., Minneapolis, USA) in patients with refractory CH; in patient who do not respond such modality after an adequate stimulation period with optimal parameters' settings, we offer the patient the replacement of the occipital electrodes with stereotactically-positioned hypothalamic ones.

Several other brain structures could anyway be involved in pathogenesis of painful facial syndromes; an involvement of the parasympathetic system has been suggested by Mauskop [24] and the role of hypothalamus in modulation of the autonomic nervous system is notorious.

Vagal nerve stimulation (VNS), which has been originally employed for treatment of drug-resistant major depression and several epileptic syndromes, has been shown to be effective in reducing intensity of migraine attacks in four patients who had received VNS for intractable seizures [25]; furthermore, Mauskop in 2003 reported improvement in 2 patients with chronic CH and in 2 patients with Chronic Migraine after VNS [26].

VNS has the capability to influence parasympathetic nervous system and has been shown to change blood flow in several brain structures such as posterior cingulated gyrus, hippocampus, amygdala, temporal cortex, thalamus, putamen, postcentral gyrus, insula and cerebellum [27–29]; the widespread central connections of ascending vagal pathways comprise numerous brainstem and diencephalic structures, including Nucleus of Tractus Solitarius, Nucleus Parabrachialis, Locus Coeruleus and several other nuclei harboring widespread projections to thalami and cortical structures. Through these pathways vagus nerve gains access to a variety of cortico-subcortical associative and limbic subcircuits, and affects neurotransmitter system which is also involved in facial painful syndromes.

## Discussion and conclusion

A delicate balance between peripheral and central functional mechanisms seems to underlie TACs as well as other headache types. Central structures addressed in the genesis of these diseases comprise hypothalamus, whose involvement is suggested by the profound influence on sympathetic and parasympathetic nervous systems. The central origin of CH is supported by some clinical characteristics (circadian and circannual rhythms of the attacks, alterations in circadian release of hormones [30] and by autonomic signs (ptosis, miosis, conjunctival injection, lacrimation, nasal congestion and rhinorrhoea) which often predominate in the clinical manifestations of CH and SUNCT. TACs involve primary or secondary dysfunction of pain modulating structures and intracranial vasculature, which is in turn supplied by autonomic fibers originating from otic, sphenopalatine and superior cervical ganglia, and by sensory fibers originating from trigeminal ganglion.

Positron emission tomography (PET) studies have been performed during both spontaneous and nitroglycerine-induced CH attacks [12, 31]; these studies have shown activation of the posterior inferior hypothalamus ipsilateral to the side of pain. Such findings have also been demonstrated for SUNCT [32] Furthermore, an increased hypothalamic neuronal density (as measured with Voxel-based morphometry) has been pointed out in the remission phase of CH [33].

Beside central mechanisms, several reports suggest a role for peripheral mechanisms in genesis of TACs. Though being less performed with respect to the past, ablative procedures provided some degree of benefit in patients affected from these disabling conditions; a recent report by Narouze et al. [9] reported satisfactory results in patients with chronic CH treated with Sphenopalatine Ganglion Radiofrequency Ablation. Jarrar in 2003 [10] reported effectiveness of trigeminal nerve section with "acceptable morbidity".

We recently treated with hypothalamic DBS a patient with CH secondary to unresectable infiltrating angiolipoma of the hemiface ipsilateral to the side of pain attacks and normal brain MR (unpublished data); initial results seem to be encouraging. Though control of symptomatology has been obtained by means of central stimulation, there is little doubt that, in this specific case, cluster headache episodes harbour a primarily peripheral origin.

The discover of the "trigeminocervical" complex as a functional brainstem unit (characterized by overlap in trigeminal and upper cervical painful receptive fields) could lead to revaluate migraine conditions as consequences of brain dysfunction or hypersensitivity rather than of blood vessels's dysfunctions; trigeminocervical complex has brought into light Occipital Nerve Stimulation for primary treatment in refractory TACs; the electrical stimulation of the posterior branch of C2 nerve (Greater Occipital Nerve of Arnold) seems to affect neural transmission at supra-segmental levels, influencing rostral pain-modulating structures. This therapeutical option has proven to be effective in treatment of several painful facial syndromes including CH, and could be offered to the patients as first-line surgical treatment before DBS.

The role of VNS as peripheral stimulation therapy of TACs is, at present, more controversial, given the multitude of brain structures reached by neuronal pools belonging to the "Dorsal Medullary Complex of Vagal Nerve [34]. The above-mentioned reports seem anyway encouraging for implementation of such technique in the treatment of these conditions; furthermore, it is possible to speculate that, given the widespread central vagal connections and influences exerted on the different cortico-subcortical circuits, VNS could also affect neuro-transmitter-mediated painful responses.

At our Institution we recently performed VNS on a patient with drug refractory Chronic CH who, having initially benefited from DBS, underwent recurrence of symptomatology after trivial head trauma (in presence of structural and functional preservation of DBS system), although not reaching the severe presurgical conditions; intracerebral electrode and pulse generator were left in situ and after implantation of VNS he is gradually improving and has halved daily drug posology (*unpublished data*). This latter case could be an example of the co-existence of peripheral and central pathophysiological mechanisms of TACs, given that the last clinical improvement was clearly due to the presence of both stimulation systems.

In conclusion, an imbalance between central and peripheral nociception mechanisms involved in pain perception and modulation seem to be involved in the genesis of TACs, as pointed out by several clinical, surgical, neurophysiological, functional and structural neuroimaging data. Neuromodulation appears to be the most advanced minimally invasive surgical therapy that may be proposed to patients affected by drugs refractory cranial pain syndromes.

However, only future prospective and randomized clinical trials including different surgical procedures including DBS, ONS and VNS and supported by functional neuroradiological assessment will be able to bring into light the real relationships between all of the above-mentioned hypothetical considerations.

**Conflict of interest statement** The authors declare that they have no conflict of interest related to the publication of this manuscript.

## References

1. Headache classification committee of the international headache society (2004) The international classification of headache disorders (2nd edn). Cephalalgia 24:1–195
2. Kudrow L (1980) Cluster headache mechanism and management, 1st edn. Oxford University Press, New York
3. Gardner WJ, Stowell A, Dutlinger R (1947) Resection of the greater superficial petrosal nerve in the treatment of unilateral headache. J Neurosurg 4:105–114
4. Trownbridge WV, French JD, Bayless AE (1953) Greater superficial petrosal neurectomy for orbitofacial pain: Preliminary report. Neurology 3:707–713
5. Sachs E Jr (1969) Further observations on surgery of the nervus intermedius. Headache 9:159–161
6. Rowed DW (1990) Chronic cluster headache managed by nervus intermedius section. Headache 30(7):401–406
7. Pieper DR, Dickerson J, Hassenbuch SJ (2000) Percutaneous retrogasserian glicerol rhizolysis for treatment of chronic cluster headache: long-term results. Neurosurgery 46:363–368
8. Sanders M, Zuurmond WW (1979) Efficacy of sphenopalatine ganglion blockade in 66 patients suffering from cluster headache: a 12- to 70-month follow-up evaluation. J Neurosurg 87(6):876–880
9. Narouze S, Kapural L, Casanova J, Mekhail N (2008) Sphenopalatine Ganglion Radiofrequency Ablation for the Management of Chronic Cluster Headache. Headache Sep 9. (Epub ahead of print)

10. Jarrar RG, Black DF, Dodick DW, Davis DH (2003) Outcome of trigeminal nerve section in the treatment of chronic cluster headache. Neurology 60(8):1360–1362
11. Taha JM, Tew JM Jr (1995) Long-term results of radiofrequency rhizotomy in the treatment of cluster headache. Headache 35(4):193–196
12. May A, Bahra A, Buchel C, Frackowiak RS, Goadsby PJ (1998) Hypothalamic activation in cluster headache attacks. Lancet 352:275–278
13. Leone M, Proietti Cecchini A, Franzini A, Broggi G, Cortelli P, Montagna P, May A, Juergens T, Cordella R, Carella F, Bussone G (2008) Lessons from 8 years' experience of hypothalamic stimulation in cluster headache. Cephalalgia 28:789–797
14. Franzini A, Ferroli P, Leone M, Bussone G, Broggi G (2004) Hypothalamic Deep Brain Stimulation for the Treatment of Chronic Cluster Headaches: A Series Report Neuromodulation 1:1–8
15. Gildenberg PL, Lozano AM, Tasker RR (2009) Textbook of stereotactic and functional neurosurgery, (in press)
16. Bartsch T, Goadsby PJ (2003) Increased responses in trigeminocervical nociceptive neurons to cervical input after stimulation of the dura mater. Brain 126:1801–1813
17. Piovesan EJ, Kowacs PA, Oshinsky ML (2003) Convergence of cervical and trigeminal sensory afferents. Curr Pain Headache Rep 5:377–383
18. Malick A, Strassman RM, Burstein R (2000) Trigeminohypothalamic and reticulohypothalamic tract neurons in the upper cervical spinal cord and caudal medulla of the rat. J Neurophysiol 84(4):2078–2112
19. Parè D, Smith Y, Parent A, Steriade M (1989) Neuronal activity of identified posterior hypothalamic neurons projecting to the brainstem peribrachial area of the cat. Neurosci Lett 107(1–3): 145–150
20. Schwedt TJ (2008) Occipital nerve stimulation for medically intractable headache. Curr Pain Headache Rep 12(1):62–66
21. Schwedt TJ, Dodick DW, Trentman TL, Zimmerman RS (2006) Occipital nerve stimulation for chronic cluster headache and hemicrania continua: Pain relief and persistence of autonomic features. Cephalalgia 6:1025–1027
22. Slavin KV (2008) Peripheral nerve stimulation for neuropathic pain. Neurotherapeutics 5(1):100–106
23. Slavin KV, Nersesyan H, Wess C (2006) Peripheral neurostimulation for treatment of intractable occipital neuralgia. Neurosurgery 58:112–119
24. Mauskop A (2001) Vagus nerve Stimulation for refractory migraine. Neurology 56(Suppl 3):A65
25. Hord ED, Evans MS, Mueed S, Adamolekun B, Naritoku DK (2003) The effect of vagus nerve stimulation on migraines. J Pain 4(9):530–534
26. Mauskop A (2005) Vagus nerve stimulation relieves chronic refractory migraine and cluster headaches. Cephalalgia 25(2): 82–86
27. Ko D, Heck C, Grafton S, Apuzzo MJ et al (1996) Vagus Nerve Stimulation activates central nervous system structures in epileptic patients during PET $H_2^{15}$ O blood flow imaging. Neurosurgery 39:426–431
28. Henry TR, Votaw JR, Pennell PB, Epstein CM, Bakay RAE, Faber TL et al (1997) Acute Vagus Nerve stimulation selectively alters blood flow in somatosensory and limbic cortex and the cerebellum of patients with complex partial seizures. Epilepsia 38(Suppl 8):144
29. Conway CR, Chibnall JT, Li X, George MS (2002) Changes in brain metabolism in response to chronic vagus nerve stimulation in depression. Biol Psychiatry 51:8S
30. Leone M, Bussone G (1993) A review of hormonal findings in cluster headache. Evidence for hypothalamic involvement. Cephalalgia 13:309–317
31. Sprenger T, Boecker H, Toelle TR, Bussone G, May A, Leone M (2004) Specific hypothalamic activation during a spontaneous cluster headache attack. Neurology 3:516–517
32. May A, Bahra A, Buchel C, Turner R, Goadsby PJ (1999) Functional MRI in spontaneous attacks of SUNCT: short-lasting neuralgiform headache with conjunctival injection and tearing. Ann Neurol 46:791–793
33. May A, Ashburner J, Buchel C, McGonigle DJ, Friston KJ, Frackowiak RSJ, Goadsby PJ (1999) Correlation between structural and functional changes in brain in an idiopathic headache syndrome. Nat Med 5:836–838
34. Henry TR (2002) Therapeutical mechanisms of vagal nerve stimulation. Neurology (Sept) 24;59(6 Suppl 4):S3–S14

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SYMPOSIUM

# Chronic migraine and chronic tension-type headache: are they the same or different?

**G. C. Manzoni · P. Torelli**

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**Abstract** The question in the title of this article arises from ambiguities in the diagnostic criteria for chronic migraine (CM) included in the 2004 International Classification of Headache Disorders, 2nd Edition (ICHD-II), and in the 2006 revision. More broadly speaking, it also arises from the fact that to date the general subject of chronic daily headaches (CDH) has not been approached in a correct and appropriate way. For all its limitations, ICHD-II has unquestionable merits and remains a fundamental tool. However, it is a tool that gets a snapshot picture of headache; so, it is not applicable to a dynamic form that evolves from and is transformed by a chain of events. If these events are ignored, there will be no accurate interpretation of the final clinical picture. Today, we still do not have any classification of headache syndromes to complement ICHD-II. Currently, then, the only way to approach the CDH issue is to put patients at the center and to focus on their life histories. If we reason strictly in terms of diagnostic classification criteria, which for this headache subtype are artificial and ambiguous, we may have trouble finding an answer to the title question. However, if we reason in broader clinical terms, putting at the center of our reasoning not only headache features, but patients with all their histories, the answer can only be that CM and chronic tension-type headache are two different clinical entities.

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**Keywords** Migraine · Chronic migraine · Chronic tension-type headache · Medication overuse headache · Chronic daily headache

## Introduction

For a correct approach to the relationship between chronic migraine (CM) and chronic tension-type headache (CTTH), we should first discuss two aspects that are inherently relevant to the issue: the first is the connections between migraine without aura and episodic tension-type headache, and the second is characterization of chronic daily headaches (CDH).

## Discussion

The first aspect has been widely debated for decades. Although opinions are somewhat conflicting [1–3], researchers are currently inclined to consider migraine without aura and episodic tension-type headache as two completely separate clinical entities. The international headache classifications themselves, which have been used as a guiding reference for investigators and clinicians in the last two decades, are consistent with this line of reasoning [4, 5]. On the other hand, if we were convinced that these two primary headache subtypes are a single entity, we should necessarily believe that CM and CTTH are also a single entity. Asking the title question, then, would not make any sense.

The second aspect is more complex, but at the same time it is also more intriguing and worthy of detailed critical reflection.

Interest in CDH rose in the early 1980s, when Mathew et al. claimed attention to the fact that migraine, a form of primary headache characterized by acute attacks, could sometimes change over the years into a daily headache, with the disappearance of disease-free intervals between one attack and the next [6].

The debate over this question has then grown in the following years to include the whole group of CDH and the role played by symptomatic drug abuse. Ample literature has certainly provided new and important knowledge. Unfortunately, though, there is not yet consensus on a subject that resembles a complicated puzzle with many pieces still missing.

The current "official" viewpoint on CDH originates from a compromise between the indications given by Silberstein's group in the 1990s [7], the criteria included in the 2004 ICHD-II [5], and their revision proposed by the members of the second headache classification subcommittee [8].

This viewpoint can be summed up as follows:

(a) The term "chronic daily headache" has merely a descriptive value. It can only be used for a general description of a heterogeneous group of headaches that have nothing in common but a distinctive pain temporal pattern. Therefore, CDH is not recognized as a separate entity by the international headache classification.

(b) Two rare headache subtypes, hemicrania continua (HC) and new daily persistent headache (NDPH), already included by Silberstein et al. [7] in their proposed classification of CDH, are recognized as separate clinical entities and are coded to Group 4 "Other primary headaches" of ICDH-II [5].

(c) The term "chronic migraine", which officially appeared for the first time in ICHD-II [5], is now preferred to "transformed migraine" (TM).

(d) The 2006 revised diagnostic criteria for CM [8], are now preferred to the official 2004 ICHD-II criteria [5] (Table 1), also in consideration of recent validation results [9].

(e) The same applies to alternative diagnostic criteria for medication overuse headache (MOH) [8], which are now preferred to the official criteria [5] (Table 2).

(f) CTTH always evolves from an episodic form. NDPH is a tension-type headache subtype that has been present every day since onset.

(g) CM, CTTH and MOH are three separate clinical entities. In cases of CM or CTTH with MOH, multiple diagnoses must be made and the option of probability diagnosis should be considered.

(h) The minimum time limit for diagnosis of the major CDH subtypes, i.e. CM, CTTH and MOH, is the presence of headache on at least 15 days a month for 3 months. In addition, the criteria for MOH diagnosis require intake of symptomatic medication for 10–15 days a month (depending on the type of medication) on a regular basis for 3 months. In the alternate diagnostic criteria for CM and MOH, time limits were left unchanged.

**Table 1** Current and revised International Headache Society criteria for chronic migraine

| |
|---|
| Current criteria (ICHD-II, 2004) (5) |
| 1.5.1 Chronic migraine |
| A. Headache fulfilling criteria C and D for 1.1 *Migraine without aura* on ≥15 days/month for >3 months |
| B. Not attributed to another disorder |
| Revised criteria (2006) (8) |
| Appendix 1.5.1 Chronic migraine |
| A. Headache (tension-type and/or migraine) on ≥15 days per month for at least 3 months |
| B. Occurring in a patient who has had at least five attacks fulfilling criteria for 1.1 Migraine without aura |
| C. On ≥8 days per month for at least 3 months headache has fulfilled C1 and/or C2 below, that is, has fulfilled criteria for pain and associated symptoms of migraine without aura |
| 1. Has at least two of a–d |
| (a) unilateral location |
| (b) pulsating quality |
| (c) moderate or severe pain intensity |
| (d) aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs) |
| and at least one of a or b |
| (a) nausea and/or vomiting |
| (b) photophobia and phonophobia |
| 2. Treated and relieved by triptan(s) or ergot before the expected development of C1 above |
| D. No medication overuse and not attributed to another causative disorder |

A few substantial objections can be raised to this approach to CDH in general and to its subtypes in particular.

If we are confronted with a problem that researchers' sustained efforts over many years have been unable to solve completely, we should pause to reflect on the reason for these difficulties and wonder whether it is really a complex issue or whether instead we are on the wrong track.

Far from denying that CDH is truly a complex issue, we should try to consider the second hypothesis and ask ourselves: what are we investigating and with what means?

We are dealing with a group of primary headache subtypes and, as we all know, the diagnosis of these forms depends only on accurate data collection from patients' histories.

**Table 2** Current and revised International Headache Society criteria for medication overuse headache

| |
|---|
| Current criteria (ICHD-II, 2004) (5) |
| 8.2 Medication overuse headache |
| A. Headache present on >15 days/month with at least one of the following characteristics as defined under subforms of 8.2 |
| Ergotamine, Analgesics, Combination medications: |
| 1. bilateral |
| 2. pressing/tightening quality |
| 3. mild or moderate intensity |
| Triptans: |
| 1. predominantly unilateral |
| 2. pulsating quality |
| 3. moderate or severe intensity |
| 4. aggravated by or causing avoidance of routine physical activity (e.g. walking or climbing stairs) |
| 5. associated with at least one of the following: |
| (a) nausea and/or vomiting |
| (b) photophobia and phonophobia |
| Opioids: headache characteristics not reported |
| B. Regular overuse for >3 months of one or more acute/symptomatic treatment drugs as defined under sub forms of 8.2 |
| 1. Ergotamine, triptans, opioids, or combination analgesic medications on ≥10 |
| days/month on a regular basis for >3 months |
| 2. Simple analgesics on ≥15 days/month on a regular basis for >3 months |
| C. Headache has developed or markedly worsened during medication overuse |
| D. Headache resolves or reverts to its previous pattern within 2 months after discontinuation of overused medication |
| Revised criteria (2006) (8) |
| Appendix 8.2 Medication overuse headache |
| A. Headache present on ≥15 days/month |
| B. Regular overuse for >3 months of one or more acute/symptomatic treatment drugs as defined under sub forms of 8.2 |
| 1. Ergotamine, triptans, opioids, or combination analgesic medications on ≥10 days/month on a regular basis for >3 months |
| 2. Simple analgesics or any combination of ergotamine, triptans, analgesics opioids on ≥15 days/month on a regular basis for >3 months without overuse of any single class alone |
| C. Headache has developed or markedly worsened during medication overuse |

In CDH even more than in primary acute headaches, patient history data do not merely describe the headache, but they help retrace how this headache evolved in the years, often the decades, preceding the first observation and they also enable investigators to reconstruct everything that happened over that period of time; in other words, they tell a life story.

As its promoters themselves expressly stated, ICHD-II is a classification of headache attacks: a very important, useful and worthy classification, but certainly not applicable to CDH without artificial and unprofitable adjustments.

ICHD-II provides a snapshot of headache: for CM, CTTH and MOH this snapshot focuses on the last 3 months of the disease and neglects all that happened before. But we know that all that happened before is a story of many years. By contrast, what happened in the last 3 months is often not indicative, because it may have been influenced by a number of comorbid conditions, primarily but not only psychiatric, and by the use or abuse of medication.

In CDH, at center stage there must be the patient with all his/her life history: one final snapshot will not tell us much and sometimes what it does tell us may be misleading.

The 1988 classification of the International Headache Society (IHS) [4] did not pay any attention to the CDH issue. In response to criticism raised from various parts in the following years, the 2004 ICHD-II [5] tried to remedy this omission by including CM in the migraine group using diagnostic criteria that were soon to be revised [8].

As set forth in ICHD-II [5], the diagnostic criteria for CM merely indicate a migraine without aura with a high-frequency of attacks in the last 3 months. However, this has nothing to do with patients who come to seek treatment at headache clinics because they have seen their migraine transformed for several years into a daily chronic headache.

The diagnostic criteria set forth in the 2006 revision [8] describe CM as a migraine without aura or a combination of migraine without aura and tension-type headache occurring at least 15 days in the past 3 months, with at least five attacks totaling at least 8 days of migraine [8] (Table 1). In their current formulation, these criteria certainly apply to many migraine forms that over time evolve into TM or CDH, but they can also apply to less severe forms, including some not so rare forms that may last only a few months and combine migraine without aura and episodic tension-type headache. In other words, CM becomes a hodgepodge that includes three very different clinical entities: high-frequency migraine without aura, a combination of migraine without aura and episodic tension-type headache, and TM. When we consider that a 3-month history of headache with no medication overuse is enough to make a diagnosis of CM, then it is easy to understand that CM is a non-severe form of primary headache, that TM has come in through the window but goes out through the door because there is no TM without medication overuse, and that CDH so frequently seen in headache clinics and so difficult to treat still lacks an appropriate nosographic classification.

The problem of CDH—of true CDH—and of its main subtype, that is migraine evolving over the years into CDH (no matter that we call it CM or TM) will be solved only if we are willing to reconsider the time limits for frequency (number of days in a month) and duration (months or years

of "chronicity"). If we raise those limits, we will no longer run the risk of including very different therapeutic options and totally different prognoses under a single umbrella of severity. We will then avoid a number of dangers, such as having unreliable epidemiologic data (indicating, for example, that 3% of the general population suffers from CDH!) or falsely encouraging therapeutic results.

One thing is patients who for 3 months have had frequent migraine without aura or a combination of migraine and tension-type headache occurring at least 15 days a month, or who for 3 months have taken symptomatic medication 10 days a month. Quite another thing is patients who, after suffering from migraine without aura for a long time, have not had a headache-free day for many years now and every day take one or more symptomatic drugs.

In terms of nosographic classification, the problem of CDH—of true CDH—and especially CM or TM, will finally be solved when we develop a classification of syndromes, or in other words a classification of patients, to complement such an important and well-designed classification of attacks as ICHD-II truly is.

## Conclusion

At the beginning of this article, I said that to find an answer to the title question we needed first to discuss the issue of CDH. The discussion has necessarily been broad and extensive, but the answer to the title question will be brief, because it comes out naturally from the reflections made in the discussion.

CM and CTTH are surely different clinical entities! More precisely, true CM—or true TM—and CTTH are two totally different clinical entities. Patients with migraine that evolves into CDH have nothing to do with patients with episodic tension-type headache evolving into CTTH! Nor can we reasonably expect that a patient with worsening migraine becomes a CTTH sufferer.

Let me be rude. The question in the title does not make sense. If we look at the patients that we see in our headache clinics, this question does not make sense. It does only if we reason in purely theoretical terms of strict diagnostic criteria. But these are artificial criteria that put a distance between us and our patients and unnecessarily raise doubts, if they are accepted critically.

It is true that over time migraine without aura often loses some of its distinctive features. For example, nausea and vomiting are reduced during attacks. It is even more true that many distinctive features of migraine often disappear in patients evolving to CDH forms. It is also true, though, that pain characteristics are heavily affected by intake of symptomatic medication one or more times a day. All this, however, is no justification for us to say that CM is the same thing as CTTH, not even if a strict application of diagnostic criteria would enable us to.

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

## References

1. Rasmussen BK (1996) Migraine and tension-type headache are separate disorders. Cephalalgia 16:217–220
2. Leston JA (1996) Migraine and tension-type headache are not separate disorders. Cephalalgia 16:220–222
3. Tietjen GE (1996) The primary headache disorders–apple sauce or fruit cocktail? Cephalalgia 16:223
4. Headache Classification Committee of the International Headache Society (1988) Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 8(Suppl 7):1–96
5. Headache Classification Committee of the International Headache Society (2004) The international classification of headache disorders, 2nd edn. Cephalalgia 24(Suppl 1):9–160
6. Mathew NT, Stubits E, Nigam MP (1982) Transformation of episodic migraine into daily headache: analysis of factors. Headache 22:66–68
7. Silberstein SD, Lipton RB, Sliwinski M (1996) Classification of daily and near-daily headaches: field trial of revised HIS criteria. Neurology 47:871–875
8. Olesen J, Bousser MG, Diener HC, Dodick D, First M, Goadsby PJ, Goebel H, Lainez MJA, Lance JW, Lipton RB, Nappi G, Sakai F, Schoenen J, Silberstein SD, Steiner TJ (2006) New appendix criteria open for a broader concept of chronic migraine. Cephalalgia 26:742–746
9. Zeeberg P, Olesen J, Jensen R (2009) Medication overuse headache and chronic migraine in a specialized headache centre: field-testing proposed new appendix criteria. Cephalalgia 29:214–220

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SYMPOSIUM

# Treatment of chronic migraine with medication overuse: is drug withdrawal crucial?

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**Abstract** Chronic headaches have increasingly become a focus within the field of head pain. For the most part patients with frequent headaches eventually overuse their medications, and if it happens (the percentage is approximately 4%), the diagnosis of chronic migraine with medication overuse headache is clinically important, because patients rarely respond to preventive medications whilst overusing acute medications. Properly treating medication overuse with adequate strategies is an essential component for helping these patients to improve and for preventing relapses. The necessity of withdrawal performed by different treatment schedules, outcomes, and the long-term durability of treatment are discussed.

**Keywords** Chronic headache · Medication overuse headache · Withdrawal protocols

## Clinical considerations

Epidemiological studies indicate that chronic headache is common with prevalence estimates ranging between 2 and 5%. The prevalence of chronic headache associated with medication overuse is about 4% [1].

In particular medication overuse is a major health problem all over the world, considering the potential secondary effects of chronic drug overuse on different organ systems (kidney, liver, etc.) and its significant increase in the last 15 years reflects the importance of this problematic condition.

Although the IHS classification offers explicit criteria [2], the diagnosis of chronic forms of headache does not require any specific examination that is needed only to exclude a symptomatic origin of chronic headache.

The headache is daily or nearly daily, it may change in intensity, type and location from time to time. A patient's intake of symptomatic medication is daily or nearly daily and concomitant prophylactic treatment is typically ineffective while patients are taking excessive amounts of symptomatic medications [1].

Emerging evidence shows that a number of behavioural/psychological risk factors are associated with progression of headache from episodic to chronic and daily and that psychological distress may play an even greater role in the transformation and chronicity of headache than does analgesic overuse or abuse. The identification of these psychological variables is a key component for establishing the adequate treatment regimen for these patients and it can also be of value in developing more specific treatment strategies [1–3].

Education is necessary for healthcare providers who treat patients suffering from headache and also the selection of different and specific therapeutic strategies which can help these patients to return at the original migraine pattern and to stop the medication overuse.

## Is withdrawal crucial for these patients?

Patients with chronic headaches and medication overuse are particularly difficult to treat and, although several

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studies have been published about chronic headaches and medication overuse, it is difficult to make comparative statements [1, 3].

Also, there are few investigations examining the natural course of chronic headaches with medication overuse. One of the most important points is: is drug withdrawal the most appropriate and effective first step to manage chronic headaches with medication overuse? And if yes, which are the adequate modalities for doing an effective withdrawal?

Many recent clinical experiences and reviews promote withdrawal of medication used to treat acute episodes of headache; moreover, it is under discussion which can be the best modality to perform the withdrawal itself.

In fact drug withdrawal strategies vary: no clear consensus exists on the best strategy, so in the most part of the studies, clinical experiences with different kinds of approach are discussed and compared.

The necessity of withdrawal is commonly accepted by the authors, and it has been largely confirmed in the last reports.

In a recent study a comparison of the outcome between two groups of patients has been conducted: the first group was treated by inpatient withdrawal, while the second group did not receive any treatment to stop the overuse. In the first group the percentage of patients whose chronic headaches became less frequent or episodic after one year was 70.7% and in the second group was 15.3% [4].

Nevertheless isolated clinical experiences show that pharmacological prophylaxis can be given without any withdrawal [5, 6].

In our clinical experience at the Neurological Institute "C. Besta" in Milan, the withdrawal is encouraged and the programme, which can vary in strategy and modality, always includes a complete explanation to the patients about the problem; also it is necessary to select with patients the best solution for their withdrawal, according to their characteristics, motivation to stop analgesics and compliance and finally to reinforce and to support the patients towards the goals from the beginning to the end of the therapeutic program [7, 8].

Where patients show a good compliance and motivation to stop analgesics misuse, this can help them to consider carefully the serious consequences derived from analgesics consumption, to identify the problems at the origin of the chronification process and to be adequately educated, supported and helped to strongly go towards the goals and to stop quickly the drug overuse.

The withdrawal is essential for giving patients the perfect consciousness of the problem, to be enforced to resolve it for ameliorating their clinical situation and this may be independent from the modalities by which the withdrawal is performed.

## Withdrawal strategies: one or more?

Drug withdrawal strategies can be different.

Abrupt withdrawal seems to be the most appropriate modality for stopping analgesics overuse. Some clinical experiences use a progressive interruption of medication overused, but this is necessary only for analgesics containing barbiturates: in this case in fact the abrupt interruption can favour seizure or other neurological symptoms [7].

The different modalities include: in-patient withdrawal, out-patient withdrawal or withdrawal in a day hospital setting.

Until now the in-patient withdrawal seems the most helpful and employed method: the patients can be carefully followed and monitored all day long and supported during the therapy programme [7, 9, 10].

Inpatient therapy is necessary for patients who take barbiturates, (as seizures or hallucinations, although rare, are observed as a consequence of barbiturates overuse) and for those who are not able to stop taking medications as outpatients or those with high levels of depression.

The typical withdrawal symptoms last 2–10 days [mean 3–5 days] and include withdrawal headache, nausea, vomiting, hypotension, tachycardia, sleep disturbances and anxiety. Patients often show signs of physical and emotional dependence and some form of psychological involvement.

These symptoms are less severe for patients overusing triptans.

Treatment components for the acute phase of drug withdrawal vary considerably between studies. They generally include fluid replacement, analgesics when strictly necessary for severe rebound headache, tranquillisers, sometimes neuroleptics and steroids and antiemetic drugs.

Steroids effectively reduce withdrawal symptoms, including rebound headache. The use of steroids for helping patients during withdrawal has been largely debated: different clinical experiences support the use of steroids for ameliorating and better managing the symptoms induced from the withdrawal during the first phase of it [7, 11].

In our clinical practice the intensity of the rebound symptoms is less evident by using steroids and patients control much better their pain and the vegetative symptoms of the rebound [7].

Besides, withdrawal headache can be treated with non-steroidal antiinflammatory drugs as in some cases, intravenous dihydroergotamine or subcutaneous sumatriptan or, in some patients, anxiolitics [12, 13].

Patients need to be supported and encouraged by the physician, nurses, allied health care providers, and family members to follow the instructions carefully to stop the vicious cycle between medication overuse and headache

increase in order to be effectively treated by prophylactic agents for migraine after discharge. It is necessary to follow the patients for an extended period of time with specific therapies for avoiding the risk of relapsing to former medication overuse.

Some clinical experiences support the hypothesis that an out-patient treatment can be helpful in particular patients who [14, 15] take a single drug or analgesic not containing barbiturates, or in patients motivated, self-disciplined, and who do not have a high level of depression or anxiety. To follow patients is necessary by phone calls to monitor clinical situation.

Another helpful alternative can be withdrawal within a day hospital setting. This approach, effective in motivated and self-disciplined patients, gives them the possibility to stay in the hospital for 5–6 h during the infusion therapy, and to stay at home (or at a local motel) for the last part of the day and during the night. In this case too, instructions have to be clear so that the patients avoid using medications for the rebound headache during the time they spend at home. Pini [16] and Grazzi [17] showed encouraging results, also if in the first case the follow-up period was too short (4 months); in the second report instead the follow-up was pretty longer (1 year) to encourage this kind of withdrawal.

After the acute phase of the withdrawal therapy is completed, a prophylaxis for migraine or tension-type headache can be started. The clinical, physical and psychological characteristics of the individual and the comorbid situations that are present (hypertension, depression, anxiety, tachycardia, sleep disturbances, obesity and so on) need consideration when designing treatment.

Proper instructions and appropriate surveillance are necessary in order to avoid relapse. In particular patients who suffer from migraine and tension-type headache have to be instructed to use antimigraine agents only for a severe attack.

Adequate time has to be dedicated to encourage patients to follow the instructions carefully in order to obtain the best clinical results from the withdrawal and the subsequent prophylactic therapy.

The headache diary is important to record attacks and medications consumed.

Also several follow-up appointments at regular intervals are necessary to monitor the clinical course.

The possibility to use behavioural approaches can be considered as these treatments are very helpful for patients and some encouraging results have been obtained during follow-up in terms of avoiding relapses in medication overuse [18].

Behavioural techniques, such as relaxation therapies and stress management, should be started as soon as possible after the acute withdrawal phase to increase the efficacy of any prophylaxis and to encourage and teach patients to manage the pain and the stressful events which often induce or increase the migraine episodes. Grazzi et al. have shown that the addition of behavioural treatment can enhance outcome over drug treatment alone, with respect to both symptom reduction and relapse prevention [18].

Criteria for determining success of withdrawal therapy have varied across studies. It has been suggested that success can be defined as no headache at all or an improvement of more than 50% in terms of headache days.

In the outcome studies that have been completed, follow-up intervals have varied considerably. Several studies have reported outcomes for periods of 12 months or less. All of these studies show that this category of patients requires intensive treatment and a careful analysis of their clinical condition for obtaining significant clinical improvement and significant decrease in analgesic consumption [10, 18, 19].

In particular at the 1 year follow-up of patients treated by an inpatient programme, Monzon [20] found 55% of patients recorded significant clinical improvement ranging 26–30%.

On the other side the follow-up periods have been fairly brief for adequately assessing the risk of relapse and new chronicity. Recently other authors have been able to conduct studies with longer term follow-up in order to provide a more thorough analysis of relapse and clinical course [21, 22].

Our group too showed results at the 5 year follow-up for a group of patients after an inpatient withdrawal programme. A significant clinical improvement with a significant decrease in the amount of analgesic consumption was recorded and maintained with a low percentage of relapses [23].

Also significant results were obtained at the 1 year follow-up in a group of patients after a withdrawal performed in a day hospital setting [17].

In all these papers, a part from the clinical results, it emerges that patients have greater risk of relapsing within the first 12 months after withdrawal, and they have a decreased risk of relapsing if they have avoided medication overuse for 12 months after withdrawal therapy.

Although the findings concerning the clinical results after withdrawal are highly encouraging, with a long follow-up period, they are by no means definitive. The major limitation is the absence of a control or comparison condition. On the basis of these reports, comparative outcome investigations, incorporating appropriate control and/or comparison conditions, appear warranted. Also if from our results we can confirm that withdrawal remains an effective procedure for these patients.

## Concluding remarks

Patients with medication overuse headache are particularly difficult to treat. No clear consensus exists about treatment strategies to be used also if it seems largely confirmed that the withdrawal has to be the first step for managing these patients. Notable improvement both in headache parameters and analgesics consumption can occur coincident with withdrawal treatment independently from the modality. Future studies need to incorporate improved methodologies in order to provide firmer conclusions about patient treatment interactions.

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## References


1. Diener HC, Limmroth V (2004) Medication overuse headache: a worldwide problem. Lancet Neurol 3:475–483
2. Headache Classification Subcommittee of the International Headache Society (2004) The International Classification of Headache Disorders. Cephalalgia 24:Suppl 1
3. Diener HC, Mathew NT (2000) Drug induced headache. In: Diener HC (ed) Drug treatment of migraine and other frequent headaches, vol 17. Karger Press, Basel, pp 347–356
4. Bigal ME, Rapoport AM, Sheftell FD, Tepper SJ, Lipton RB (2004) Transformed migraine and medication overuse in a tertiary headache centre–clinical characteristics and treatment outcomes. Cephalalgia 24:483–490
5. Mathew NT, Kailasam J, Meadors L (2002) Prophylaxis of migraine, transformed migraine and cluster headache with topiramate. Headache 42:796–803
6. Hagen K, Albretsen C, Vilming ST, Salvesen R, Gronnin M, Helde G, Gravdahl G, Zwart JA, Stovner LJ (2008) Management of medication overuse headache: 1 year randomized multicentre open-label trial. Cephalalgia 29:221–232
7. Grazzi L, Andrasik F, D'Amico D, Usai S, Kass S, Bussone G (2004) Disability in chronic migraine patients with medication overuse: Treatment effects at 1 year follow-up. Headache 44:678–683
8. Grazzi L (2008) Behavioural approach to the difficult patient. Neurol Sci 29:S96–S98
9. Freitag F, Lake AL III, Lipton R, Cady R, Diamond S, Silberstein S (2004) Inpatient treatment of headache: an evidence-based assessment. Headache 44:342–360
10. Lake AEIII, Saper J, Madden S, Kreeger C (1993) Comprehensive inpatient treatment for intractable migraine: a prospective long-term outcome study. Headache 33:55–62
11. Krymchantowski AV, Barbosa JS (2000) Prednisone as initial treatment of analgesic-induced daily headache. Cephalalgia 20:107–113
12. Raskin NH (1986) Repetitive intravenous diydroergotamine as therapy for intractable migraine. Neurology 36:995–997
13. Diener HC, Haab J, Peters C, Ried S, Dichgans J, Pilgrim A (1990) Subcutaneous sumatriptan in treatment of headache during withdrawal from drug-induced headache. Headache 31:205–209
14. Hering R, Steiner TJ (1991) Abrupt outpatient withdrawal of medication in analgesic-abusing migraineurs. Lancet 337:1442–1443
15. Krymchantowski AV, Moreira PF (2003) Outpatient detoxification in chronic migraine: comparison of strategies. Cephalalgia 23:982–993
16. Pini LA, Bigarelli M, Vitale G, Sternieri E (1996) Headaches associated with chronic use of analgesic: a therapeutic approach. Headache 36:433–439
17. Grazzi L, Andrasik F, Usai S, Bussone G (2008) In-patient vs day-hospital withdrawal treatment for chronic migraine with medication overuse and disability assessment: results at one year follow-up. Neurol sci 29(Suppl 1):S161–S163
18. Grazzi L, Andrasik F, D'Amico D, Leone M, Usai S, Kass S, Bussone G (2002) Behavioral and pharmacologic treatment of transformed migraine with analgesic overuse: outcome at 3 years. Headache 42:483–490
19. Baumgartner C, Wessely P, Bingol C, Maly J, Holzner F (1989) Longterm prognosis of analgesic withdrawal in patients with drug-induced headaches. Headache 29:510–514
20. Monzon M, Lainez M (1998) Quality of life in migraine and chronic daily headache patients. Cephalalgia 18:638–643
21. Silberstein SD, Silberstein JR (1992) Chronic daily headache: long-term prognosis following inpatient treatment with repetitive IV DHE. Headache 32:439–445
22. Schnider P, Aull S, Baumgartner C, Marterer A, Wober C, Zeiler K, Wessely P (1996) Long-term outcome of patients with headache and drug abuse after inpatient withdrawal: five-year follow-up. Cephalalgia 16:481–485
23. Andrasik F, Grazzi L, Usai S, D'Amico D, Kass S, Bussone G (submitted) Disability in chronic migraine with medication overuse: treatment effects through 5 years

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SYMPOSIUM

# Non-pharmacological approaches to treating chronic migraine with medication overuse

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**Abstract** Medication overuse headache (MOH) is now recognized as a biobehavioral disorder, a condition wherein emotion and pain are intermingled. This review discusses the steps to consider when treating this condition. The first step involves educating patients about MOH and the pathways to chronicity. The second step concerns working with patients to identify risk factors and behaviors that are present and contributing to the condition. The final step involves behavioral intervention. Examples for accomplishing each step are provided.

**Keywords** Non-pharmacological treatment · Chronic migraine with medication overuse · Medication overuse headache

## Introduction

We began our research with chronic migraine complicated by excessive medication consumption in the late 90s. Noting even at that time the relative poor response that occurred when using pharmacological treatment alone led us to design a rather straightforward comparison of drug treatment alone to drug treatment combined with a very basic behavioral treatment (a relatively short course of biofeedback, accompanied by brief training in progressive muscle relaxation training) [1]. All patients underwent a brief structured in-hospital drug withdrawal program and were immediately placed on a course of appropriate prophylactic medication. Some began the behavioral treatment while still on the inpatient unit, and continued to receive this additional treatment for a total of 8 weeks. Not knowing fully what to expect we decided to follow these patients prospectively for a minimum of several years. At the early followup evaluations we were pleased to note significant improvement for both conditions, such that the levels of improvement were indistinguishable statistically. However, between the 1-year and 3-year followup, a most interesting finding emerged. The group of patients receiving behavioral treatment in addition to medication treatment continued to hold their ground. In fact, they even obtained further gains. The individuals that received medication alone began to lose some ground, such that they now were statistically less improved when compared to the combination condition. Perhaps the most striking finding at 3 years is illustrated by the percentage of patients receiving medication alone who had relapsed in the intervening period (see Fig. 1). Obviously, something significant was occurring in the combination condition, but we had not thought to collect the ancillary data that would allow us to determine precisely what was going on in the years that intervened between years 1 and 3 of followup (or even if events that intervened were sufficiently different for the two groups and that this might be playing a part in accounting for the findings). Continuing to work with these difficult patients has given us new insights into their

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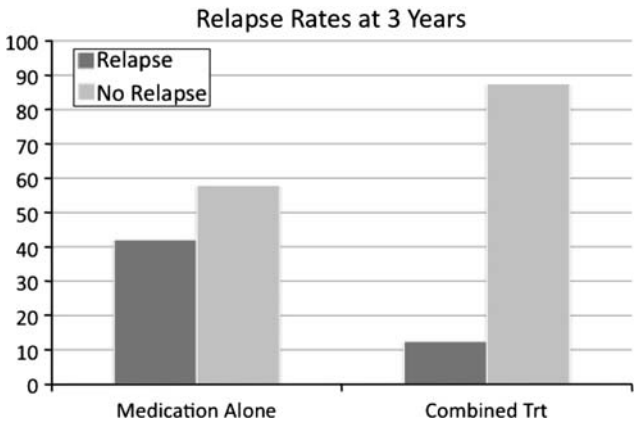


**Fig. 1** Percentage of patients relapsing to overuse of medication at the 3-year followup evaluation. Data extracted from Grazzi et al. [1]

dynamics and needs. In a separate paper in this special series [2] and elsewhere [3] we discuss some of the lessons learned regarding optimal ways to address the medication and medical needs of these patients. In the present paper we focus on the aspect that is all too often overlooked when treating chronic forms of headache accompanied by medication overuse—the cognitive and behavioral influences and determinants.

We and others have come to realize that medication overuse headache (MOH) is clearly a biobehavioral disorder. [4] As Saper et al. [4] have articulated so well, MOH is much more than a painful condition residing in receptor physiology; it is more aptly recognized as a condition wherein emotion and pain are intermingled. Lake [5] subsequently identified the basic psychological issues that can be key contributors to MOH:

- A belief that medication is the only treatment option
- The presence of "cephalagiaphobia" or pain panic (anticipatory fear of pain)
- Intolerance or difficulty dealing with pain
- Soporophilia (seeking sedation)
- The need to continue to function, outside pressures
- The presence of psychiatric comorbidities (Axis I and II on the DSM-IV)

Consider for a moment how the dynamics inherent in the above issues might come to bear. Take the case of the migraine patient whose headache attacks initially are infrequent and are effectively controlled by an abortive medication when taken in a timely manner. However, further suppose that when the abortive agent is not taken early, an extremely intense, debilitating headache results. This perhaps may plant the seed for a belief that medication is, if not the only solution, it is certainly the preferred solution. It is not a stretch to understand how the migraineur might begin an over focus on symptoms or sensations that may be suggestive of an impending migraine and begin further to anticipate (and fear and dread) attack onset. As Saper et al. [4] point out, it is more than a coincidence that the drugs most often overused have strong anxiolytic and/or sedating effects. Finally, assume it is Friday afternoon and the patient has a "must attend" function that night. Taking stock the patient notes peculiar physiological sensations and initial feelings of anxiety. Not wanting to take a chance, the *abortive* and/or *analgesic* medication is now taken as a *prophylaxis*. One does not have to imagine many such events need occur before MOH rears its ugly head.

Of course, this is just one scenario. Bigal and Lipton [6] provide insights into other pathways to chronicity that often interact with MOH. In their treatise, they distinguish between risk factors that are non-remediable (gender, age, socioeconomic status, head injury) and those that are potentially remediable. These modifiable risk factors consist of headache frequency, obesity, medication overuse (the focus of this review), caffeine, snoring/sleep apnea, depression, and stressful life events, all of which are subject to behavioral as well as medical/pharmacological modification. Patients may not at first blush be open to discussion of these factors. Using open-ended questions [7] (as opposed to close-ended questions) and applying the "Ask-Tell-Ask" strategy [8], which is based on the theory that education requires determining what the patient already knows and believes and then building on that knowledge, can lead to more effective communication and better identification of problem areas [9–12].

Considering the above, what behavioral actions are suggested? The first is educating patients about MOH and the pathways to chronicity. Second, and of equal importance, is working with the patient to identify risk factors and behaviors that are present and contributing to the condition. The third and most difficult action is behavioral intervention.

## Patient education

Patient education is exceeding important, because, in the final analysis, the patient is the one who decides which attacks to treat, when to treat, how to treat, and what if any behavioral or lifestyle changes are attempted [13]. A number of studies have documented the value of intensive patient education, not just for facilitating reductions in pain parameters, but also for obtaining meaningful improvements in functional status and quality of life, decreases in depression, and reduced use of medical services [14–17]. It is well known that patients do not always *hear* the message that is *spoken* to them. Rains et al. [18] provide the following suggestions for maximizing the value of patient education:

1. Limit discussion to a maximum of four topics.
2. Use simple, everyday language, and model or demonstrate when possible.
3. Provide supplemental written material.
4. Involve family members and/or significant others.
5. Ask patients to restate key information back to you.
6. Repeat and reinforce key concepts.

Asking patients to repeat back what has been said to them can be especially useful, as it helps identify concepts that have not been grasped and warrant further mention and concepts that have been misunderstood and need correction. It might seem a simple matter for patients to understand how to self-administer abortive medications, but many do not do so properly. Improper timing may be one of the factors leading to overuse. Specific, detailed education can significantly improve self-dosing and effectiveness [19].

## Motivation to change

Even when fully and properly informed, patients do not automatically act. Consideration of several behavior change models provides some insights into why this is so and suggests ways to motivate patients to act [20–25]. Fundamental to these models is the notion that behavior change and motivation are based upon three basic components:

1. The patient's readiness for change.
2. The patient's belief that they possess the requisite skills (self-efficacy).
3. 3. The patient's belief that application of the skills will lead to the desired outcome (outcome self-efficacy).

It is seen that knowledge and skills alone are not sufficient. The patient not only must want to change, but the patient must believe that he or she can make the required changes and that these changes will lead to the desired outcomes. Application of the "transtheoretical model" [23] can aid in understanding a patient's readiness and motivation for change, while application of the techniques of "motivational interviewing" [24, 25] may be useful in moving patients to higher stages of action. The transtheoretical model categorizes a patient's readiness and motivation into one of five stages (see Table 1). Movement among the stages is not always orderly and a patient may *lapse* from a higher state to a lower state before resuming progress. These models prefer the term *lapse* to *relapse* to emphasize that backward movement is not a permanent state or failure. Motivational interviewing focuses on the patient's stage of readiness and explores their beliefs, concerns, perspective, and ambivalence about behavior change, and it is an approach that has proven of particular value in addressing addictive behaviors. The therapist seeks to help the patient realize the importance of change, while maintaining an empathic, supportive, nonjudgmental stance. Motivation for change is enhanced when patients are helped to examine the pros and cons of change and arrive at decisions themselves (as opposed to being passive recipients of instructions for the therapist).

**Table 1** The five stages of the transtheoretical model (adapted from Prochaska et al. [23])

| Stage | Description |
|---|---|
| 1. Precontemplation | Patient not thinking about change, does not recognize the need for change or acknowledge that a problem exists |
| 2. Contemplation | Patient recognizes the need for change or that a problem exists, begins to think about change, may even be developing a plan, but no action is being taken |
| 3. Preparation | Patient has researched, consulted, and developed a plan, may being making minor changes/actions |
| 4. Action | Patient is actively engaged in behavior change or new actions |
| 5. Maintenance | Patient continues plan and behaviors necessary to maintain changes |

## Risk factors and behavioral intervention

The list of behavioral interventions is extensive and selection of techniques is guided by history and presence of risk factors. Cognitive behavioral stress coping training, biofeedback, and assorted relaxation treatments have been used extensively and require no further discussion at this point (see Buse and Andrasik [26], Andrasik [27], and Nestoriuc et al. [28]). Given the heightened presence of comorbid psychiatric conditions among migraineurs (depression, anxiety, social phobia, panic disorder, bipolar disorder, and suicide attempts) [e.g., [29–31]], screening, assessment, referral, and education about these common comorbidities need careful consideration. Maizels et al. [32] provide a review of brief screening instruments useful for assessing presence of depression and anxiety. Information obtained from these instruments can be reviewed with the patient. This may facilitate discussion about areas of concern and further inform treatment decisions, which may point to the need for a multimodal treatment. Smitherman et al. [33] suggest a number of very practical strategies for assisting patients with the comorbid conditions of depression and anxiety, the psychiatric conditions seen most often. A number of the strategies they identify apply equally, and some are specific to the co-presenting

**Table 2** Strategies for behavioral management of comorbid depression and anxiety

| Strategy | Depression | Anxiety |
|---|---|---|
| Educate the patient about the relationship between thoughts, behaviors, and emotions | X | X |
| Articulate that changing thoughts and behaviors can help improve condition | X | X |
| Advise the patient in initiating a regular program of physical activity/exercise | X | X |
| Provide training in active coping skills and/or general stress management | X | X |
| Help the patient realize he/she can live a valued life despite having chronic pain | X | X |
| Be alert to the potential for medication-overuse and underlying sleep disturbances | X | X |
| Help the patient develop a plan to identify and increase avoided activities | X | |
| Increase access to positive reinforcement in the patient's environment | X | |
| Implement methods for expanding the patient's social support network | X | |
| Limit exposure to contexts associated with negative emotions | X | |
| Have the patient chart, hour-by-hour, his/her activities during the course of a week | X | |
| Have the patient self-monitor desired behaviors and patterns of negative thinking | X | |
| Focus on generating rational alternatives to these patterns | X | |
| Have the patient identify and list his/her positive qualities and achievements | X | |
| Encourage initiation of a new hobby or action toward achieving a neglected long-term goal | X | |
| Help patient identify overt and covert methods of avoiding feared stimuli | | X |
| Decrease avoidance behavior through imaginal or in vivo exposure exercises | | X |
| Have the patient write in a diary about a past traumatic experience and associated emotions | | X |
| Have the patient monitor avoidance behaviors and patterns of negative thinking | | X |
| Focus on generating rational alternative to these patterns | | X |
| Have the patient chart fearful predictions and the actual incidence of their occurrence | | X |
| Incorporate relaxation training (such as progressive muscle relaxation commonly used with headache | | X |
| Instruct the patient to set aside 20–30 min each night for worry (rather than worrying throughout the entire day) | | X |

Adapted from Smitherman et al. [33], with permission of Wiley-Blackwell

condition. Their suggestions are reproduced in Table 2. Further information about addressing comorbid conditions may be found in Lake [5], Buse and Andrasik [26], Smitherman et al. [33], and Lipchik et al. [34].

## Summary

Lake [4] provides a succinct summary of the benefits to be gained from incorporating behavioral treatments with medication management when treating MOH. Although behavioral treatments rarely provide the quick relief that can occur with medication, patients undergoing behavioral treatments:

> "…learn to restructure their cognitive approach to pain, in essence learning how to tolerate discomfort, reduce pain-related emotional distress, stop the overly frequent pharmacological preemptive treatment of an impending headache, and reduce limbic escalation of the pain experience. If reinforced and maintained over time, these learned behaviors can help reduce the likelihood of overusing pain medication and MOH relapse." (page S95)

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## References

1. Grazzi L, Andrasik F, D'Amico D, Leone M, Usai S, Kass S, Bussone G (2002) Behavioral and pharmacologic treatment of transformed migraine with analgesic overuse: outcome at 3 years. Headache 42:483–490
2. Grazzi L, Andrasik F, Usai S, Bussone G (2009) Treatment of chronic migraine with medication overuse: is drug withdrawal crucial? Neurol Sci (this issue). doi:10.1007/s10072-009-0079-x
3. Grazzi F, Andrasik F, Usai S, Bussone G (2008) Headache with medication overuse: treatment strategies and proposal of relapse prevention. Neurol Sci 29:93–98
4. Saper JR, Hamel RL, Lake AEIII (2005) Medication overuse headache (MOH) is a biobehavioural disorder. Cephalalgia 25:545–546
5. Lake AEIII (2006) Medication overuse headache: biobehavioral issues and solutions. Headache 46(Suppl 3):S88–S97
6. Bigal ME, Lipton RB (2006) Modifiable risk factors for migraine progression. Headache 46:1334–1343
7. Martin LR, Jahng KH, Golin CE, DiMatteo MR (2003) Physician facilitation of patient involvement in care: correspondence between patient and observer reports. Behav Med 28:159–164
8. Boyle D, Dwinnell B (2005) Invite, listen and summarize: a patient-centered communication technique. Acad Med 80:29–32

9. Hahn SR (2008) Communication in the care of the headache patient. In: Silberstein SD, Lipton RL, Dodick DW (eds) Wolff's headache and other head pain. Oxford University Press, New York, pp 805–824
10. Buse DC, Lipton RB (2008) Facilitating communication with patients for improved migraine outcomes. Curr Pain Headache Rep 12:230–236
11. Lipton RB, Hahn SR, Cady RK et al (2008) In-office discussions of migraine: results from the American Migraine Communication Study. J Gen Intern Med 23:1145–1151
12. Hahn SR, Lipton RB, Sheftell FD et al (2008) Healthcare provider-patient communication and migraine assessment: results of the American Migraine Communications Study (AMCS) Phase II. Curr Med Res Opin 24:1711–1718
13. Cady R, Farmer K, Beach ME, Tarrasch J (2008) Nurse-based education: an office-based comparative model for education of migraine patients. Headache 48:564–569
14. Lemstra M, Stewart B, Olszynski W (2002) Effectiveness of multidisciplinary intervention in the treatment of migraine: a randomized clinical trial. Headache 42:845–854
15. Harpole L, Samsa G, Jurgelski A et al (2003) Headache management program improves outcome for chronic headache. Headache 43:715–724
16. Blumenfeld A, Tischio M (2003) Center of excellence for headache care: group model at Kaiser Permanente. Headache 43:431–440
17. Rothrock JF, Parada VA, Sims C et al (2006) The impact of intensive patient education on clinical outcome in a clinic-based migraine population. Headache 46:726–731
18. Rains JC, Penzien DB, Lipchik GL (2006) Behavioral facilitation of medical treatment for headache—part II: theoretical models and behavioral strategies for improving adherence. Headache 46:1395–1403
19. Holroyd KA, Cordingley GE, Pingel JD et al (1989) Enhancing the effectiveness of abortive therapy: a controlled evaluation of self-management training. Headache 29:148–153
20. Bandura A (1986) Social foundations of thought and action: a social cognitive theory. Prentice Hall, Englewood Cliffs
21. Elder JP, Ayala GX, Harris S (1999) Theories and intervention approaches to health-behavior change in primary care. Am J Prev Med 17:275–284
22. Jensen MP (2002) Enhancing motivations to change in pain treatment. In: Turk DC, Gatchel RJ (eds) Psychological approaches to pain management: a practitioner's handbook, 2nd edn. Guilford Press, New York, pp 71–93
23. Prochaska JO, Redding A, Evers KE (1997) The transtheoretical model and stages of change. In: Glanz K, Lewis FM, Rimer BK (eds) Health behavior and health education. Jossey-Bass, San Francisco, pp 60–84
24. Miller WR, Rollnick S (2002) Motivational interviewing: preparing people for change, 2nd edn. Guildford Press, New York
25. Miller WR (1996) Motivational interviewing: research, practice, and puzzles. Addict Behav 21:835–842
26. Buse DC, Andrasik F (2009) Behavioral medicine for migraine. Neurol Clin 27:445–465
27. Andrasik F (2007) What does the evidence show? Efficacy of behavioural treatments for recurrent headaches in adults. Neurol Sci 28:S70–S77
28. Nestoriuc Y, Martin A, Rief W, Andrasik F (2008) Biofeedback treatment for headache disorders: a comprehensive efficacy review. Appl Psychophysiol Biofeedback 33:125–140
29. Breslau N, Davis GC (1993) Migraine, physical health and psychiatric disorder: a prospective epidemiologic study in young adults. J Psychiatr Res 27:211–221
30. Jette N, Patten S, Williams J et al (2008) Comorbidity of migraine and psychiatric disorders: a national population-based study. Headache 48:501–516
31. Lanteri-Minet M, Radat F, Chautard H-H et al (2005) Anxiety and depression associated with migraine: influence on migraine subjects' disability and quality of life, and acute migraine management. Pain 118(3):319–326
32. Maizels M, Smitherman TA, Penzien DB (2006) A review of screening tools for psychiatric comorbidity in headache patients. Headache 46(Suppl 3):S98–S109
33. Smitherman TA, Maizels M, Penzien DB (2008) Headache chronification: screening and behavioral management of comorbid depressive and anxiety disorders. Headache 48:45–50
34. Lipchik GL, Smitherman TA, Penzien DB, Holroyd KA (2006) Basic principles and techniques of cognitive-behavioral therapies for comorbid psychiatric symptoms among headache patients. Headache 46(Suppl 3):S119–S132

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SYMPOSIUM

# Practical strategies for treating chronic migraine with medication overuse: case examples and role play demonstrations

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**Abstract** Patients with chronic migraine headaches complicated by medication overuse (MO) present some of the most difficult treatment challenges for headache practitioners. Recent research has identified a variety of risk factors (including MO) that appear to be associated with the escalation of the frequency and severity of migraine headache. Management of such patients with medication overuse headaches (MOH) may become more problematic due to co-morbid psychiatric issues common with migraine patients and the patient's reluctance to limit/eliminate "overused" abortive medications. Medication adherence becomes an important treatment concern. The present article will highlight treatment issues that must be considered in the assessment and treatment of patients with chronic migraine and MOH. Case examples will be offered to illustrate the process of the implementation of these strategies.

**Keywords** Medication overuse headache · Chronic migraine

## Introduction

The clinical presentation of headaches (especially migraine) is highly prevalent [1, 2] and affects not only individual patients (and their families) [3], but also, society at large. Social and economic systems suffer from the direct and indirect costs of disability due to headaches [4, 5]. Population-based studies have shown that most patients with migraine (1) fail to seek medical care for their headaches, (2) nearly half never receive a headache diagnosis, and (3) their headaches are sub-optimally treated [6]. Such findings are especially problematic as migraine headache may represent a progressive disorder in that episodic migraine sufferers develop transformed migraine at the rate of 2.5% per year [7].

Data from a specialized headache center in Germany [8] found that 14% of 450 episodic migraine patients developed chronic migraine headache (CM) within 1 year. Relative to episodic migraine patients, CM populations have been found to have higher rates of a variety of co-morbid conditions (psychiatric disorders, pain states, respiratory illness, and disease associated with cardiac risk) [9]; greater polypharmacy and social impediments [10]; and post-traumatic stress disorder [11]. In a recent review [12], it was noted that as the frequency of headache increases, patients will often increase consumption of acute headache medications which paradoxically causes "rebound headaches" and leads to chronic medication overuse headache (MOH) [13, 14].

The prevalence of MOH in North America, Europe, and Asia has been estimated to be 1–2% [14–16]. It was found that the percentage of patients with probable MOH at a North American headache center had remained relatively stable over the past several years (ranging from 64% in 1990 to 59.3% in 2005) [17]. One caution in the estimate of prevalence of MOH at any point in time is that there is a high rate of recidivism for patients despite appropriate treatment [18] which contributes to fluctuation of the number of cases in the population.

## Assessment

Medication overuse headache occurs when usually effective abortive agents become "overused", and their

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consumption leads to decreased efficacy regarding headache relief. This could lead to a rebound phenomenon in which the use of abortive agents paradoxically increases the frequency and severity of head pain. Numerous studies have noted the need to eliminate these agents from the patient's treatment as ongoing "overuse" negatively impacts both pharmacological and nonpharmacological interventions [19, 20].

When evaluating patients and formulating a treatment strategy, a careful medication history is important. It is important to assess not only what medications the patient takes (both prescription and over-the-counter preparations), but also, at what point in the pain process that the patient medicates. Many patients medicate in the anticipation of pain escalation which leads to increased (and possibly unnecessary) medication consumption. Other patients fail to take their migraine medication early in the headache process which minimizes the likelihood of becoming pain-free, increases the duration of the headache, and ultimately, leads to the use of more abortive medication.

## Treatment

An essential component to the treatment of MOH is the withdrawal of the "overused" medication [21]. Such strategies involve effective communication with the patient about the discontinuation/detox schedule regarding the offending agent [12]. Education regarding the "washout period" (the period of time that it may take the patient to experience significant improvement) is critical. Treatment typically takes place on an outpatient basis if patients have a relatively short period of MO, use only one or two substances at low doses, have adequate support systems, and are highly motivated [22]. Patients with more complicated medication regimens and greater medical/psychiatric co-morbidities may require inpatient treatment.

Headache calendars or diaries are necessary to document adequately the patient's treatment progress. Such documentation should include the detox schedule and the doses/frequency/limits of medication allowed. Appropriate preventive medications should be started. Patients may need to be seen frequently early in the treatment process of MOH in order to assist them during the "washout period".

In addition to the above medication strategies, non-pharmacological treatment is also indicated [12]. The combination of both pharmacological and nonpharmacological treatment has been shown to be superior to each individually [23] and appears to maximize long-term therapeutic benefit in MOH patients [24]. In addition, effective non-pharmacological strategies help to ensure pharmacological treatment compliance (which has been shown to be a significant problem with headache patients) [25, 26].

What follows are four clinical cases that illustrate some of the issues to consider in the treatment of migraine patients with MOH. Specific treatment strategies will be proposed.

## Clinical cases

### Case 1

A 33-year-old female noted an increasing frequency of migraine over the past year. Attack frequency had gone from two to eight migraines each month leading to 20 headache days per month. Attacks were associated with greater disability as her usually effective triptan offered less and less efficacy, and she had increased its use to over 15 days per month. She noted increased stress at work, trouble falling asleep, lethargy in the morning, and increased caffeine use during the day ("to help me stay alert"). She had not seen her physician in over a year as "I can't take time off". In addition, she noted that she had gained 10 pounds over the past year as she had no time to exercise (as she had done in the past).

It is essential to recognize and treat risk factors for headache progression when they become apparent. A variety of "modifiable" risk factors have been identified regarding headache progression in migraine patients [27]. These include increase in attack frequency, obesity, MO, stressful life events, caffeine overuse, and snoring/sleep apnea. Even though this patient is not experiencing daily headaches, aggressive treatment is warranted to prevent further headache progression.

The patient must be educated as to the concept of MOH, and she would be required to reduce her triptan usage and caffeine consumption. This could involve the use of a medication "bridge therapy" to help in the reduction. It would be advisable to reduce headache attack frequency by the use of preventive medication [28] especially one that could facilitate sleep. Behavioral treatment should be implemented to target (1) pain control during the "washout period" of the abortive medication reduction, (2) issues of sleep disturbance, (3) stress management regarding work issues, and (4) weight reduction and increased exercise [29].

### Case 2

A 45-year-old male noted that his migraine frequency had increased from one to ten severe attacks per month with a mild, "background headache" each day. The frequency had escalated over the past 5 months. The efficacy of his

triptan had been less, and he was taking it 4 days each week. In addition, he had post-traumatic "back pain" 8 months ago that was treated with an opioid. His back pain subsided after 1 month and, as his headaches increased, he began to take the opioid 2 or 3 days per week for his migraine ("it works though I have to take it more frequently now and more of it"). He returned to his headache physician because he had no refills on the opioid.

The use of pain medication has long been frowned upon for the treatment of migraine headache. A recent, population-based study [30] found that the use of barbiturates or opiates led to an increased risk of developing transformed migraine. Such data were consistent with earlier clinic-based studies in which migraine patients treated with opioids for other biological or pain issues were likely to develop transformed migraine [31–33]. Hence, extreme caution should be the rule in the use of opioids or butalbital agents in migraine patients even for other issues.

In the present case, education is essential regarding the need to decrease and eliminate his opiod use and to decrease his triptan consumption. "Bridge therapy" and the use of preventive medications would likely be necessary. Frequent physician contact and/or nonpharmacological pain management treatment would be helpful to ensure medication compliance. The use of headache calendars is important with such patients.

Case 3

A 33-year-old female experienced a significant increase in her migraines over the past year. Her attack frequency had increased from six times a year to 8 days per month of severe to incapacitating headache associated with daily, mild to moderate head pain. She had seen a physician 18 months previously who had diagnosed her as having intermittent migraine and prescribed a triptan for her attacks. She took the triptan on two occasions and had total relief. A family member told her that "triptans are 'strong medicines' and shouldn't be taken". She went back to using two over the counter analgesics for her migraines and increased the usage as attack frequency increased and she had little relief. Presently, she was taking two tablets three times each day.

She returned to her physician. Neurological exam and studies were negative, and she had no other neurological symptoms other than daily headaches. The patient was told that she had chronic migraine and MOH. She was educated that she would have to discontinue her analgesics, and a preventive medication was recommended to reduce migraine frequency. The patient refused the preventive medication because she was concerned about the possibility of side-effects.

As noted above, there are significant problems with respect to non-adherence to pharmacological treatment of headache and other medical disorders [25, 26]. It has been estimated that up to 40% of headache patients fail to return for treatment after consultation [34]. With respect to abortive medications, 70% of patients failed to take ergotamine correctly [35] and 20% of triptan prescriptions were never filled [36]. Approximately 25–50% of headache patients failed to take preventive medication correctly [37, 38]. It is an unfortunate irony that frequently clinicians will change treatment course without adequately assessing medication adherence.

With respect to preventive medication adherence, a variety of factors have been shown to affect whether patients take medications as prescribed. Positive factors include whether the clinician involves the patient in decision-making, whether the physician takes time to explain potential side-effects, and whether the physician relates to the patient published efficacy data [39]. Negative factors regarding adherence included whether the proposed preventive medication could cause weight gain or sedation.

In the present case, the patient needs to be educated as to the process of MOH and the potential negative consequences of daily use of over the counter analgesics. This risk needs to be weighed (by the patient) relative to a short-term trial of preventive medication that would likely speed improvement in head pain. If the patient agreed, pharmacotherapy should be simplified, and she should be given a written schedule of medications. Medication adherence should be noted on her headache calendars and checked closely at each visit.

Consequences of noncompliance to pharmacotherapy include "treatment failures" (including patients who have their treatment changed without adequate treatment trials); overuse of analgesic and "more potent" medications in an attempt to achieve headache relief; and increasingly more complex pharmacotherapy with the possibility of problematic drug interactions. For the patient, there is greater disability and greater disturbance in the performance of life tasks. For the clinician, there is an increased number of acute care or emergency department visits and/or more telephone contacts to the physician's office.

It has been found that both pharmacological and behavioral treatments are more effective when utilized early in the headache process and/or when pain is at a mild level. Despite the admonitions to medicate early in the headache process, many patients fail to do so. Delay in medicating migraine, however, is somewhat of a confusing treatment variable as it has been found that most migraineurs in tertiary care settings can correctly self-identify a headache as a migraine [40].

A recent study involving migraine patients [41] found that 45% of migraine patients delayed treatment beyond

what was advised. Reasons listed included "the need to reserve medications for a more severe headache" (51.2%), "did not have medication on hand" (34.9%), "health plan limits" (27%), "inability to swallow because of nausea" (18.7%), "not having access to fluid" (17.3%), and "not having privacy" (13.5%). Other research has found that the tendency to medicate a headache early in the pain process increases if there are associated symptoms of aura or photophobia, if the attack occurs during leisure activity, in the absence of other primary headaches, and when the patient is consistently instructed to medicate early by their physician [42].

Case 4

A 30-year-old female with a long-standing history of migraine, daily use of pain medications, and MOH comes to you for consultation. She maintains that the only medications that offer even limited relief contain either butalbital or opiates. Several attempts at detox have been short-lived, and the patient typically returns to daily or near-daily consumption. Triptans offer no relief although she has not had any extended period free of MO. She notes daily severe to incapacitating headache and significant disability. The patient has a prior psychiatric history of anxiety and depression. She takes anxiolytics in an effort to "at least have some sort of life". Her family is concerned that she is becoming more despondent and helpless.

Identification of subgroups of patients with MOH has been shown to predict treatment outcome. One approach [22] divides MOH patients into two groups—those with Type 1 or "simple" histories (relatively short-term drug overuse, relatively modest amounts of overused medications, minimal psychiatric contribution, and no history of relapse of after drug withdrawal) vs. those with Type 2 "complex" histories (multiple psychiatric co-morbidities and history of relapse). It is believed that the Type 1 group should be treated aggressively to prevent evolution into Type 2 patients. Non-pharmacological treatments are strongly recommended in addition to appropriate pharmacotherapy. It is essential that the Type 2 group have both pharmacological and non-pharmacological treatments.

There is an impressive literature that notes headache (especially migraine) is highly comorbid with depression, anxiety, and bipolar affective disorder [43]. In large scale population studies, migraine patients were 2.2 to 4.0 times more likely to have clinical depression [44]. It was found that the relationship between migraine and depression was bidirectional (i.e., the presence of either was more likely to predict the emergence of the other) [45]. Migraine was found to be comorbid with anxiety disorders as odds ratios ranged from 3.5 to 5.3 in generalized anxiety disorder and 3.7 with panic disorder [44]. With respect to bipolar affective disorder, the odds ratios have ranged from 2.9 to 7.3 [44].

The present patient is obviously in the Type 2 group requiring comprehensive treatment and frequent contact early on. In addition to appropriate pharmacological, non-pharmacological/behavioral treatment, psychiatric consultation would be warranted to assist in the management of this patient. Education is important regarding the discontinuation of her "pain" medications. Strict limits on medications and refills are essential. The patient's family should be involved as to maximize the likelihood that this treatment attempt will not fail (as others have in the past).

## Conclusion

Headache patients present with a history of experiences and expectations that affect both pharmacological and behavioral treatments. Chronic migraine complicated by MO is frequently a treatment challenge for the clinician. Effective treatment begins with establishing a therapeutic relationship with patients that has an expectation of treatment compliance. Patients must be "active participants" in the management of their headache disorder. Treatment goals must be defined behaviorally and objectively.

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

## References

1. Stewart WF, Lipton RB, Celentano DD et al (1992) Prevalence of migraine headache in the United States: relation to age, income, race, and other sociodemographic factors. JAMA 267:64–69
2. Lipton RB, Hamelsky SW, Stewart WF (2001) Epidemiology and impact of headache. In: Silberstein SD, Lipton RB, Dalessio DJ (eds) Wolff's headaches and other head pain, 7th edn. Oxford University Press, Oxford, pp 85–107
3. Lipton RB, Hamelsky SW, Kolodner KB et al (2000) Migraine, quality of life, and depression: a population-based case-controlled study. Neurology 55:629–635
4. VonKorff M, Stewart WF, Simon DJ et al (1998) Migraine and reduced work performance: a population-based diary study. Neurology 50:1741–1745
5. Hu HX, Markson LE, Lipton RB et al (1999) Burden of migraine in the United States: disability and economic costs. Arch Intern Med 159:813–818
6. Lipton RB, Bigal ME (2007) Ten lessons in the epidemiology of migraine. Headache 47(Suppl 1):S2–S9
7. Bigal ME, Serrano D, Scher A et al (2008) Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. Headache 48(Suppl 4):S3
8. Katsarava Z, Schneeweiss S, Kurth T et al (2004) Incidence and predictors for chronicity of headache in patients with episodic migraine. Neurology 62:788–790
9. Lipton RB, Buse D, Serrano D et al (2008) Differences in rates of common comorbid medical and psychiatric conditions in chronic and episodic migraine individuals. Headache 48(Suppl 4):S4

10. Ferrari A, Leone S, Vergoni AV et al (2007) Similarities and differences between chronic migraine and episodic migraine. Headache 47:65–72
11. Peterlin BL, Tietjen G, Meng S et al (2008) Post-traumatic stress disorder in episodic and chronic migraine. Headache 48:517–522
12. Rapoport A (2008) Medication overuse headache: awareness, detection, and treatment. CNS Drugs 22(12):995–1004
13. Cupini LM, Calabresi P (2005) Medication-overuse headache: pathophysiological insights. J Headache Pain 6:199–202
14. Diener HC, Limroth V (2004) Medication-overuse headache: a worldwide problem. Lancet 3:475–483
15. Colas R, Munoz P, Temprano R et al (2004) Chronic daily headache with analgesic overuse: epidemiology and impact on quality of life. Neurology 62:1338–1342
16. International Classification of Disorders, Committee of the International Headache Society (2004) Classification and diagnostic criteria for headache disorders, cranial neuralgia, and facial pain. Cephalalgia 24(Suppl 1):1–150
17. Meskunas CA, Tepper SJ, Rapoport AM et al (2006) Medications associated with probable medication overuse headache reported in a tertiary care headache center reported over a 15-year period. Headache 46:766–772
18. Dodick D, Freitag F (2006) Evidence-based understanding of medication overuse headache: clinical implications. Headache 46(Suppl 4):S202–S211
19. Mathew NT, Kurman R, Perez F (1990) Drug-induced refractory headache-clinical features and management. Headache 30:634–638
20. Ward TN (2008) Drug-induced refractory headache. Headache 48:728–729
21. Mathew NT (1990) Drug-induced headache. Neurol Clin 8:903–912
22. Lake AE (2006) Medication overuse headache: biobehavioral issues and solutions. Headache 46(Suppl 3):S88–S97
23. Holroyd KA, O'Donnell FJ, Stensland M et al (2001) Management of chronic tension-type headache with tricyclic antidepressant medication, stress-management therapy, and their combination: a randomized controlled trial. JAMA 285:2208–2215
24. Grazzi L, Andrasik F, D'Amico D et al (2002) Behavioral and pharmacologic treatment of transformed migraine with analgesic overuse: outcome at three years. Headache 42:483–490
25. Rains JC, Lipchik GL, Penzien DB (2006) Behavioral facilitation of medical treatment for headache—part I: review of headache treatment compliance. Headache 46:1387–1394
26. Rains JC, Penzien DB, Lipchik GL (2006) Behavioral facilitation of medical treatment for headache—part II: theoretical models and behavioral strategies for improving adherence. Headache 46:1395–1403
27. Bigal ME, Lipton RB (2006) Modifiable risk factors for migraine progression. Headache 46:1334–1343
28. Lipton RB, Bigal ME, Diamond M et al (2007) Migraine prevalence, disease burden, and the need for preventive therapy. Neurology 68:343–349
29. Nicholson R, Bigal M (2008) Screening and behavioral management: obesity and weight management. Headache 48:51–57
30. Bigal ME, Serrano D, Buse D et al (2008) Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. Headache 48:1157–1168
31. Wilkinson SM, Becker WJ, Heine JA (2001) Opiate use to control bowel motility may induce chronic daily headache in patients with migraine. Headache 41:303–309
32. Bahra A, Walsh M, Menon S et al (2003) Does chronic daily headache arise de novo in association with regular use of analgesics? Headache 43:179–190
33. Paemeleire K, Bahra A, Evers S et al (2006) Medication-overuse headache in patients with cluster headache. Neurology 67:109–113
34. Rozen TD (2008) Migraine prevention: what patients want from medication and their physician. Headache 48:750–753
35. Spierings EL, Miree LF (1993) Non-compliance with follow-up and improvement after treatment at a headache center. Headache 33:205–209
36. Holroyd KA, Cordingley GE, Pingel JD et al (1989) Enhancing the effectiveness of abortive therapy: a controlled evaluation of self management training. Headache 29:148–153
37. Gallagher RM, Kunkel R (2003) Migraine medication attributes important for patient compliance: concerns about side effects could delay treatment. Headache 43:36–43
38. Mulleners WM, Whitmarsh TE, Steiner TJ (1998) Noncompliance may render migraine prophylaxis useless, but once-daily regimens are better. Cephalalgia 18:52–56
39. Packard RC, Brown F (1986) Multiple headaches in a case of multiple personality disorder. Headache 26:99–102
40. Ng-Mak DS, Cady R, Chen Y et al (2007) Can migraineurs accurately identify their headaches as "migraine" at attack onset? Headache 47:645–653
41. Golden W, Katic BJ, Hu H (2008) Factors associated with early treatment of acute migraine headache pain. Headache 48(Suppl):S42–S43
42. Golden W, Katic BJ, Hu H (2008) Why did migraine patients not treat migraine attacks as early as they desired? Headache 48(Suppl):S42
43. Hamelsky SW, Lipton RB (2006) Psychiatric comorbidity of migraine. Headache 46:1327–1333
44. Low NCD, Merikangas KR (2003) The comorbidity of migraine. CNS Spectr 8:433–444
45. Breslau N, Lipton RB, Stewart WF et al (2003) Comorbidity of migraine and depression: investigating potential etiology and prognosis. Neurology 60:1308–1312

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ORAL COMMUNICATION

# Vagus nerve stimulation in drug-resistant daily chronic migraine with depression: preliminary data

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**Abstract** Drug refractory chronic daily headache (CDH) is a highly disabling condition. CDH is usually regarded as the negative evolution of chronic migraine (CM) and is characterized by high prevalence of psychiatric disorders, especially mood disorders. Vagal nerve stimulation (VNS) is an established treatment option for selected patients with medically refractory epilepsy and depression. Neurobiological similarities suggest that VNS could be useful in the treatment of drug-refractory CM associated with depression. The aim of the study was to evaluate the efficacy of VNS in patients suffering from drug-refractory CM and depressive disorder. We selected four female patients, mean age 53 (range 43–65 years), suffering from daily headache and drug-refractory CM. Neurological examination and neuroradiological investigations were unremarkable. Exclusion criteria were psychosis, heart and lung diseases. The preliminary results in our small case series support a beneficial effect of chronic VNS on both drug-refractory CM and depression, and suggest this novel treatment as a valid alternative for this otherwise intractable and highly disabling condition.

**Keywords** Vagus nerve stimulation · Chronic pain · Drug resistance · Depression

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## Introduction

Drug-refractory chronic migraine (CM) is a highly disabling condition, which constitutes a challenge in clinical practice. This condition is usually complex and is characterized by chronic daily headache (CDH), medication overuse headache (MOH) with no response to any preventive medication and is aggravated by depression [1]. This complex condition frequently requires hospitalization for withdrawal treatment, and relapses are common. Quite often, these patients develop a bio-behavioral pattern of dependence from symptomatic drugs (MOH), complicated by concomitant anxiety and depression, and decreased physical, mental and social functioning [1]. Migraine is comorbid with a large spectrum of diseases, from epilepsy [2] to stroke [3] and, mostly, psychiatric disorders [4]. The mechanisms through which migraine is transformed in drug-refractory CM and CDH with MOH are still poorly understood. Both migraine and depression are recurrent disorders and can become progressively chronic; in turn, chronicity induces changes in the underlying neurobiology of both pain perception and mood, further worsening the condition. In fact, it is well known that depression plays a role in the processing and perception of pain, and that depressed patients are more vulnerable to painful physical symptoms. A number of risk factors are known to be associated with the inability to achieve remission of chronic headache and they include life stress events and/or

enduring stressors, substance abuse, concurrent severity and duration of depression. Improvement of depression associated with chronic headache may improve the chance to revert the chronic pattern into episodic. Successful treatment of depression may be important for optimizing chronic headache treatment outcomes. Vagus nerve stimulation (VNS) is a procedure already available for resistant epilepsy [5], and it has been recently approved by the US Food and Drug Administration as an adjunctive treatment in chronic or recurrent medication-resistant depression [6]. Moreover, in retrospective studies, VNS has been shown to improve episodic migraine [7]. We applied VNS in four severely affected patients suffering from drug-refractory CDH and depression.

## Methods, patients' selection and surgical procedures for VNS

Patients suffering from drug-refractory CDH and depression for at least 2 years were selected. They had a history of medication overuse and several hospitalizations for withdrawal treatment despite adequate trials of all preventive treatments for migraine headache and depression suggested by current guidelines (exception made for those otherwise contraindicated), used alone or in combination. Furthermore, a main selection criterion for the surgical procedures was the severity of disability with significant impact on quality of life. Finally, in order to be selected, patients had to undergo regular follow-up at our Headache Centre for at least 1 year before surgery in order to attain a deep knowledge of the patient and verify both the consistency of reported high frequency of headache—daily or most days—and the patient's compliance, not only to the pharmacological treatment but also to report about analgesics intakes [8]. Exclusion criteria were psychosis, heart and lung diseases. Under these conditions, patients were implanted on a compassionate ground, after they gave an informed consent. They were assessed with the following procedures:

- full medical evaluation and brain MRI to exclude secondary headache forms;
- Structured Clinical Interview for DSM-IV (SCID) for Axis I diagnosis conducted by a psychiatrist;
- MIDAS questionnaire for headache disability;
- Hamilton Rating Scale for Depression (HRSD28).

Patients were asked to complete the daily headache diary reporting symptomatic intakes in the 6 months before and after ongoing surgery. Follow-up examinations were scheduled every 2 weeks for the first month, then monthly.

VNS consists of a subcutaneous pulse generator (Cyberonics®) implanted typically in the left chest wall connected by a wire to the bipolar lead wrapped around the left cervical vagus nerve. The initial stimulation parameters consisted of 30 Hz frequency, 500 ms pulse width with trains of 30 s in duration and stimulation intervals of 5 m. Current was titrated by step of 0.25 mA every 15–30 days to the maximally tolerated level, between 1 and 2.25 mA in our case series.

## Results

Four patients fulfilled selection criteria. They received full information about the procedure and gave their written informed consent. The VNS devices were implanted between December 2007 and July 2008. None reported post-surgical adverse effects. VNS was well tolerated; in the early stage of stimulation, mild disturbances related to the current were felt. These included voice alteration or hoarses, dyspnea, cough. Only in one case (case 4), it has been necessary to decrease the output intensity from 1.5 to 1.25 mA because of intolerance.

### Case 1

A 43-year-old Spanish female, victim of a dog's aggression at the face in 1999, developed a post-traumatic stress disorder and was hospitalized several times and intensively followed in psychiatry for 18 months. At the same time, she started to suffer severe migraine attacks, treated with cafergot and paracetamol, and transformed in a couple of years into a CDH with medication overuse. After having moved to Italy in 2001, she was hospitalized in a Headache Centre for a withdrawal treatment. Later, she underwent several prophylaxes without improvement, with increasing disability up to the work retirement in 2004. Headache was persistent, on a daily base, but the severity was decreased. In 2007, she suffered from a major depressive episode that precipitated, furthermore, the severity of headache exacerbations, especially during sleep time, and was treated with both sumatriptan 6 mg and paracetamol, avoiding NSAID because of gastritis. Finally, she passed further detoxification treatment in our Headache Centre in 2007. On the evidence of total refractoriness to pharmacological treatment of both headache and depression, on July 2008, she underwent implantation of VNS device. Just before the implantation, she stopped topiramate 100 mg because of no effect and continued taking sertraline 100 mg with olanzapine 5 mg. MIDAS was 100 with 86 number of headache days in last 3 months, the average intensity of headache VAS was 7.

She improved starting from the very beginning, with only seven abortive medication on the first month. At 14-month follow-up, she reports a mean of two to three

migraine attacks per month in menstrual period, and was responsive to sumatriptan 100 mg (1 tablet). Mood also improved greatly and she has started a new commercial activity. Sertraline has been reduced to 50 mg, while olanzapine was stopped. In the meantime, because of mild hypertension, she was started with ramipril 2.5 mg. VNS parameters are 1.5 mA, 30 Hz, 500 ms.

Case 2

A 47-year-old woman presented with chronic migraine in the last 4 years. She had experienced typical menstrual migraine since teenage. After delivery, at 22, her migraine gradually worsened, with severe menstrual status migrainous refractory to acute treatment. Since 2005, she has been hospitalized twice for MOH (indomethacin, eletriptan: about 50 doses/month, plus benzodiazepin), while several prophylactic treatments failed to control migraine and comorbid anxiety and mood disorder: dihydroergotamine, amitriptyline, propranolol, verapamil, lobivolol, venlafaxine, topiramate 100/day, and finally valproate 900/day plus trazodone 75 mg. She has always been anxious, but in the last 3 years she became depressed because of frequent headache increasingly disabling with forced work days loss, on average 10 days/month. A further detoxification treatment in June 2007, without stable clinical improvement, has led to the VNS implantation in December 2007. After the first month, she had still 21 headache days, with 43 abortive drug intakes. Headache improved starting from the second month and after 6 months she was satisfied with only two perimenstrual migraine attacks per month. The response to symptomatic treatment was faster and complete. She did not lose more work days. Anxiety and panic states became very mild, while depressive mood improved. VNS parameters are 2.25 mA, 30 Hz, 500 ms, well tolerated together with sertraline 100 mg/day and clonazepam 3 mg/day.

Case 3

A 49-year-old woman with a history of menstrual migraine, in 2000, has developed persistent facial pain on left side after an accidental domestic facial trauma with fractures of the orbital bone. After 2 years, she had retired from work because of persistent pain and medication overuse. She has been treated with CBZ 600/day, percutaneous microcompression of left-Gasser Ganglion, gabapentin, topiramate 300/day, lamotrigine 100/day, diazepam + aloperidhol, olanzapine 10 mg/day, paroxetine 20 mg/day, codeine 60 mg × 3/day, gamma-knife radiosurgery on left V and further anesthetic blocks, without any benefit. Then, amytriptiline 150 mg with clonazepam 6 mg/day, pregabalin 600/day and oxcarbazepine 1200/day and phenobarbital, mirtazapine 30 mg, trazodone 75 mg have been tried. She has been hospitalized twice in our centre. She is totally disabled and spends all the time at home, using tramadol 200 mg/day up to 600/day or paracetamol + codeine 6–8 tablets per day. The mood is severely compromised. She appears resigned, aphatic, claims and declares feelings of anger.

On May 2008, she was implanted with VNS device. Following the VNS implant, although she stated that facial pain was almost the same as before, she felt better and more active, with positive feelings such that pain was more tolerable and she greatly reduced—at least to half—the amount of symptomatic intakes. After 4 months, her painful attacks and the symptoms became worse, she used up to eight analgesic tablets per day together with BDZ overuse. She returned severely depressed as well. By this time, she had tried psychotherapy, but she felt worse and stopped soon. Even the last increase of sertraline to 200 mg/day with lithium 600/day, pregabalin 300/day, had not led to any improvement. VNS parameters are 2.25 mA, 30 Hz, 500 ms, well tolerated.

Case 4

A 63-year-old woman with a history of CDH, since age 30 started after the second delivery. She used optalidon (perfenazone + butalbital) daily: for the first 10 years, one suppository per day, slowly with increasing intakes up to eight per day in the last years. She was highly disabled and severely depressed. At the age 38, she got divorced and at age 42, she retired from work because of chronic headache; at the same age, she underwent decompressive ethmoid-sphenectomy, without pain relief. She has been treated with propranolol, valproate, topiramate, pizotifen, amitriptyline, diidergot, mirtazapine, tizanidine, flunarizine, gabapentin, delorazepam, triazolam and others. Withdrawal treatment did not produce any improvement. Thus, in July 2008, she received VNS. Mood improved starting from the second month, while headache persisted daily. Initially, she was satisfied with relative resumption of daily activity and reduction of drug intakes, but 5 months after the implant the headache worsened again. Voltage had to be decreased from 1.5 mA to 1.25 mA because of intolerance, and she was put on sertraline 100 mg/day, amisulpiride 25 mg/day.

## Discussion

Our study shows that VNS offers a potential novel approach to improve drug-refractory CDH associated with depression. This condition is highly disabling and is a challenge for headache specialists. VNS has the potential to modulate and restore normal function in many brain

regions involved in pain modulation as well as in mood and behavior. A retrospective study conducted in drug-refractory epileptic patients with migraine reported an improvement of migraine consisting of reduction in both headache frequency and intensity [9]. In the present study, two patients (50%) improved for both headache and depression 1–3 months after VNS was started. In drug-refractory epilepsy, VNS-induced improvement can be observed as a cumulative long-term effect [10]. Thus, for the two patients with limited or no improvement, long-term follow-up, more than 6 months, could be necessary in order to probe VNS efficacy.

In conclusion, the preliminary results in our small case series support a beneficial effect of chronic VNS in patients suffering from drug-refractory CDH and depression, suggesting this novel treatment as a valid alternative for this otherwise intractable and highly disabling condition.

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

## References

1. D'Amico D, Leone M, Grazzi L, Bussone G (2008) When should "chronic migraine" patients be considered "refractory" to pharmacological prophylaxis? Neurol Sci 29(Suppl 1):S55–S58
2. Diener HC, Küper M, Kurth T (2008) Migraine-associated risks and comorbidity. J Neurol 255(9):1290–1301
3. Bousser MG, Welch KM (2005) Relation between migraine and stroke. Lancet Neurol 4(9):533–542
4. Jette N, Patten S, Williams J, Becker W, Wiebe S (2008) Comorbidity of migraine and psychiatric disorders–a national population-based study. Headache 48(4):501–516
5. DeGiorgio CM, Schachter SC, Handforth A et al (2000) Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. Epilepsia 41(9):1195–1200
6. Nahas Z, Marangell LB, Husain MM et al (2005) Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. J Clin Psychiatry 66(9):1097–1104
7. Multon S, Schoenen J (2005) Pain control by vagus nerve stimulation: from animal to man…and back. Acta Neurol Belg 105:62–67
8. Leone M, Proietti Cecchini A, Mea E, D'Amico D, Tullo V, Grazzi L, Bussone G (2008) Therapeutic neurostimulation in chronic headaches: problems of patient selection. Neurol Sci 29(Suppl 1):S59–S61
9. Hord ED, Evans MS, Mueed S, Adamolekun B, Naritoku DK (2003) The effect of vagus nerve stimulation on migraines. J Pain 4(9):530–534
10. Heck C, Helmers SL, DeGiorgio CM (2002) Vagus nerve stimulation therapy, epilepsy, and device parameters: scientific basis and recommendations for use. Neurology 59(6 Suppl 4):S31–S37

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ORAL COMMUNICATION

# Spectral changes of near-infrared spectroscopy signals in migraineurs with aura reveal an impaired carbon dioxide-regulatory mechanism

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**Abstract** Subjects suffering from migraine with aura (MwA) present an altered cerebral autoregulation during migraine attacks. It is still unclear whether MwA sufferers present a normal autoregulation during attack-free periods. In this study, we characterized cerebral autoregulation in the frequency domain by analyzing the spontaneous oscillations superimposed on the cerebral hemodynamic signals, as detected by near-infrared spectroscopy (NIRS). Ten healthy women (age: 38.4 ± 9.5 years) and ten women suffering from MwA (age: 35.2 ± 10.5 years) underwent NIRS recording in resting conditions and during breath-holding (BH). Being the NIRS signals during BH nonstationary, we used the Choi–Williams time–frequency distribution to perform spectral analysis. We considered 256 s of signals and quantified the variation in the power of the very-low frequencies (VLF: 20–40 mHz) and of the low frequencies (LF: 40–140 mHz) as response to BH. Results showed that BH increases the power in the LF band both in healthy and MwA subjects. Considering the signal of the deoxygenated hemoglobin, the average power increase in the LF band was equal to 20% ± 15.4% for the healthy group and significantly lower, 4.8% ± 8.3%, in the MwA group (Student's $t$ test, $P < 0.02$). No significant difference was observed in the VLF band or in the oxygenated hemoglobin signal power variations of the LF and VLF bands. The resulting data reveal a possible impairment in the carbon dioxide-regulatory mechanism in MwA subjects.

**Keywords** Near-infrared spectroscopy · Migraine with aura · Cerebral autoregulation · Time–frequency distributions

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## Introduction

Over the last few years, there has been a growing interest in the investigation of cerebral autoregulation of migraine sufferers. Moreover, particular interest has been devoted to the cerebral hemodynamic assessment of patients suffering from migraine with aura (MwA). Even if cerebral autoregulation impairment has been observed during MwA attacks, it is still unclear whether MwA sufferers present a normal autoregulation during attack-free periods [1].

Cerebral hemodynamics can be effectively characterized in the frequency domain [2]. Spontaneous oscillations superimposed on the cerebral hemodynamic signals can be detected by near-infrared spectroscopy (NIRS). These oscillations can be subdivided into two frequency bands: very low frequencies (VLF), also known as B-waves, ranging from 20 to 40 mHz and low frequencies (LF), also called M-waves, ranging from approximately 40 to 140 mHz. At the brain level, VLF are thought to be generated by brain stem nuclei, which modulate the lumen of

the small intracerebral vessels; LF reflects the M-wave systemic oscillations of the arterial blood pressure and are modulated by the sympathetic system activity [3].

Functional stimuli modulate the amplitude of VLF and LF oscillations [2]. This study was aimed at the evaluation of the power changes of the VLF and LF oscillations, as assessed by NIRS, in a group of MwA sufferers, compared to a group of healthy subjects. Breath-holding (BH), which has already proven efficacious for cerebral autoregulation assessment, was used as an active stimulation [4].

## Subjects and methods

### Subjects

After having obtained written informed consent, ten healthy women (age: 38.4 ± 9.5 years) and ten women suffering from MwA (age: 35.2 ± 10.5 years) were enrolled into the study. MwA was diagnosed according to the International Classification of Headache Disorders, second edition (ICHD-II) [5]. The presence of vascular, neurological, psychological, cardiac pathologies and/or cardiac defects were excluded for all subjects on the basis of clinical and instrumental examinations. Breath-holding was performed in a quiet room with dimmed lighting and the subjects lying in a supine, comfortable position, with their eyes closed. Before and after BH, they rested for about 5 min.

An NIRO300 (Hammamatsu Photonics, Australia) was used to record the NIRS signals. The light source was positioned on the forehead, about 2 cm alongside the midline and 3 cm above the supraorbital ridge. The distance between the source and the receiver was equal to 5 cm, and the differential path length factor was set to 5.97. The sampling frequency of the signals was equal to 2 Hz.

### Signal processing

Since during BH the concentrations of the oxygenated ($O_2Hb$) and reduced hemoglobin (HHb) change very rapidly, the NIRS signals are to be considered as nonstationary. This implies that the time–frequency distributions should be used instead of the traditional Fourier-based spectral analysis. We used the Choi–Williams distribution, which is a bilinear transformation belonging to the Cohen's class [6]. Essentially, a series of instantaneous spectra of the signal under analysis may be obtained using this technique. These instantaneous spectra are then aligned up side-by-side, one for each time instant. Hence, the spectral content of a signal is represented in a bidimensional plane, as a function of time (on the horizontal axis) and frequency (on the vertical axis). In this way, the nonstationary nature of the NIRS signals during BH may be managed, making it possible to carry out a precise observation of the spectral component of the NIRS signals, at each single specific time instant. A time–frequency representation of an HHb NIRS signal is reported in Fig. 1.

The $O_2Hb$ and HHb signals were analyzed in the time–frequency plane and the percentage of signal power in the VLF and LF bands (referred to the total power of the signal) calculated before and after BH. We considered

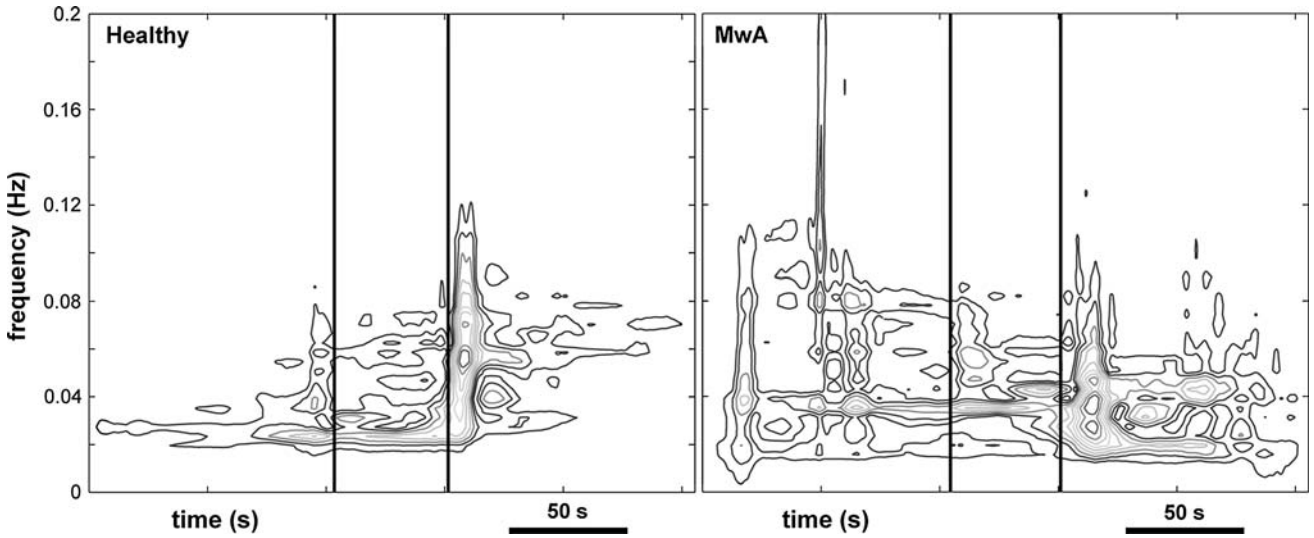


**Fig. 1** Representation by level curves of the time–frequency transform of the HHb signal of a healthy subject (*left panel*) and an MwA patient (*right panel*). The *horizontal axis* reports time and the *vertical axis*, frequency. The *black vertical lines* represent the onset and offset of the BH. The BH caused the power in the LF band (0.04–0.14 Hz) to increase strongly in the healthy subject (+33%), with only a weak increase in the MwA subjects (+6%)

signals lasting 256 s, with the BH event in the middle of the analysis window (see Fig. 1). Hence, spectral resolution was better than 4 mHz, which has been shown to be a suitable value to clearly separate the two frequency bands.

## Results and discussion

Figure 1 shows the TF distribution of the HHb signals in a healthy subject (left panel) and an MwA sufferer (right panel). The graph has been depicted by level curves. The black vertical lines indicate the onset and offset of the BH. Although it was observed that BH increases the power in the LF band in both the figures, in healthy subjects LF increased by about 33%, whereas in the MwA subjects there was only a 6% increase. Moreover, in healthy subjects the increase was sudden and instantaneous, whereas in the MwA subjects the LF power was dispersed over a larger time window.

On the global population, the average power increase in the LF band was equal to $20 \pm 15.4\%$ for the healthy group and $4.8 \pm 8.3\%$ in the MwA group. Healthy subjects showed a significant increase in the LF power compared to MwA patients (Student's $t$ test, $P < 0.02$). No significant difference was observed in the VLF band, nor was there any statistically significant difference in the $O_2Hb$ signal power variations of the LF and VLF bands.

The resulting data revealed a possible impairment in the carbon dioxide-regulatory mechanism in MwA subjects. In healthy subjects, at a microvascular level, the LF oscillations, which substantially reflect the sympathetic system activity, follow the macrovascular oscillations and become delayed in the presence of a hemodynamic impairment [7]. Hence, our results may show a possible impaired hemodynamic autoregulatory mechanism in MwA subjects.

**Conflict of interest statement** The authors declare that they have no conflict of interest related to the publication of this manuscript.

## References

1. Vernieri F, Tibuzzi F, Pasqualetti P et al (2008) Increased cerebral vasomotor reactivity in migraine with aura: an autoregulation disorder? A transcranial Doppler and near-infrared spectroscopy study. Cephalalgia 28:689–695
2. Obrig H, Neufang M, Wenzel R et al (2000) Spontaneous low-frequency oscillations of cerebral hemodynamics and metabolism in human adults. Neuroimage 12:623–639
3. Sliwka U, Harscher S, Diehl RR et al (2001) Spontaneous oscillations in cerebral blood flow velocity give evidence of different autonomic dysfunctions in various type of headache. Headache 41:157–163
4. Molinari F, Liboni W, Grippi G, Negri E (2006) Relationship between oxygen supply and cerebral blood flow assessed by transcranial Doppler and near-infrared spectroscopy in healthy subjects during breath-holding. J Neuroeng Rehabil 19:3–16
5. Headache Classification Subcommittee of the International Headache Society (IHS) (2004) The international classification of headache disorders (2nd edn.). Cephalalgia 24(Suppl 1):1–151
6. Cohen L (1989) Time–frequency distributions: a review. Proc IEEE 77(7):941–981
7. Reinhard M, Wehrle-Wieland E, Grabiak D, Roth M et al (2006) Oscillatory cerebral hemodynamics: the macro- vs microvascular level. J Neurol Sci 250:103–109

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ORAL COMMUNICATION

# Prevalence and characteristics of right-to-left shunt in migraine with aura: a survey on 120 Italian patients

**L. Caputi · Domenico D'Amico · S. Usai · L. Grazzi · E. A. Parati · G. Bussone**

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**Abstract** Many lines of research have suggested a relationship between migraine with aura (MA) and patent foramen ovale. Right-to-left shunt (RLS) of blood might explain both the occurrence of MA attacks, as well as the increased risk of ischaemic stroke in these patients. We evaluated the prevalence and the characteristics of RLS in a series of 120 MA patients, who were studied with contrast-enhanced Transcranial Doppler examination. We found RLS in 61 of them. A latent RLS was found in 28%, a permanent RLS in 72%, a shower-curtain pattern was detected in 52% of the studied patients.

**Keywords** Migraine with aura (MA) · Right-to-left shunt (RLS) · Prevalence · Contrast-enhanced Transcranial Doppler (cTCD)

## Introduction

Several retrospective studies and recent large prospective cohort studies indicate that a history of migraine, and in particular a history of migraine with aura (MA), may predispose to ischaemic stroke [1, 2].

Patent foramen ovale (PFO) may be a risk factor for ischaemic stroke according to two meta-analyses of case–control studies [3, 4], and to more recent surveys [5, 6].

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Several studies suggested an association between migraine, and particularly MA, and PFO. The prevalence of RLS among MA patients is significantly higher than that found in non-migraineurs. These data derived from surveys on samples of patients with cerebrovascular events possibly related to paradoxical embolization due to the presence of right-to-left shunt (RLS), and, in a minority of studies, from "pure" MA patients [7–10].

Furthermore, numerous studies indicated that percutaneous PFO closure could improve MA [7–10], with a marked reduction in attack frequency in most cases, and complete resolution in around 50% of them (range 29–92%). However, all published studies present methodological problems, which imply that outcomes could have been influenced by major recall bias as well as by a placebo effect. Furthermore, the results of the only prospective, randomized, sham procedure-controlled trial were negative [11]. Migraine resolved in only a small percentage of cases who underwent PFO closure, and there was no significant difference in post intervention attack frequency between the two groups [11].

Based on these findings, it has been speculated that PFO may be involved in the pathogenesis of MA, and that it may represent a link between MA and stroke. The fact that agents, such as serotonin, may bypass the pulmonary filter through RLS, could eventually favour those neurovascular events (such as cortical spreading depression), which may trigger MA attacks. On the other hand, RLS may allow venous microemboli to reach the cerebral arteries—and mainly the posterior circulation—increasing the risk of stroke in these patients.

If RLS is so important in MA, the assessment of the degree of RLS should be crucial, as it seems reasonable that the larger the shunt the higher might be the likelihood of presenting frequent MA attacks, and the higher the risk of developing cerebral ischaemic events.

In fact, some authors reported that the proportion of moderate/large shunts may be significantly greater in MA patients than in non-migraineurs, both in studies with transesophageal contrast echocardiography (TTE) or contrast-enhanced Transcranial Doppler (cTCD) [12–16].

The aim of the study was to assess the prevalence of RLS in a sample of "pure" MA patients, and to evaluate the size of their shunting.

## Methods

This was a prospective, observational study. All consecutive patients attending the Headache Centre of the C. Besta Neurological Institute from January 2006 to December 2007 with a diagnosis of MA were enroled in the study. Diagnosis was made according to the ICDH-II criteria [17]. All patients underwent cTCD according to standardized procedures [18, 19]. RLS was considered small if we detected $\geq$5 microbubbles $\leq$20 s after the start of injection of 10 ml of air-mixed saline into the right antecubital vein, without shower or curtain pattern; a large RLS was diagnosed with a shower or curtain pattern (uncountable RLS). RLS was considered latent if it occurred only after Valsalva manoeuvre; permanent when it occurred also at rest.

## Results

A total of 120 patients with MA (28 men and 92 women; mean age 37.5 years, SD 11.3 years) participated to the study.

We found RLS in 61 out of 120 patients (51%). A latent RLS was found in 17 patients (28%); a permanent RLS was detected in 44 patients (72%) patients. A large RLS (shower-curtain pattern) was detected in 32 patients (52% of the total sample, 27% of those with RLS).

## Discussion

Many lines of research have suggested a relationship between MA and PFO. RLS of blood across the PFO has been suggested to explain the occurrence of MA attacks, as well as the increased risk of ischaemic stroke in these patients. The evaluation of RLS presence and size may be important: in clinical samples, to better understand the PFO/MA relationship; in the individual patient, to investigate his/her potential risk of a more "complicated" headache form.

We evaluated the prevalence and the characteristics of RLS in 120 MA patients. Overall, our results were consistent with data in the literature. Our figure of a RLS prevalence at cTCD of 51% among MA patients is similar to the estimated prevalence of PFO reported in previously published studies (around 54%) [9–11]. We found permanent RLS in more than 70%. A large RLS (shower-curtain pattern) was detected in about half of our patients. Also these findings are substantially in line with previous studies with cTCD. In those studies in which the characteristics of RLS were systematically investigated, MA patients tended to present moderate-large shunts in 38–77% cases, with evidence of shunting both at rest and after Valsalva manoeuvre [11–16], and generally with a significant difference versus control subjects [15].

Further studies are needed to explore the possibility of a causal relationship between PFO/RLS and MA, as well as the possible role of PFO closure as a therapeutic option in MA patients, to reduce attack frequency and to prevent stroke. In this context, studies meant to evaluate the functional and anatomical characteristics of shunting in these patients might contribute to a better understanding of this unsolved topic.

**Conflict of interest statement** The authors declare that they have no conflict of interest related to the publication of this manuscript.

## References

1. Etminan M, Takkouche B, Isorna FC, Samii A (2005) Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies. Br Med J 330:63
2. Kurth T, Diener HC (2006) Current views of the risk of stroke for migraine with and migraine without aura. Curr Pain Headache Rep 10(3):214–220
3. Overell JR, Bone I, Less KR (2000) Interatrial septal abnormalities and stroke. A meta-analysis of case-control studies. Neurology 55:1172–1179
4. Amarenco P (2005) Patent foramen ovale and the risk of stroke: smoking gun guilty by association? Heart 91:441–443
5. Handke M, Harloff A, Olschewski M et al (2007) Patent foramen ovale and cryptogenic stroke in older patients. N Engl J Med 357:2262–2268
6. Homma S, Sacco RL, DiTullio MR, for PICSS Investigators et al (2002) Effect of medical treatment in stroke patients with patent foramen ovale. Circulation 105:2625–2631
7. Schwerzmann M, Wiher S, Nedeltchev K et al (2004) Percutaneous closure of patent foramen ovale reduces the frequency of migraine attacks. Neurology 62:1399–1401
8. Post M, Thijs V, Herroelen L, Budts W (2004) Closure of a patent foramen ovale is associated with a decrease in prevalence of migraine. Neurology 62:1439–1440
9. Diener HC, Kurth T, Dodick D (2007) Patent foramen ovale, stroke, and cardiovascular disease in migraine. Curr Opin Neurol 20:310–319
10. D'Amico D, Usai S, Caputi L, Bussone G (2008) Does closure of a patent foramen ovale have a role in the treatment of migraine with aura? Neurol Sci 29(Suppl 1):S23–S27
11. Dowson A, Mullen MJ, Peatfield R et al (2008) Migraine Intervention With STARFlex Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex

septal repair implant to resolve refractory migraine headache. Circulation 117:1397–1404
12. Schwerzmann M, Nedeltchev K, Lagger F et al (2005) Prevalence and size of directly detected patent foramen ovale in migraine with aura. Neurology 65:1415–1418
13. Carod-Artal FJ, da Silveira Ribeiro L, Braga H et al (2006) Prevalence of patent foramen ovale in migraine patients with and without aura compared with stroke patients. A transcranial Doppler study. Cephalalgia 26:934–939
14. Anzola GP, Morandi E, Casilli F, Onorato E (2006) Different degrees of right-to-left shunting predict migraine and stroke: data from 420 patients. Neurology 66:765–767
15. Jesurum JT, Fuller CJ, Velez CA et al (2007) Migraineurs with patent foramen ovale have larger right-to-left shunt despite similar atrial septal characteristics. J Headache Pain 8:209–216
16. Anzola GP, Meneghetti G, Zanferrari C, SAM Study Group et al (2008) Is migraine associated with right-to-left shunt a separate disease? Results of the SAM study. Cephalalgia 28(4):360–366
17. Headache Classification Subcommittee of the International Headache Society (2004) The international classification of headache disorders: 2nd edition. Cephalalgia 24(Suppl 1):1–160
18. Jauss M, Zanette E (2000) Detection of right-to-left shunt with ultrasound contrast agent and transcranial Doppler sonography. Cerebrovasc Dis 10:490–496
19. Schwarze JJ, Sander D, Kukla C et al (1999) Methodological parameters influence the detection of right-to-left shunts by contrast transcranial Doppler ultrasonography. Stroke 30:1234–1239

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ORAL COMMUNICATION

# Is allodynia influenced by psychological profile in headache patients?

**Carlo Lovati · D. D'Amico · P. Bertora · E. Morandi · C. Mariani · G. Bussone**

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**Abstract** Cutaneous allodynia is a frequent complain in headache patients, particularly in those with migraine. A stronger association is present in patients with migraine with aura and with chronic or transformed migraine. The aim of the present study was to investigate if the psychological profile may be related to the presence/absence of allodynia in a sample of headache patients. The psychological profile of patients was assessed by the SCL90R; the presence of allodynia was assessed by a set of semi-structured questions used in previous studies. For the purpose of the study, patients were divided into subgroups according to the headache type (ICDH-II diagnoses), as well as to the temporal pattern (episodic or chronic). A total of 213 consecutive headache patients were studied. Most patients had episodic migraine (116); 37 had tension-type headache. Overall, 156 patients had episodic headache forms, and 57 had chronic forms. As far as allodynia, 93 were non-allodynic; 120 presented allodynic symptoms during their headaches. No significant difference was found between allodynic and non-allodynic patients neither if studied in a whole group ($t$ test, $P = 0.10$ NS) nor when patients were evaluated comparing different subgroups on the basis of headache type, and of the episodic/chronic pattern. Our results suggest that the presence/absence of allodynia may not be influenced by the psychological profile.

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**Keywords** Allodynia · Psychological profile · Migraine · SCL90

## Introduction

Allodynia is the perception of pain induced by a non-noxious stimulus. According to several reports, allodynia is present in a large proportion of migraineurs. The migraine/allodynia association is stronger for migraine with aura and for the chronic forms (chronic or transformed migraine) [1, 2].

Allodynia seems to be favoured by the persistence of pain sensation that is able to induce central sensitisation in the caudal nucleus of the trigeminal nerve, but our knowledge is not yet complete: the reasons why the frequency of allodynia in migraine patients is not always related to the number nor to the severity of migraine attacks remain unexplained. Different pathogenetic mechanisms may be involved in the development of allodynia in migraineurs, including genetic, environmental, and psychological elements [2]. Furthermore, recent studies shown that head skin allodynia is not exclusive of migraine but is also present in other forms of primary headache, although in a lower proportion [3].

Recent researches suggested that alterations in central processing of sensory input might be facilitated by exposure to psychosocial and environmental stressors [4]. Several studies examining the neuropsychological correlates of migraine suggesting that mild dysfunctions may be observed in this regard amongst migraineurs, especially those with chronic forms [5–7]. The structural and functional changes observed in the central nervous system of migraineurs seem in turn to be influenced by psychological and neuropsychological factors [8].

We evaluated the relationship between psychological aspects and allodynia in a sample of migraineurs in a previous study [9], without finding any significant difference between allodynic and non-allodynic migraineurs as far as their psychological profile. Filatova et al. found central sensitisation levels to be unrelated to depression in a group of patients with chronic headache of various types [10]. Conversely, in patients with migraine and transformed migraine, allodynic symptoms were more severe in individuals with associated major depression as evaluated with the Allodynia Symptom Checklist [1]. The possible role of psychological aspects in the development of allodynia deserve more attention.

The aim of the present study was to investigate if the psychological profile of patients with different kinds of headaches, and not only migraine, may be related to the presence/absence of allodynia.

## Methods

We enroled a sample of patients presenting consecutively at the Headache Centre of the Ospedale L. Sacco from May to November 2008.

The psychological profile was assessed in each patient by the SCL90R [11], a 90-item self-report psychological symptom questionnaire that evaluates the following fields: somatization, obsessive-compulsive attitude, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. This tool gives the possibility to obtain a score for each psychological area, and a total mean score (global gravity index) that defines the global psychological condition.

The presence of allodynia was assessed by a set of semi-structured questions, which was used by our group in previous studies [3, 9]. This tool investigates if the patient experiences abnormal scalp sensitiveness and/or discomfort during headache episodes and activities able to enhance this symptom, such as touching head skin, combing hair, brushing hair, wearing glasses, and so on.

Patients were divided in to subgroups according to the headache type (on the basis of the ICHD II criteria) [12]. They were also divided in two subgroups according to the temporal pattern, i.e. episodic forms (14 or less days with headache/month) and chronic forms (15 or more days with headache/month), for each diagnostic group, as well as in the whole sample.

The *t* test was applied to compare the mean global gravity indexes obtained in allodynic and non-allodynic migraineurs out of each group.

## Results

A total of 213 headache patients were enroled. The diagnoses found in the studied sample are reported in the Table 1. Overall, 156 patients had episodic headache forms, and 57 had chronic forms.

Allodynia was found in 120 patients, while 93 were non-allodynic. The number of allodynic/non-allodynic patients in each subgroup is reported in the Table 1.

No differences emerged at statistical analysis between allodynic and non-allodynic patients of each subgroup, i.e. ICDH-II diagnoses, as well as episodic/chronic pattern, as far as the mean SCL90 global gravity index (see Table 1).

**Table 1** Presence of allodynia and SCL90 scores in the studied patients, according to ICDH-II diagnoses and to the episodic/chronic headache pattern (*SCL90 GGI* global gravity index at the SCL90 test, *NS* no significant difference at *t* test, *NA* statistical analysis not applicable)

| | | Non-allodynic | | Allodynic | | *t* test (*P* value) |
|---|---|---|---|---|---|---|
| | | Number of patients | Mean SCL90 GGI | Number of patients | Mean SCL90 GGI | Mean SCL90 GGI allodynic versus non-allodynic |
| 213 | Total headache patients | 93 | 0.64 | 120 | 0.76 | NS |
| 57 | Chronic forms | 17 | 0.62 | 40 | 0.93 | NS |
| 15 | Chronic migraine with aura | 1 | 0.33 | 14 | 1.00 | NA |
| 35 | Chronic migraine without aura | 10 | 0.74 | 25 | 0.91 | NS |
| 7 | Chronic tension-type headache | 1 | 0.47 | 6 | 0.24 | NA |
| 156 | Episodic forms | 76 | 0.64 | 80 | 0.76 | NS |
| 38 | Migraine with aura | 13 | 0.57 | 25 | 0.76 | NS |
| 78 | Migraine without aura | 36 | 0.60 | 42 | 0.66 | NS |
| 37 | Tension-type headache | 25 | 0.74 | 12 | 0.59 | NS |
| 3 | Others | 2 | 0.85 | 1 | 0.65 | NA |
| 180 | Females | 70 | 0.64 | 110 | 0.79 | NS |
| 33 | Males | 23 | 0.67 | 10 | 0.45 | NS |

## Discussion

As previously observed in a pilot study on a sample of migraineurs [9], our results on a sample of headache patients showed that the presence/absence of allodynia seems not to be influenced by the psychological profile. This lack of significant association was found both when patients were divided according to different ICDH-II diagnoses and when patients were divided according to the episodic or chronic headache pattern. These results reinforce the hypothesis that allodynia is a "somatic" symptom, which may be not significantly influenced by psychological aspects, at least as assessed by the specific tool we used in our survey (SCL90).

**Conflict of interest statement** The authors declare that they have no conflict of interest related to the publication of this manuscript.

## References

1. Bigal ME, Ashina S, Burstein R, Reed ML, Buse D, Serrano D, Lipton RB, AMPP Group (2008) Prevalence and characteristics of allodynia in headache sufferers: a population study. Neurology 70(17):1525–1533
2. Lovati C, D'Amico D, Bertora P (2009) Allodynia in migraine: frequent random association or unavoidable consequence? Expert Rev Neurother 9(3):395–408
3. Lovati C, D'Amico D, Bertora P, Rosa S, Suardelli M, Mailland E, Mariani C, Bussone G (2008) Acute and interictal allodynia in patients with different headache forms: an Italian pilot study. Headache 48(2):272–277
4. Bradley LA (2008) Pathophysiologic mechanisms of fibromyalgia and its related disorders. J Clin Psychiatry 69(Suppl 2):6–13
5. Puca FM, Antonaci F, Genco S, Savarese MA, Piazzolla G, Prudenzano MP (1989) Psychologic factors in chronic headache: assessment by means of the SCL-90-R inventory. Cephalalgia 9(1):33–51
6. O'Bryant SE, Marcus DA, Rains JC, Penzien D (2005) Neuropsychology of migraine: present status and future directions. Expert Rev Neurother 5(3):363–370
7. O'Bryant SE, Marcus DA, Rains JC, Penzien DB (2006) The neuropsychology of recurrent headache. Headache 46(9):1364–1376
8. Marcus DA (2003) Central nervous system abnormalities in migraine. Expert Opin Pharmacother 4(10):1709–1715
9. Lovati C, D'Amico D, Brambilla A, Mariani C, Bussone G (2008) Personality profile and allodynic migraine. Neurol Sci 29(Suppl 1):S152–S154
10. Filatova E, Latysheva N, Kurenkov A (2008) Evidence of persistent central sensitization in chronic headaches: a multi-method study. J Headache Pain (5):295–300
11. Derogatis LR (1977) SCL-90-R, administration, scoring and procedures manual-I for the revised version. Johns Hopkins University School of Medicine, Baltimore
12. Headache Classification Subcommittee of the International Headache Society (2004) The international classification of headache disorders. Cephalalgia 24(Suppl. 1):24–36

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ORAL COMMUNICATION

# Behavioral plus pharmacological treatment versus pharmacological treatment only for chronic migraine with medication overuse after day-hospital withdrawal

**Licia Grazzi · Susanna Usai · Anna Prunesti · Gennaro Bussone · Frank Andrasik**

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**Abstract** Chronic migraine with medication overuse is a difficult problem to manage. Different withdrawal approaches have been tried, with different results. Withdrawal in a day-hospital setting is a recent modality. Results obtained from this last approach have been encouraging. Behavioral techniques combined with pharmacological therapies are effective to enforce the clinical improvement in chronic migraine patients with medication overuse. In this study, a clinical experience where day-hospital withdrawal is followed by pharmacological treatment and on the other side pharmacological treatment is combined with behavioral approach is discussed.

**Keywords** Chronic migraine · Medication overuse · Withdrawal · Behavioral therapies

## Introduction

Chronic migraine with medication overuse is a difficult problem to manage and it is a challenge for physicians and specialists who have to help these problematic patients. No consensus exists about specific treatment strategies for this category of patients and clinical experiences are based on different procedures [1, 2] also if withdrawal seems to be the most effective method for treating these patients effectively.

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Different withdrawal approaches have been tried, with different results as the groups of patients and the protocols employed are so heterogeneous [1].

Withdrawal in a day-hospital setting is a recent modality used at our center: the patients can stay in the hospital during the day for the intravenous therapy and then they can go back to their house for the night or in a local motel [3, 4].

Results obtained from this last approach have been encouraging [3, 4]. The day-hospital setting is also more saving money and saving time for clinicians and hospitals.

After withdrawal, generally the patients are given pharmacologic treatment for migraine prevention according to individual characteristics, or past experiences of preventive therapies or kind of their headache.

Clinical experiences in the past showed that behavioral techniques combined with pharmacological therapies are effective to enforce the clinical improvement in these patients and to maintain it upon the time [5, 6].

Purpose of this study was to determine the clinical course of a sample of chronic migraine patients with medication overuse submitted to a day-hospital withdrawal followed by two different treatment approaches: in the first group (Group A) pharmacological treatment was given for migraine prevention; in the second group (Group B) a behavioral treatment was added to the pharmacological therapy in order to verify the effectiveness of the behavioral option.

Moreover, an evaluation of disability parameters before and after treatment was performed.

## Methods

A sample of 84 patients suffering from chronic migraine with medication overuse was included in the study.

Diagnosis was made according with the International Headache Society criteria [7].

All patients were treated for medication overuse by a day-hospital withdrawal. The patients were in the hospital for 5 days from 9 a.m. to 5 p.m. for the detoxication procedure by intravenous therapy. The withdrawal was realized according to the method described in preceding reports [5].

Patients were instructed to avoid medications for headache episodes.

After withdrawal two different therapeutic programs were fixed: Group A, 52 patients, was treated by pharmacological prophylaxis for migraine prevention; Group B, 41 patients, was treated by a behavioral approach pharmacological therapy.

The behavioral approach consisted of a limited-contact relaxation training, according to the Bernstein and Borkovec method [8] in small groups of patients, four sessions, one session every 15 days, and every session lasted 45 min. Moreover, all the patients were encouraged to practice relaxation at home by tapes, daily.

The follow-up for patients of both groups were fixed up 3, 6 and 12 months after treatment.

Psychological variables concerning disability were tested before treatment and at every follow-up by using test and Migraine Disability Assessment Questionnaire (MIDAS) [9].

## Results

Patients included in the study were 84.

In Group A, we had 52 patients, 32 of them arrived to the last follow-up meeting, 1 year after treatment (61%), 14 (27%) did not come to the appointment for different reasons (decision for psychotherapy, non compliance to pharmacological therapies); 1 patient relapsed and he needed to be treated as in-patient, 5 patients did not achieve the last follow-up yet.

In Group B (pharmacological therapy + behavioral therapy), 41 patients were recruited, 25 of them (60.9%) were seen at the last follow-up session at 1 year, 3 patients (7.3%) were missed as they refused to come to complete the sessions, 2 patients needed to be hospitalized for an inpatient withdrawal, 11 patients have to reach the last follow-up yet.

All patients of Group B came regularly for the sessions, practiced routinely, they appeared to be compliant and accepting of treatment, although we did not assess this formally.

From the clinical point of view, the two groups recorded a significant improvement after 1 year both for headache days per month and for analgesics consumption.

In particular in Group A: days of headache/month: $24 \pm 5.4$ pre versus $9.2 \pm 6.9$ at 1 year follow-up and analgesic consumption: $29.1 \pm 16.9$ pre versus $8.5 \pm 5.9$.

In Group B, $29.1 \pm 2.8$ pre versus $15.6 \pm 10.2$ at 1 year; analgesic consumption: $49.4 \pm 24.3$ pre versus $13.6 \pm 8.2$ at 1 year.

The disability level was assessed by the MIDAS questionnaire and it revealed a decrease in the total value of disability from the beginning to the last follow-up after treatment: in Group A MIDAS total score before treatment was $58.1 \pm 43.6$ post-treatment it was $22.8 \pm 28.2$; in Group B MIDAS total score before treatment was $86.3 \pm 59.8$; post-treatment it was $42 \pm 49.4$.

## Discussion

Chronic migraine with medication overuse has considerable social and economic impact (marked disability, poor quality of life). Patients with chronic forms of migraine and medication overuse are problematic, serious and so difficult to treat that international experiences are trying to find adequate solutions for helping these patients to manage their problem. On one side, attention is driven to reduce headache days and on the other side to reduce the analgesic consumption.

Consequently, many clinical protocols have been developed for managing these patients.

Withdrawal in a day-hospital setting seems to be an effective procedure as well as inpatient treatment, which remains suitable in selected and problematic cases.

Clinical experiences showed that behavioral techniques combined with pharmacological therapies are effective to enforce the clinical improvement in these patients and to maintain it upon the time [5].

In this report, the two groups of patients recorded a significant improvement after the two treatment modalities at 1 year follow-up. This result seems to be different from those emerged in our preceding study, where the group of patients treated by adding behavioral therapy improved more significantly than the other group. It is likely that in the preceding experience, the long-term follow-up (3 years) [5] and the different relaxation program (we used a relaxation training program with weekly sessions for individual patients instead of a limited-contact program with 4 sessions, every 15 days, and exercises at home as in this last case) has reinforced the effectiveness of the behavioral approach.

Nevertheless, we showed that the limited-contact modality seems to be as useful as other behavioral approaches that require a greater investment of time (by patients and therapists), without unpleasant side effects [10].

An important point that emerges from this study is that, although clinical significant results were obtained in both groups after long-term follow-up, relaxation therapy seems to be more accepted than medication and the patients compliance seems to be higher as we see from the significant lower percentage of missed patients (27 vs. 7%).

Compliance and therapeutic effectiveness partly depend on patients knowledge, perceptions and a positive therapeutic alliance and active involvement of patients is a distinctive plus for this kind of treatments.

An integrated and flexible approach combining medication and behavioral can be more effective than drug alone to alleviate pain, but most of all, to reinforce the patients' motivation to follow the program and to maintain the clinical improvement upon time as already showed [5].

Education of patients to practice relaxation for managing pain can avoid the onset of chronic forms of migraine associated to medication overuse and so these techniques can be helpful to support and educate young migraine patients too, to use alternative method before starting the vicious cycle between pain and analgesic consumption and overuse.

Because the sample sizes are small in a non-randomized study, these conclusions are tentative. Data collection will continue on larger sample of patients.

**Conflict of interest statement** The authors declare that they have no conflict of interest related to the publication of this manuscript.

## References


1. Grazzi L, Andrasik F (2006) Medication-overuse headache: description, treatment and relapse prevention. Pain Headache Rep 10(1):71–77
2. Diener HC, Limmroth V (2004) Medication overuse headache: a worldwide problem. Lancet Neurol 3:475–483
3. Grazzi L, Andrasik F, Usai S, Bussone G (2008) In-patient vs day-hospital withdrawal treatment for chronic migraine with medication overuse and disability assessment: results at one-year follow-up. Neurol Sci 29:S161–S163
4. Pini LA, Bigarelli M, Vitale G, Sternieri E (1996) Headaches associated with chronic use of analgesic: a therapeutic approach. Headache 36:433–439
5. Grazzi L, Andrasik F, D'Amico D, Leone M, Usai S, Kass S, Bussone G (2002) Behavioral and pharmacologic treatment of transformed migraine with analgesic overuse: outcome at 3 years. Headache 42:483–490
6. Andrasik F (2007) Can behavioural therapy influence neuromodulation? Neurol Sci 28(Suppl 2):S124–S129
7. Headache Classification Subcommittee of the International Headache Society (2004) The International classification of headache disorders. Cephalalgia 24(Suppl 1):9–160
8. Bernstein DA, Borkovec TD (1973) Progressive relaxation training. Research Press, Champagne
9. D'Amico D, Mosconi P, Genco S (2001) The Migraine Disability Assessment (MIDAS) questionnaire: translation and reliability of the Italian version. Cephalalgia 21:947–995
10. Andrasik F, Grazzi L, Usai S, D'Amico D, Leone M, Bussone G (2003) Brief neurologist-administered behavioral treatment of pediatric episodic tension-type headache. Neurology 60:1215–1216

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ORAL COMMUNICATION

# Efficacy of Ginkgolide B in the prophylaxis of migraine with aura

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**Abstract** In a multicentric, open, preliminary trial, we evaluated the use of ginkgolide B, a herbal constituent extract from Ginkgo biloba tree leaves, in the prophylactic treatment of migraine with aura (MA). Fifty women suffering from migraine with typical aura, or migraine aura without headache, diagnosed according to International Headache Society criteria, entered a six-month study. They underwent a two month run-in period free of prophylactic drugs, followed by a four month treatment period (subdivided into two bimesters, TI and TII) with a combination of 60 mg ginkgo biloba terpenes phytosome, 11 mg coenzyme Q 10, and 8.7 mg vitamin B2 (Migrasoll®), administered twice daily. A detailed diary reporting neurological symptoms, duration, and frequency of MA was compiled by patients throughout the trial. The number of MA significantly decreased during treatment (from $3.7 \pm 2.2$ in the run-in period, to $2.0 \pm 1.9$ during TI and to $1.2 \pm 1.6$ during TII; Anova for repeated measures: $P < 0.0001$). There was also a statistically significant decrease in the average MA duration, which was $40.4 \pm 19.4$ min during run-in, $28.2 \pm 19.9$ during TI, and $17.6 \pm 20.6$ during TII. Total disappearance of MA was observed in 11.1% patients during TI and in 42.2% of patients during T2. No serious adverse event was provoked by Migrasoll® administration. Ginkgolide B is effective in reducing MA frequency and duration. The effect is clearly evident in the first bimester of treatment and is further enhanced during the second.

**Keywords** Aura · Ginkgolide B · Migraine · Platelet activating factor · Prophylaxis

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## Introduction

Migraine with aura is characterized by transient and reversible dysfunction of the brain cortex. Visual aura (scotoma and/or fortification spectra), that move across the visual fields, make up the symptomatological counterpart of this cortical anomaly. The aura generally lasts less than one hour and may be followed by the headache attack of migraine or, less frequently, of tension- type headache [1]. The possible cause of the aura is a hyperexcitability of the cortex due to an increase in the amount of excitatory neurotransmitters, i. e. glutamate and aspartic acids, in the synaptic clefts [2].

Although these attacks are usually limited to 2–3 over the space of a year, no prophylactic treatment is required

for migraine with aura; at times their frequency increases and a prophylactic treatment is necessary. It is well known that drugs able to modulate glutamate in the central nervous system (CNS), such as lamotrigine, are very effective in preventing aura [3, 4]. However, the side effects and the long time lapse it takes to reach the proper dose limits its use.

Ginkgolide B, a herbal constituent extract from Ginkgo biloba tree leaves, is a natural modulator of the action of glutamate in the CNS [5]. Moreover, it is a potent anti-platelet activating factor (PAF). PAF is a potent pro-inflammatory and nociceptive agent released during the inflammation process [6]. Indeed, PAF, released from platelets and leukocytes, during the first phase of migraine attack, may sensitize the trigeminal-vascular endings and induce pain [7, 8]. Therefore, ginkgolide B may be considered a promising pharmacological aid for the treatment of migraine with aura.

On the basis of this evidence, we assessed the efficacy of ginkgolide B in the treatment of migraine with aura, in a group of patients who complied for at least one aura/month. This was done by an open-label, multicentric study, which investigated into the efficacy of ginkgolide B in reducing the duration and/or abolishing the number of auras.

## Patients and methods

A total of 50 patients (37 females, 13 males, mean age 36.7 ± 11.5 years, range 18–64) suffering from migraine with aura, were enrolled in the study after having obtained written informed consent. The diagnosis was made in agreement with the diagnostic criteria established by the International Classification of Headache Disorders, second edition (ICHD-II) [9] for typical aura with migraine headache ($n = 42$) or typical aura without headache ($n = 8$), The trial lasted six-months.

Inclusion criteria were as follows: age range from 18 to 65 years; a minimum of two years' history of migraine with aura and/or aura without migraine; auras occurring at least once a month; no past or present diseases and, in particular no history of cerebral focal activation; no pregnancy or lactation.

They underwent a two-month run-in period free of prophylactic drugs, followed by a four-month treatment period (subdivided into two bimesters, TI and TII) with a combination of 60 mg ginkgo biloba terpenes phytosome, 11 mg coenzyme Q 10, and 8.7 mg vitamin B2 (Migrasoll®) administered twice daily. No other migraine prophylaxis was allowed during the study, other than Migrasoll® and within the last month prior to the beginning of the trial; no restriction was placed on analgesic intake. A detailed diary reporting symptoms, duration, and frequency of MA was compiled by patients throughout, and carefully and systematically reviewed during the trial.

The statistical evaluation of aura frequency and duration was performed by an ANOVA test for repeated measures and a *post-hoc* Bonferroni *t* test was then applied to localize the source of variance. All analyses were performed by the Statistical Package for the Social Sciences (SPSS) software program (version 15.0). All values given in the following text are reported as arithmetic means (±1 SD)

## Results

Of the 50 patients enrolled in the study, five withdrew from the trial; three were due to mild adverse events during treatment (abdominal discomfort = 2 cases; vertigo = 1 case) and two were lost to follow-up. The results herein reported are therefore related to the remained 45 patients (34 females, 11 males, mean age 33.6 ± 10.2, range 18–64). The run in frequency and duration of aura for each patient are summarized in Table 1.

The attacks frequency decreased significantly from 3.7 ± 2.2 in the run-in bimester to 2.0 ± 1.9 during the first treatment period and to 1.2 ± 1.6 during TII (ANOVA for repeated measures: $P < 0.0001$; Bonferroni *t* test: run-in vs. T I = $P < 0.05$; run-in vs. T II = $P < 0.05$; T I vs. T II = $P < 0.05$).

There was total disappearance of MA in 5/45 (11.1%) patients during TI and in 19/45 (42.2%) patients at the end of treatment period; only five patients were completely unresponsive to treatment (Table 1). Aura duration (expressed in minutes) was markedly reduced throughout the entire treatment course and was 40.4 ± 19.4 during the run-in, 28.2 ± 19.9 during TI and 17.6 ± 20.6 during TII (ANOVA for repeated measures: $P < 0.0001$; Bonferroni *t* test: run-in vs. TI = $P < 0.05$; run-in vs. TII = $P < 0.05$; T I vs. T II = $P < 0.05$).

Although individual changes in MA symptomatology are not considered in this article, it is noteworthy that there was an overall marked improvement in the neurological symptoms of aura during treatment. Among the patients who completed the study no serious adverse events were reported.

## Discussion

This study shows that Ginkgolide B, contained in the terpenic fraction of Ginkgo Biloba, is effective in reducing both aura frequency and duration in our patient group. The effect is clearly evident in the first two months of treatment and is either maintained, or even further increased during

**Table 1** Frequency and duration of auras in each patient studied

| PT. | | | | Run-in | | T I | | T II | |
|---|---|---|---|---|---|---|---|---|---|
| Nr | Sex | Age | Onset | N. auras | Duration | N. auras | Duration | N. auras | Duration |
| 1 | F | 41 | 32 | 4 | 60 | 2 | 60 | 2 | 60 |
| 2 | F | 27 | 15 | 2 | 55 | 0 | – | 0 | – |
| 3 | F | 35 | 6 | 3 | 60 | 1 | 50 | 0 | – |
| 4 | F | 26 | 19 | 2 | 45 | 1 | 50 | 1 | 10 |
| 5 | M | 37 | 15 | 4 | 90 | 1 | 70 | 1 | 60 |
| 6 | F | 30 | 12 | 2 | 95 | 1 | 50 | 0 | – |
| 7 | F | 26 | 20 | 3 | 40 | 2 | 40 | 0 | – |
| 8 | F | 18 | 15 | 4 | 25 | 2 | 25 | 1 | 30 |
| 9 | F | 25 | 10 | 4 | 40 | 1 | 30 | 2 | 30 |
| 10 | F | 39 | 16 | 3 | 50 | 1 | 40 | 1 | 40 |
| 11 | M | 25 | 20 | 3 | 30 | 1 | 10 | 0 | – |
| 12 | F | 35 | 25 | 6 | 20 | 6 | 20 | 6 | 20 |
| 13 | M | 46 | 20 | 5 | 25 | 2 | 20 | 0 | – |
| 14 | F | 26 | 22 | 2 | 10 | 2 | 10 | 0 | – |
| 15 | F | 24 | 19 | 2 | 20 | 0 | – | 0 | – |
| 16 | M | 33 | 17 | 3 | 45 | 1 | 30 | 1 | 45 |
| 17 | F | 34 | 28 | 2 | 65 | 2 | 65 | 1 | 30 |
| 18 | M | 22 | 18 | 2 | 20 | 0 | – | 0 | – |
| 19 | M | 23 | 20 | 2 | 15 | 3 | 15 | 3 | 15 |
| 20 | F | 64 | 30 | 2 | 20 | 1 | 20 | 0 | – |
| 21 | F | 36 | 21 | 2 | 30 | 2 | 15 | 1 | 5 |
| 22 | M | 48 | 44 | 4 | 35 | 1 | 20 | 0 | – |
| 23 | F | 19 | 7 | 8 | 60 | 1 | 15 | 0 | – |
| 24 | F | 31 | 14 | 6 | 25 | 3 | 15 | 3 | 15 |
| 25 | F | 38 | 20 | 4 | 50 | 3 | 30 | 2 | 15 |
| 26 | F | 27 | 24 | 11 | 30 | 5 | 20 | 8 | 10 |
| 27 | F | 32 | 12 | 3 | 35 | 1 | 10 | 0 | – |
| 28 | M | 38 | 29 | 4 | 55 | 3 | 35 | 3 | 35 |
| 29 | F | 52 | 27 | 2 | 70 | 1 | 70 | 2 | 70 |
| 30 | M | 26 | 15 | 3 | 15 | 2 | 10 | 1 | 10 |
| 31 | F | 33 | 16 | 2 | 30 | 2 | 40 | 1 | 40 |
| 32 | F | 44 | 22 | 4 | 20 | 1 | 20 | 0 | – |
| 33 | F | 53 | 16 | 2 | 50 | 2 | 35 | 2 | 40 |
| 34 | F | 22 | 11 | 3 | 25 | 1 | 20 | 0 | – |
| 35 | F | 45 | 14 | 2 | 40 | 2 | 25 | 1 | 15 |
| 36 | M | 36 | 13 | 7 | 35 | 8 | 35 | 7 | 35 |
| 37 | F | 25 | 11 | 6 | 50 | 4 | 45 | 4 | 30 |
| 38 | F | 38 | 31 | 5 | 40 | 1 | 10 | 0 | – |
| 39 | F | 23 | 15 | 2 | 50 | 1 | 50 | 1 | 30 |
| 40 | F | 39 | 35 | 4 | 30 | 0 | – | 0 | – |
| 41 | F | 48 | 18 | 2 | 40 | 2 | 40 | 2 | 40 |
| 42 | F | 30 | 22 | 10 | 20 | 8 | 20 | 4 | 5 |
| 43 | F | 28 | 18 | 8 | 55 | 6 | 15 | 0 | – |
| 44 | M | 20 | 15 | 3 | 25 | 0 | – | 0 | – |
| 45 | F | 47 | 14 | 5 | 70 | 3 | 70 | 2 | 60 |

*Run-in* Bimester of observation before therapy; *T I* First bimester of therapy; *T II* Second bimester of therapy; *Onset* Age at onset of MA; *N. auras* Total number of auras in the period considered; *Duration* Total duration of aura symptoms expressed in minutes

the following two months. It is very unlikely that this positive effect is the primary result of the other components contained in Migrasoll®, since Vitamin B2 and Coenzyme Q 10 are present in very low concentrations. Although, to date, the mechanism of action of ginkgolide B on the CNS is still only partially understood, it is believed that the main therapeutical effect may be related to its properties in the modulation of the excitatory function of glutamate in the CNS [10]. Glutamate plays a critical role in initiating and propagating spreading depression (SD), through a stimulation of specific glutamate receptors linked to NMDA channels, and it has been demonstrated that aura is linked to a sudden occurrence of neuronal depolarization and SD on the human cortex [11, 12]. These neurological phenomena are precipitated when an excessive amount of glutamic and aspartic acids are released from neurons and glia in the synaptic clefts [13]. Indeed, an increased level of these amino acids were found in plasma, platelets, and CSF of migraine with aura sufferers, suggesting that the cortex of these patients may be hyperexcitable [14]. The favorable effect of ginkgolide B in reducing or abolishing the aura in our patients may be due to the modulation and/or reducing the excitatory effect of glutamate in the CNS.

Another important pharmacological property of ginkgolide B is to hinder the pathological action of PAF, a phospholipid that, under some physiopathological circumstances in the CNS, such as SD, determines a release of glutamic acid into the CNS, contributing to its hyperexcitability [15]. A further beneficial effect of ginkgolide B in migraine patients may be its activity against the formation and the deposition of free radicals in the CNS [16, 17]. Indeed, recent evidence suggests that the high frequency of migraine attacks is associated to an abnormal amount of free radicals present in the CNS [18]. The inhibition of free radical production and deposition may reduce the recurrence of the aura.

Our preliminary study indicates that Migrasoll® is a safe product, that can be used routinely to reduce both MA frequency and length, with only minor possible side effects. Nevertheless, even if our preliminary data are encouraging, as this is an open study, it should be interpreted with caution and confirmed by larger placebo controlled studies and longer follow-up periods.

**Conflicts of interest statement** Giovanni D'Andrea is a consultant and is on the speaker's bureau of Pharmaval Srl, Italy.

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## References

1. D'Andrea G, Bonavita V, Rigamonti A, Bussone G (2003) Treatment of migraine with aura: comment and prospectives. Neurol Sci 23:271–278
2. Welch KMA, D'Andrea G, Tepley N, Barkley GL, Ramadan NM (1990) The concept of migraine as a state of central neuronal hyperexcitability. Neurol Cin 8:817–828
3. D'Andrea G, Granella F, Cadaldini M, Manzoni GC (1999) Effectiveness of lamotrigine in the prophylaxis of migraine with aura: an open pilot study. Cephalalgia 19:64–66
4. Lampl C, Katsarava Z, Diener HC, Limmroth V (2006) Lamotrigine reduces migraine with aura attacks in patients with migraine with aura. J Neurol Neurosurg Psychiatry 76:1730–1732
5. Williams B, Watanabe CMH, Schultz PG, Rimbach G, Kruker T (2004) Age-related effects of Ginkgo Biloba extract on synaptic plasticity and excitability. Neurobiol Aging 25:955–962
6. Akisu M, Kultursay N, Coker I, Huseyinov A (1998) Platelet-activating factor is an important mediator in hypoxic ischemic brain injury in the newborn rat. Flunarizine and Ginkgo Biloba extracts reduce PAF concentration in the brain. Biol Neonate 74(6):439–444
7. D'Andrea G, Hasselmark L, Alecci M, Cananzi A, Perini F, Welch KMA (1994) Platelet secretion from dense and α-granules in vitro in migraine with or without aura. J Neurol Neurosug Psychiatry 57(5):557–561
8. Sarchielli P, Alberti A, Coppola F, Baldi A, Gallai B, Floridi A, Capecchi G, Gallai V (2004) Platelet-activating factor (PAF) in internal jugular venous blood of migraine without aura patients assessed during migraine attacks. Cephalalgia 24:623–630
9. The international classification of headache disorders, 2nd edn (2004) Cephalalgia 24 (suppl 1):1–160
10. Bryn W, Coran MH, Coran MH, Schultz PG, Rimbach G, Krucker T (2004) Age-related effect of Ginkgo Biloba on synaptic plasticity and excitability. Neurobiol Aging 25:955–962
11. Cananzi AR, D'Andrea G, Perini F, Zamberlan F, Welch KMA (1995) Platelet and plasma levels of glutamate and glutamine in migraine with and without aura. Cephalalgia 15:132–135
12. Bowyer SM, Aurora KS, Moran JE, Tepley N, Welch KMA (2001) Magnetoencephalografic fields from patients with spontaneous and induced migraine aura. Ann Neurol 50:582–587
13. Waltkins JC, Jane ED (2006) The glutamate story. Br J Pharmacol 147(S1):S100–108
14. D'Andrea G, Cananzi AR, Joseph R, Morra M, Zamberlan F, Ferro Milone F, Grunfeld S, Welch KMA (1991) Platelet glycine, glutamate and aspartate in primary headache. Cephalalgia 11:197–200
15. Nogami K, Hirashima Y, Endo S, Takaku A (1997) Involvement of platelet-activating factor (PAF) in glutamate neurotoxicity in rat neuronal cultures. Brain Reseach 754:72–78
16. Pincemail J, Deby C (1986) Propietés antiradicalaires de l'extrait de Ginkgo Biloba. Presse Medicale 15:1475–1479
17. Droy-Lefaix MT, Doly M (1992) EGb 761, a retinal free-radical scavenger. In: Christen Y, Constantin J, Lacour M (eds) Effect of Ginkgo Biloba Extract (EGb 761) and central nervous system. Elsevier, Paris
18. Welch KMA (2003) Contemporary concepts of migraine pathogenesis. Neurology 61:S2–S8

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ORAL COMMUNICATION

# Psychological variables in chronic migraine with medication overuse before and after inpatient withdrawal: results at 1-year follow-up

**Susanna Usai · Licia Grazzi · Domenico D'Amico · Frank Andrasik · Gennaro Bussone**

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**Abstract** Investigations on psychological variables and migraine have confirmed a strong association between migraine and depression or migraine and anxiety disorders. In particular patients suffering from chronic migraine with medication overuse have an elevated risk of mood and anxiety disorders, which may compromise treatment efforts. The aim of this study was to investigate a group of patients suffering from CM with medication overuse before and after inpatient withdrawal program after a long-term follow-up to examine clinical indexes and psychological variables changes in particular anxiety and depression by using Spielberger State-Trait Anxiety Inventory (STAI) 1, 2 and Zung Self-rating Depression Scale (Zung) tests, in order to verify if a specific psychological pattern in these patients is present, and if changes in psychological variables correspond with clinical improvement. The changes of clinical indexes and of psychological parameters are discussed and analyzed in order to address the most adequate therapeutic strategy for this kind of patients.

**Keywords** Psychological variables · Depression · Anxiety · Headache-related disability · Chronic migraine · Medication overuse

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## Introduction

The psychiatric symptoms of migraine (depressed mood, irritability, anxiety, fatigue, poor memory and attention) were recognized more than 100 years ago by Edward Leiving and subsequently confirmed by numerous studies. However, only in 1988 and again in 2004 with the International Classification of Headache Disorders [1], a systematic assessment of psychiatric comorbidity in primary headaches was conducted.

Investigations on psychological variables and migraine have confirmed a strong association between migraine and depression or migraine and anxiety disorders [2, 3]. Different studies have shown that migraine patients more often suffer from anxiety and depression than non-migraine patients. Moreover, these studies have established that patients with chronic migraine exhibit anxiety and depression more often than those with episodic migraine [4]. In particular, patients suffering from chronic migraine with medication overuse have an elevated risk of mood and anxiety disorders, which may compromise treatment efforts [5–7]. Consistent with these data, as early as 1993 some authors had pointed out that chronic and excessive use of symptomatic drugs can interfere with the symptoms of pain modulators through a depletion of serotonin [8], also if it is difficult to determine whether this increase in use of analgesics should be considered a therapeutic necessity or even the result of a behavioral habit.

Correlations among clinical behavior, psychological variables and disability levels have been observed in the last years clinical experiences [7, 9, 10] and on the basis of these preceding observations, we decide to perform this study on a group of chronic migraine patients with medication overuse.

## Objective

To study a group of patients suffering from CM with medication overuse before and after inpatient withdrawal program after a long-term follow-up to examine clinical indexes after withdrawal, disability changes by using Migraine Disability Assessment questionnaire (MIDAS), and psychological variables in particular anxiety and depression by using Spielberger State-Trait Anxiety Inventory (STAI) 1, 2 and Zung Self-rating Depression Scale (Zung) tests, in order to verify if a specific psychological pattern in these patients is present, and if changes in psychological variables correspond with clinical improvement.

## Methods

A sample of 146 consecutive patients suffering from CM and medication overuse was enrolled (122 females and 24 males; mean age 45.5 ± 12.2). Mean duration of illness was 25.6 ± 12.5 years.

The mean number of days of headache per month was from 26.5 ± 4.1; the mean number of medications/month was 51.8 ± 32. At baseline, the MIDAS total score was 78.6 ± 64.4, STAI 1 score was 44.6 ± 11.6, STAI 2 score was 46.3 ± 10.3, Zung score was 41 ± 11.2. All patients received the diagnosis of Chronic Migraine with medication overuse according to the Silberstein and Lipton Criteria [11].

### Treatment interventions

They underwent an inpatient withdrawal treatment consisting in intravenous hydration for a period of 10 days and steroids from day 1 to 5, followed by oral prescription steroids for other 5 days and then were given preventive therapy with different anti-migraine prophylactic drugs.

### Follow-up

Follow-up sessions were planned for 3, 6 and 12 months after the inpatient treatment.

### Measures

A diary card was given for recording days with headache and the medications taken for aborting headaches. The Italian versions of the MIDAS questionnaire, STAI 1.2 and Zung tests were filled in by patients at the moment of enrollment (baseline) and at follow-up visits.

## Results

Of the 146 initial patients, 84 of them (57.5%) returned for the last follow-up, 12 months after withdrawal; the headache diary was checked and the questionnaires were completed too. They were 69 females, 15 males and the mean age was 46.3 ± 12.2.

Patients improved significantly at 12 months follow-up: the mean number of days of headache per month decreased from 26.1 ± 4 to 9 ± 7 (Student $t$ test $p < 0.00001$), the mean number of medications/month decreased from 48.9 ± 29.1 to 12 ± 18.2 (Student $t$ test $p < 0.00001$), MIDAS total score decreased (70.8 ± 59.3 vs. 34.1 ± 40.4—Student $t$ test $p < 0.0001$). The measures of anxiety slightly improved: the STAI 1 mean score was 43.4 ± 11.6 at baseline and 39.8 ± 11.7 at the 12-month follow-up (Student $t$ test $p = 0.00473$). The measure of depression slightly improved too: STAI 2 mean score was at baseline 45.6 ± 9.7 and at the follow-up visit 41.7 ± 11.9 (Student $t$ test $p = 0.00104$). Zung mean score was 39.9 ± 9.7 at baseline and 36 ± 10 at the 12-month follow-up (Student $t$ test $p = 0.00290$), showing a slightly improvement too.

## Conclusions

Patients were followed for 1 year after withdrawal to observe clinical improvement, disability changes, and behavior of the psychological variables. The clinical improvement was significant and the disability levels changed significantly too: this confirm the effectiveness of the withdrawal procedure followed by preventive therapies for migraine. At the same time, anxiety and depression scores changed significantly after withdrawal although their values were not so high before treatment. In fact, it seems to be a discrepancy among high levels of headache frequency, medication consumption and disability respect to the values of the psychological variables at the baseline. These findings suggest that the psychopathological aspects are not so evident at least in our group of patients, and they may not be influenced by headache frequency and medication use, and they can be support or not an alteration of a personality profile.

**Conflict of interest statement** The authors declare that they have no conflict of interest related to the publication of this manuscript.

## References

1. Headache Classification Subcommittee of the International Headache Society (2004) The international classification of headache disorders, 2nd edition. Cephalalgia 24(Suppl 1):9–160

2. Mathew NT, Stubita E, Nigam MP (1982) Transformation of episodic migraine into daily headache: analysis of factors. Headache 22:66–68
3. Radat F, Sakh D, Lutz G, El Amrani M, Ferreri M, Bousser MG (1999) Psychiatric comorbidity is related to headache induced by chronic substance use in migraineurs. Headache 39:477–480
4. Juang KD, Wang SJ, Fuh JL, Lu SR, Su TP (2000) Comorbidity of depressive and anxiety disorders in chronic daily headache and its subtypes. Headache 40:818–823
5. Scher AI, Lipton RB, Stewart W (2002) Risk factors for chronic daily headache. Curr Pain Headache Rep 6:486–491
6. Radat F, Swendsen J (2005) Psychiatric comorbidity in migraine: a review. Cephalalgia 25:165–178
7. Lantéri-Minet M, Radat F, Chautart MH, Lucas C (2005) Anxiety and depression associated with migraine: influence on migraine subjects' disability and quality of life, and acute migraine management. Pain 118:319–326
8. Hering R, Glover V, Pattichis K, Catarci T, Steiner TJ (1993) 5HT in migraine patients with medication-induced headache. Cephalalgia 13:410–412
9. Grazzi L, Andrasik F, D'Amico D, Leone M, Usai S, Kass SJ, Bussone G (2002) Behavioral and pharmacologic treatment of transformed migraine with analgesic overuse: outcome at 3 years. Headache 42:483–490
10. Zwart JA, Dyb G, Hagen K, Ødegård KJ, Dahl AA, Bovim G, Stovner LJ (2003) Depression and anxiety disorders associated with headache frequency. The Nord-Trøndelag Health Study. Eur J Neurol 10:147–152
11. Silberstein SD, Lipton RB (2000) Chronic daily headache. Curr Opin Neurol 13:277–283

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ORAL COMMUNICATION

# Underdiagnosis of primary headaches: results of a survey on patients attending headache centres

**N. Massetto · C. Gambini · P. Bernardoni · E. Ferrante · C. Lovati · F. Moschiano · M. C. Tonini · G. Bussone · Domenico D'Amico**

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**Abstract** Underdiagnosis of primary headaches was evaluated in 504 patients attending six Headache Centres in Lombardy. We found high figures of missed diagnoses (no diagnosis of a specific headache form), and of misdiagnosis (non-concordance between previous diagnoses made by the GP and the final diagnoses given by the headache specialist). We note that underdiagnosis in headache patients may have negative consequences, enhancing the risk of progressive worsening of primary headache syndromes, increasing their impact on individuals and on society, and favouring medication overuse.

**Keywords** Migraine (M) · Primary headaches (PH) · Headache centres (HC) · Missed diagnosis · Misdiagnosis

## Introduction

Primary headaches represent a major health problem. TTH and M are highly prevalent (life-time prevalence of 46 and 14%, respectively) [1], and may cause poor health-related quality-of-life as well as impairment in work, household and social activities [2–5]. Cluster headache (CH) and "chronic migraine" are less prevalent (life-time prevalence around 0.3 and 3%, respectively) [1], but have an even more negative impact on patients and on society, due to the severity and the daily occurrence of headaches for periods of months/years [6–8].

Application of the operational diagnostic criteria of the ICDH-II [9] allows us to make the diagnosis of a given PH on the basis of the specific symptoms reported by the patient. Nonetheless, surveys from different countries showed that underdiagnosis of migraine, and of other PH, is a relevant problem [10–14].

The aim of our study was to evaluate the occurrence of underdiagnosis in patients presenting to Headache Centres (HC) in Lombardy.

## Methods

This was a multicentre, observational study. Consecutive patients presenting for the first time to 6 HC in Lombardy, Northern Italy, during April and May 2007 were enrolled. Informed consent for sensitive data treatment was obtained from all patients. Data were collected in a database, and then analyzed, in order to evaluate the occurrence of underdiagnosis in terms of missed diagnoses = no diagnosis of a specific headache form; misdiagnosis = non-concordance between previous diagnoses made by the GP and the final diagnoses given by the headache specialist.

Diagnoses of the different forms of PH were made at the HC according to the ICDH-II criteria [9]. For patients with daily-nearly daily headaches, some neurologists used the ICDH-II criteria, while others applied the Silberstein & Lipton criteria [15]: for the purpose of this study, we

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included these patients in one diagnostic group, chronic migraine, with or without medication overuse.

## Results

### Patients

Of the 504 enrolled; 378 females, 126 males; mean age 41.7 years, SD 12.3 years.

### Previous diagnoses

HEADACHE (with no other specification) in 349 patients (69.2%); M in 63 (12.5%); M with aura in 12 (2.4%); TTH in 10 (2.0%); chronic headache in 24 (4.8%); CH in 7 (1.4%); trigeminal neuralgia in 4 (0.8%); other diagnoses in 9 patients (1.8%).

Although only patients attending for the first time an HC should be included, further check showed that 26 patients (5.2% of the enrolled patients) had been visited in the past at an HC. The diagnoses were M without aura in 18 patients (69.2%); TTH in 12 (46.1%); persistent idiopathic facial pain in 1 patient (3.8%).

### Final diagnoses

M without aura in 301 patients (59.7%); M with aura in 37 (7.3%); TTH in 130 (25.8%); chronic migraine, with or without medication overuse in 47 (9.3%); CH in 11 (2.2%); primary stabbing headache in 4 (0.8%); headache associated with sexual activity in 1 (0.2%); persistent idiopathic facial pain in 1 (0.2%); secondary headaches in 10 (1.8%); other forms in 3 (0.6%).

Final diagnoses in patients with a previous diagnosis of HEADACHE:

- M without aura in 226 (64.7%)
- M with aura in 20 (5.7%)
- TTH in 119 (34.1%)
- Secondary headaches 3 (0.9%)
- CH in 2 (0.6%)
- Diagnosis not possible in 2 (0.6%).

Final diagnoses in patients with previous diagnosis of M:

- M without aura in 44 (69.8%)
- M with aura in 7 (11.1%)
- TTH in 11 (17.5%).

Final diagnoses in patients with previous diagnosis of M with aura:

- M without aura in 3 (25.0%)
- M with aura in 10 (83.3%)
- TTH in 1 (8.3%)
- Final diagnoses in patients with previous diagnosis of trigeminal neuralgia:
- M without aura in 2 (50.0%)
- Persistent idiopathic facial pain in 2 (50.0%).

Final diagnoses in patients with previous diagnosis TTH:

- M without aura in 3 (30.0%)
- TTH in 7 (70.0%).

Final diagnoses in patients with previous diagnosis chronic headache:

- M without aura in 15 (62.5%)
- M with aura in 2 (8.3%)
- TTH in 5 (20.8%)
- CH in 1 (4.2%)
- Chronic migraine, with medication overuse in 3 (12.5%)
- Secondary headaches in 1 (4.2%).

Final diagnoses in patients with previous diagnosis CH:

- CH in 3 (42.8%)
- M without aura in 2 (28.6%)
- TTH in 2 (28.6%).

## Discussion

Missed diagnosis among headache patients is a relevant problem also in our region: 69% of patients arrived at the HC with a generic diagnosis of HEADACHE.

Also misdiagnosis occurred in a relevant proportion of patients, suffering both from the most common and the relatively uncommon forms of headache and facial pain.

Although most of the published studies have focused on migraine [10–14], our survey indicated that missed diagnosis and misdiagnosis involve not only patients with migraine, but also those with other PH forms.

We note that underdiagnosis may lead to undertreatment. If headache patients are not treated or receive suboptimal treatments, they risk a progressive worsening of their headache syndrome, with increased impact on individuals and on society, and they are more likely to indulge in "self prescription" of over-the-counter medications and medication overuse. This is the case of many patients with episodic migraine who evolve to chronic migraine and medication overuse headache [8, 16, 17].

There is an urgent need for the development of cooperative networks involving GPs, neurologists and headache specialists in order to enhance the possibility of a correct diagnosis—and of adequate treatments—for headache patients.

**Conflict of interest statement** The authors declare that they have no conflict of interest related to the publication of this manuscript.

## References


1. Lj Stovner, Hagen K, Jensen R et al (2007) The global burden of headache: a documentation of headache prevalence and disability worldwide. Cephalalgia 27(3):193–210
2. Edmeads J, Findlay H, Tugwell P et al (1993) Impact of migraine and tension-type headache on life-style, consulting behaviour, and medication use: a Canadian population survey. Can J Neurol Sci 20(2):131–137
3. Lipton RB, Bigal ME, Kolodner K et al (2003) The family impact of migraine: population-based studies in the USA and UK. Cephalalgia 23(6):429–440
4. Bussone G, Usai S, Grazzi L et al (2004) Disability and quality of life in different primary headaches: results from Italian studies. Neurol Sci 25(3):S105–S107
5. Terwindt GM, Ferrari MD, Tijhuis M et al (2000) The impact of migraine on quality of life in the general population. Neurology 55:624–629
6. D'Amico D, Rigamonti A, Solari A et al (2002) Health-related quality of life in patients with cluster headache during active periods. Cephalalgia 22(10):818–821
7. Meletiche DM, Lofland JH, Young WB (2001) Quality-of-life differences between patients with episodic and transformed migraine. Headache 41:573–578
8. D'Amico D, Grazzi L, Usai S et al (2005) Disability pattern in chronic migraine with medication overuse: a comparison with migraine without aura. Headache 45(5):553–560
9. Headache Classification Subcommittee of the International Headache Society (2004) The international classification of headache disorders: second edition. Cephalalgia 24(1):1–160
10. Lucas C, Géraud G, Valade D et al (2006) Recognition and therapeutic management of migraine in 2004, in France: results of FRAMIG 3, a French nationwide population-based survey. Headache 46:715–725
11. Tepper SJ, Dahlöf CG, Dowson A et al (2004) Prevalence and diagnosis of migraine in patients consulting their physician with a complaint of headache: data from the Landmark Study. Headache 44(9):856–864
12. Devine JW, Farley JF, Hadsall RS (2005) Patterns and predictors of prescription medication use in the management of headache: findings from the 2000 Medical Expenditure Panel Survey. Headache 45(9):1171–1180
13. Diamond S, Bigal ME, Silberstein S et al (2007) Patterns of diagnosis and acute and preventive treatment for migraine in the United States: results from the American Migraine Prevalence and Prevention Study. Headache 47:355–363
14. Cevoli S, D'Amico D, Martelletti P et al (2009) Under diagnosis and undertreatment of migraine in Italy: a survey on patients attending for the first time ten Headache Centres. Cephalalgia (in press)
15. Silberstein SD, Lipton RB, Sliwinski M (1996) Classification of daily and near-daily headaches: field trial of revised IHS criteria. Neurology 47(4):871–875
16. Scher AI, Stewart WF, Ricci JA et al (2003) Factors associated with the onset remission of chronic daily headache in a population-based study. Pain 106:81–89
17. Katsarava Z, Schneeweiss S, Kurth T et al (2004) Incidence and predictors for chronicity of headache in patients with episodic migraine. Neurology 62:788–790

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ORAL COMMUNICATION

# Painful ophthalmoplegia: a retrospective study of 23 cases

**M. Curone · V. Tullo · A. Proietti-Cecchini · C. Peccarisi · M. Leone · G. Bussone**

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**Abstract** Painful ophthalmoplegia is a rare pathologic condition caused by non-specific inflammation of the cavernous sinus, but other causes such as tumours, vasculitis, basal meningitis, neurosarcoidosis, diabetes can be responsible for the syndrome. Aim of this study is a review of the cases of painful ophthalmoplegia admitted to our Institute in the last 20 years in order to verify the incidence of symptomatic versus benign forms in a clinical case series, with particular focus on the cases in which a long term (at least 4 years) and detailed follow-up did not revealed spread of any systemic disease or other presumed causes for painful ophthalmoplegia. Twenty-three patients were retrospectively studied, 12 patients (52%) were classified as benign forms and their disease course was again evaluated and 11 cases (48%) were designated as symptomatic. The present study suggests that in the clinical practice the incidence of benign forms among the painful ophthalmoplegias is more elevate than the symptomatic ones and underlines the need of a specific nosography for benign forms.

**Keywords** Painful ophthalmoplegia · Tolosa–Hunt syndrome · Cavernous sinus

## Introduction

Painful ophthalmoplegia is a rare pathologic condition characterized by unilateral orbital pain combined with ipsilateral paralysis of one or more oculomotor nerves, sometimes associated to the loss of sensitivity in the distribution of the ophthalmic branch of the trigeminal nerve [1]. Even though the understanding of this disease has made significant progress, the difficulties encountered in the diagnosis of painful ophthalmoplegia require extreme caution when exploring patients and need resorting to specific complementary testing in order to exclude other causes [2].

Painful ophthalmoplegia may be observed in sphenoidal fissure syndrome, orbital apex or cavernous sinus or parasellar syndrome, Raeder's syndrome, Gradenigo's syndrome and various pathologic condition that must be investigated such as vasculitis, meningitis, diabetes, local space-occupying processes, vascular malformations, sinusitis; furthermore, there are clinical entities such as ophthalmoplegic migraine and Tolosa–Hunt syndrome (THS) [3–6]. Aim of the study is a retrospective review of the cases of painful ophthalmoplegia admitted to our Institute in the past 20 years in order to verify the incidence of symptomatic versus idiopathic forms in a clinical case series and an accurate evaluation of the cases in which the follow-up did not revealed any other causes responsible for the painful ophthalmoplegia.

## Methods

Patients admitted to our Institute from January 1989 to 2009 and diagnosed as suffering from painful ophthalmoplegia were retrospectively studied. Clinical history (with particular focus on symptoms, type of pain, signs, response to steroids, illness duration), associated diseases, general tests, neuroimaging findings, other relevant examinations, treatment and follow-up were obtained from the papers and reviewed. All patients received full blood evaluation and

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biochemical/metabolic tests, ophthalmic examination, contrast enhanced cerebral MRI, chest X-ray; some patients underwent CSF analysis, spinal MRI, thoracic CT scan, conventional cerebral angiography and electromyography. All the patients were followed with at least two following cerebral MRI and further examinations.

## Results

Twenty-three patients, 14 males, 9 females, mean age 36.5 years (range 15–68 years) were reviewed. In 19 cases (83%), unilateral orbital pain was the onset of the episode of painful ophthalmoplegia; in 4 cases (17%) ocular palsy coincided with the onset of the pain. In 19 cases (83%), ocular palsy followed the pain within few days (from 2 to 7 days). The sixth cranial nerve was the most involved (9 cases, 39%); the third cranial nerve was affected in seven cases (31%), the fourth in three cases (13%), and a combined ocular motor nerves palsy was observed in four patients (17%). Visual loss was described in four patients (17%). Trigeminal involvement (first branch) was noticed in 19 cases (83%). A steroid treatment (prednisone given orally 1–1.5 mg/Kg daily) was administrated in all patients, with prompt pain relief (less than 48 h) and remission of paresis within few days (from 1 to 8 days) in 21 patients (91%); in two cases the paresis lasted, respectively, for 5 and 6 weeks despite steroid use. The mean attack duration was 12.3 days (range 5–45 days). Nineteen patients (83%) developed a recurrence between 3 and 24 months and clinical presentation was the same at every onset. Cerebral MRI was normal in five cases (21%); in three cases (13%) showed cavernous sinus asymmetry; in four cases (17%) demonstrated an enhancing soft tissue compatible with granuloma confined to the cavernous sinus. In 11 cases (48%), cerebral MRI detected a specific lesion at the first hospital admission; these 11 cases were designated as symptomatic painful ophthalmoplegia. Diagnosis of the symptomatic forms was: lymphoma (1 case), sarcoidosis (3 cases), vasculitis (2 cases), hypertrophic cranial pachymeningitis (2 cases), chronic polyradicular neuropathy (1 case), posterior communicating artery aneurism (1 case), and cavernous hemangioma (1 case). Regarding the other 12 cases, in 5 patients MRI was still normal at the follow-up and in 7 patients asymmetry or granuloma of the cavernous sinus previously detected diminished or disappeared at first following MRI; none of these 12 patients developed signs of any systemic disease at long-term (4 years or more) follow-up. These cases were diagnosed as THS. CSF analysis performed in eight patients at the first attack revealed pathologic findings (proteins and angiotensin-converting enzyme both increased) in 5 patients, all of them were symptomatic forms. The mean time for signs disappearance after steroid therapy administration was non-significantly different between benign cases and symptomatic cases although secondary forms were characterized by longer attack duration and more frequent relapse after steroid withdrawal.

## Discussion

The present retrospective study of 23 cases came to our observation as painful ophthalmoplegias showed that more than half of the patients (12 cases, 52%) had a benign form and less than a half were secondary forms. Generally, we could say that these data suggest that in the clinical practice of the neurologist the incidence of benign forms among the painful ophthalmoplegias is more elevate.

The cases diagnosed as benign forms could all be classified as THS, however, in 2004 the International Headache Society redefined the diagnostic criteria for THS placing it among cranial neuralgias (Sect. 13.16) with a new diagnostic criteria added: "demonstration of a granuloma either by MR or biopsy" [7] and it is noteworthy that in our case series among the group of benign forms only in four patients a granuloma was noted while in three cases there was an increase in size of the cavernous sinus and the other 5 cases had normal cerebral MRI. Although clinical features of THS are common to several condition, the MRI demonstration of granuloma plays a key role in diagnosis of the syndrome [8]. We think that cases of painful ophthalmoplegia which fulfil the clinical criteria for THS but have normal cerebral MRI remain to be clarified [9] and a specific nosography is needed.

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

## References

1. Kline LB, Hoyt WF (2001) The Tolosa–Hunt syndrome. J Neurol Neurosurg Psychiatry 71:577–582
2. Mora de Oñate J, Pascual-Pérez-Alfaro R, Izquierdo-Vázquez C, González-Ruiz M, Aguirrebeña-Olmos A, Díez-Villalba R (2007) Painful ophthalmoplegia (pseudotumor of the orbit and Tolosa–Hunt syndrome). Arch Soc Esp Oftalmol 82:509–512
3. Lapresle J, Desi M (1977) Painful ophthalmoplegia. Acta Neurol Belg 77:331–350
4. La Mantia L, Curone M, Rapoport AM, Bussone G (2006) Tolosa–Hunt syndrome: critical literature review based on IHS 2004 criteria. Cephalalgia 26:772–781
5. Gladstone JP (2007) An approach to the patient with painful ophthalmoplegia, with a focus on Tolosa–Hunt syndrome. Curr Pain Headache Rep 11:317–325
6. Colnaghi S, Versino M, Marchioni E, Pichiecchio A, Bastianello S, Cosi V, Nappi G (2008) ICHD-II diagnostic criteria for Tolosa–Hunt syndrome in idiopathic inflammatory syndromes of the orbit and/or the cavernous sinus. Cephalalgia 28:577–584

7. The International Classification of Headache Disorders 2nd Edition ICHD-II (2004) Cephalalgia 24(Suppl 1):131
8. Schuknecht B, Sturm V, Huisman TA, Landau K (2009) Tolosa–Hunt syndrome: MR imaging features in 15 patients with 20 episodes of painful ophthalmoplegia. Eur J Radiol 69:445–453
9. Jimenez-Caballero PE, Florensa J, Marsal-Alonso C (2005) Tolosa–Hunt syndrome with normal neuroimaging. A report of three cases. Rev Neurol 41:30–33

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ORAL COMMUNICATION

# Feasibility of simultaneous vagal nerve and deep brain stimulation in chronic cluster headache: case report and considerations

**Angelo Franzini · G. Messina · Massimo Leone · Alberto Proietti Cecchini · Giovanni Broggi · Gennaro Bussone**

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**Abstract** In pathologies, such as refractory epilepsy, major depression and cluster headache, there could be indication to both vagal nerve stimulation (VNS) and deep brain stimulation (DBS). In particular, Mauskop (Cephalalgia 25:82–96, 2005) reported the efficacy and safety of VNS in chronic cluster headache. At our Institute, we perform posterior hypothalamic DBS for such clinical condition since 2000 and results appear to be encouraging. Here, we report the case of a patient with chronic cluster headache (CCH) who had initially improved after DBS, whose clinical effect subsequently diminished after head trauma; we performed VNS in the same patient, thus obtaining a new 50% reduction in frequency of pain bouts. Such benefit and the absence of any side effects (possibly due to the co-existence of the two systems) may suggest the possibility of a second therapeutical chance not only in CCH but also in the other two above-mentioned severely disabling pathological conditions.

**Keywords** Simultaneous stimulation · Vagal nerve stimulation · Deep brain stimulation · Cluster headache

## Introduction

Indications to deep brain stimulation (DBS) can sometimes overlap the indications to vagal nerve stimulation (VNS) as may happen in drug-resistant epilepsy [1, 2], major depression [4, 7, 10] and in chronic cluster headache patients [3, 6, 9]. So it may happen that patients harbouring deep brain electrodes could also be potential candidates to VNS or viceversa. The above-mentioned condition occurred in one patient affected by chronic cluster headache (CCH) who had been submitted at our Institute to ipsilateral hypothalamic DBS, which induced remission of pain bouts for 1 year. After such period, and after trivial head and neck trauma, pain bouts recurred and VNS implant was performed and activated simultaneously to the DBS system. The latter procedure led to a subsequent clear improvement of algic symptomatology.

This is the first report in literature referring to DBS and VNS systems working simultaneously in the same patient without side effects due to interferences between the two electrical systems.

## Case report

A 60-year-old patient, 20 years ago, started to complain about intense right supraorbital and intraorbital pain attacks, which was initially episodical (about one episode per month), but rapidly assumed to a frequency of about eight per month. The pain attacks were accompanied by profuse tearing, conjunctival injection, eyelid swelling and nasal congestion. The clinical diagnosis of cluster headache was then formulated and patient initiated pharmacological daily treatment with verapamil, lithium, methysergide, valproate, topiramate, lamotrigine, pregabalin, gabapentin and other drugs including steroids in increasing dosages and several combinations, though without any clinical benefit. The only treatment which led to a partial and temporary amelioration of symptoms was sumatriptan,

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which the patient assumed at on-need basis at the onset of attacks.

Intensity and frequency of pain bouts anyway continued to increase with time despite such treatment; their duration ranged from 30 min to 4 h, and they presented over 200 times per month. After neurological and neurosurgical evaluations, in 2003, he then underwent DBS of right posterior hypothalamus [6] at our Institute.

The stimulation parameters were set at 2 V, contacts 0 and 1 as cathodes and case as anode, 30 Hz in frequency and 60 μs as pulse width. The postoperative course was characterized by prompt and significant improvement of symptomatology with total remission of cluster headache attacks for 1 year. The surgical treatment allowed the patient to suspend the pharmacological treatment as a whole.

Unfortunately, after tan accidental trauma of the head and neck occurred at 1 year after surgery, painful attacks gradually recurred, though not reaching the preoperative severity (duration of about 30 min, frequency of about 9 per day).

Radiological evaluation and pulse generator's check did confirm the structural integrity and functionality of the system and ruled out exhaustion of the battery of the pulse generator. The patient also underwent seriate clinical evaluations with progressive increase of stimulation amplitude and several modification of the remaining stimulation parameters, again without substantial clinical benefit; the previous employed parameters were then reset.

Pharmacological treatment was resumed, but again the only beneficial drug was sumatriptan, assumed at the onset of attacks. So the patient assumed an average dosage of 60 mg sumatriptan in 24 h.

Taking into account the beneficial effect of VNS in CCH previously reported in the literature [9], we decided to perform implantation of VNS system to add peripheral neuromodulation to the still acting central modulation sustained by DBS.

Left VNS system implantation was performed in January 2008; the preoperative frequency and mean duration of pain attacks were about 270 per month and 30 min, respectively.

After VNS, the patient underwent regular clinical follow-up evaluations (every week for the first postoperative month and then on a monthly basis for 1 year in order to record both clinical changes and eventual side effects). The final VNS parameters (set at 1 month postoperatively) were: 0.75 mA, 30 Hz, 500 μs, 30 s on stimulation and 5 min off stimulation.

The improvement of symptomatology began after 3 weeks from intervention and progressed gradually over time; at the last observation carried forward, the frequency of pain attacks was 120 per month and their mean duration was of 15 min with a reduction of 50% for both compared to pre-VNS period.

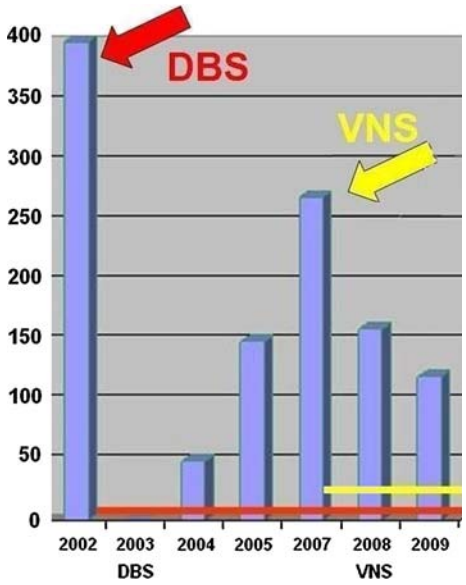


**Fig. 1** Monthly frequencies of cluster headache pain bouts in our patient in function of time and presence of the two stimulating systems

It is important to note that impedance testing of both stimulation systems were repeatedly performed at every postoperative visit, and their values did not change when the two systems were working together with respect to each of the two systems working alone (the other one being voluntarily switched off). Furthermore, no adjunctive stimulation-related side effects, potentially due to each of the two electrodes, were reported by the patient after the second intervention (VNS).

The course of frequency of pain attacks in this patient with respect to time is schematized in Fig. 1.

## Discussion and conclusions

Emerging applications and recognized applications of VNS may overlap the field of DBS. This potential "double indication" may take place in the treatment of severe refractory diseases such as CCH [3, 6, 9], major depressive disorder [4, 7, 10] and unresectable refractory epilepsy [1, 2]. Patients harbouring DBS may take further advantage from VNS as happened in this reported case. Otherwise it is likely that patients not responding to VNS performed to treat depression or epilepsy could undergo DBS to treat the same disease.

Nevertheless, the interactions between peripheral neuromodulation (VNS) and central neuromodulation (DBS) are still poorly known and investigations in this field are needed. VNS has been reported to benefit CCH patients

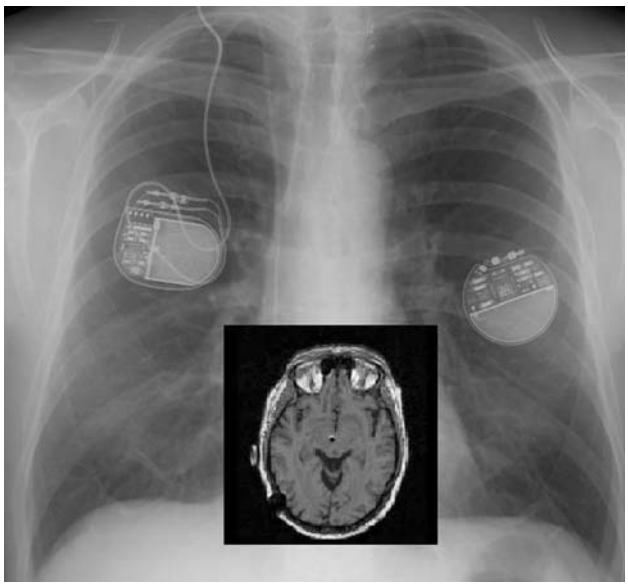

**Fig. 2** Postoperative chest X-ray image of out patient showing the presence of the (*right* and *left*) infraclavicular pulse generators belonging to the two different stimulation system; at the *left*, the VNS IPG; at the *right*, the DBS IPG. In the small *inset*, the patient's postoperative brain MR showing the location of the right hypothalamic DBS electrode

through peripheral mechanisms [2] different from the central mechanisms invoked to explain the therapeutic effects of posteromedial hypothalamic stimulation [3].

The reported case demonstrate that working VNS and DBS at therapeutical levels may cohabitate in the same patient without side effects provoked by the interactions of the two electrical fields (Fig. 2). In our opinion it may happen because VNS is a bipolar stimulation between two very close active contacts. DBS may also work in bipolar modality, but usually chronic stimulation is performed in unipolar configuration with case positive. A possible synergic effect could be suggested by the improvement observed in these patients after that VNS was added to DBS. Different monopolar and bipolar configuration have been tested during VNS and both resulted safe and without side effects.

The reason why, after occurrence of a trivial head and neck trauma cluster headache attacks recurred in spite of a still working DBS system (at the same parameters which had allowed a complete disappearance of symptomatology for 1 year) is not so clear; nevertheless, it is known that the course of the disease may suddenly change in response to environmental factors and traumatisms [8, 11].

The altered balance between peripheral and central mechanisms which are considered in the physiopathology of the disease may also be responsible for the recurrence of pain bouts and a sort of tolerance to hypothalamic stimulation may be taken into account, as well as possible further worsening of the disease which could have become less responsive to DBS itself.

To explain the beneficial effect of VNS in this CCH patient we have to consider the central effects of peripheral neuromodulation which interacts with the same brainstem nuclei and circuits involved in CCH pathophysiology such as the raphe nuclei where central (DBS) and peripheral (VNS) signals may converge [5].

Anyway this case report remarks the emerging role of neuromodulation procedures in the treatment of extremely severe forms of trigeminal autonomic cephalalgias (TACs) when conservative treatments fail. The possible role of VNS originally proposed by Mauskop [9] has been confirmed and its feasibility in a patient harbouring DBS electrodes has been demonstrated.

To our knowledge, this is the first report of such a therapeutical combination in man and its value could go beyond cluster headache's treatment, stimulating the research in other fields such as major depressive disorder and refractory epilepsy, giving to these severely impaired patients a second therapeutical chance when the first choice treatment fails or loses its efficacy.

**Conflict of interest statement** The authors declare that they have no conflict of interest related to the publication of this manuscript.

## References


1. De Herdt V, Boon P, Ceulemans B, Hauman H, Lagae L, Legros B, Sadzot B, Van Bogaert P, Van Rijckevorsel K, Verhelst H, Vonck K (2007) Vagus nerve stimulation for refractory epilepsy: a Belgian multicenter study. Eur J Paediatr Neurol 11:26–269
2. Ellis TL, Stevens A (2008) Deep brain stimulation for medically refractory epilepsy. Neurosurg Focus 25(3):E11
3. Franzini A, Ferroli P, Leone M, Bussone G, Broggi G (2004) Hypothalamic deep brain stimulation for the treatment of chronic cluster headaches: a series report. Neuromodulation 7:1–8
4. Franzini A, Messina G, Marras C, Savino M, Miniati M, Bugiani O, Broggi G (2008) Hamilton rating scale for depression-21 modifications in patients with vagal nerve stimulation for treatment of treatment-resistant depression: series report. Neuromodulation 4(11):267–271
5. Henry TR (2002) Therapeutic mechanisms of vagus nerve stimulation. Neurology 24;59(6 Suppl 4):S3–14
6. Leone M, Franzini A, Broggi G, Bussone G (2006) Hypothalamic stimulation for intractable cluster headache: long-term experience. Neurology 67(1):150–152
7. Lozano AM, Mayberg HS, Giacobbe P, Hamani C, Craddock RC, Kennedy SH (2008) Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. Biol Psychiatry 64(6):461–467
8. Manzoni GC, Lambru G, Torelli P (2006) Head trauma and cluster headache. Curr Pain Headache Rep 10(2):130–136
9. Mauskop A (2005) Vagus nerve stimulation relieves chronic refractory migraine and cluster headaches. Cephalalgia 25:82–96
10. Nahas Z, Marangell LB, Husain MM et al (2005) Two year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. J Clin Psychiatry 66(9):1097–1104
11. Walker RW (2007) Cluster headache and head trauma: is there an association? Curr Pain Headache 11(2):137–140

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CASE REPORT

# A woman with abdominal pain and headache

**Manuela Vaccaro · F. Moschiano**

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**Abstract** We describe a case of a 27-year-old woman who came to the Emergency Department presenting severe abdominal pain. She was evaluated by a gynaecologist and submitted to pelvic ecography without finding relevant alterations. In the successive hours, she presented severe headache in occipital region and in the posterior neck, poorly responsive to analgesic drugs. A cerebral CT scan was performed and was normal, and the patient came to our Department of Neurology. The neurological examination on admission was normal. This woman had a 7 years of long-lasting history of headache, diagnosed in another hospital as migraine without aura, and she referred a recent and progressive worsening of both the frequency and the severity of the headache. In the suspect of subarachnoidal haemorrhage, a lumbar puncture was performed, and was negative for bleeding, showing only a mild increase in the number of cells (12 leucocytes). Following the lumbar puncture, the patient presented a dramatic improvement of the headache. In the successive days, she lamented sellar hypoesthesia and, when asked, she referred a recent history of urinary and faecal retention. She was, therefore, submitted to an NMR of the lumbar and sacral medulla with evidence of a voluminous extradural formation in the sacral region suggestive for extradural sacral meningeal cyst. She was finally despatched to the Department of Neurosurgery for surgical asportation of the cyst.

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**Keywords** Headache · Abdominal pain · Spinal meningeal cyst

## Introduction

Spinal extradural arachnoid cysts are rare and may cause different symptoms and signs due to spinal cord compression. These cysts are more common in male, the peak of incidence is in the second decade of life, and have been reported in any position, although they are most common in the middle and lower thoracic spine. The cause of spinal extradural cysts remains unclear; they are probably congenital but may also be acquired from trauma, infection or inflammation [1]. They develop from protrusions of arachnoid herniating from a small dural defect; they are in nearly every case in communication with the spinal subarachnoid space and contain cerebrospinal fluid [2].

## Case report

Our patient is a 27-year-old woman, not overweight. When she was 20 years, after a deep mourning, she started to lament episodes of pulsating headache, mainly in the posterior region, associated with phonophobia, photophobia, nausea and sometimes vomiting. She went to a Headache Centre (she lived in another country at that time), and she was evaluated by a neurologist who made diagnosis of migraine without aura. During the following years, she presented a progressive worsening of the frequency of severity and duration of migraine, which was treated last time with intramuscular indometacine with partial benefit. She was submitted to different prophylactic treatments without relevant benefit. She was, therefore,

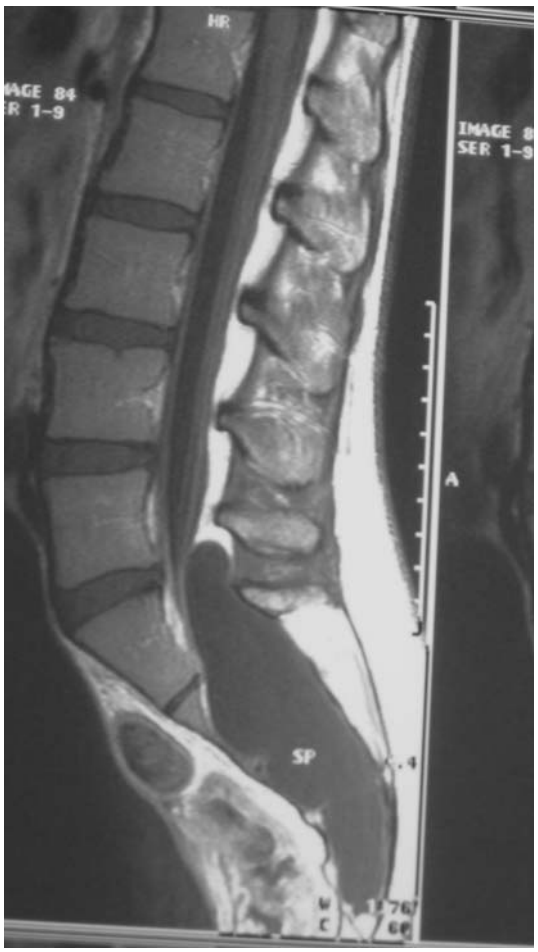


**Fig. 1** Magnetic resonance image of the meningeal cyst

submitted to a cerebral magnetic resonance which was normal. In the last month, the headache was very severe, more frequent, and usually lasted for more than 24 h with spontaneous resolution, often associated with vomiting, sometimes associated also with abdominal pain.

The patient came to the Emergency Department of our hospital presenting severe abdominal pain. She was evaluated by a gynaecologist and submitted to pelvic ultrasound scan that was normal. She was also evaluated by a surgeon and underwent abdominal X-ray with only evidence of faecal encumbrance. In the successive hours, she presented severe headache in occipital region and in the posterior neck, poorly responsive to intravenous analgesic drugs. She was evaluated by a neurologist and submitted to a cerebral CAT scan that was normal, the neurological examination and fundus oculi were normal. The patient was suffering and underwent a lumbar puncture in order to exclude a subarachnoidal haemorrhage, the examination of the cerebrospinal fluid excluded bleedings, showing only a mild increase in the number of cells (12 leucocytes). Curiously, after the lumbar puncture, the patient had a dramatic improvement of the headache.

In the following days, she lamented sensory loss in the sacral dermatomes and, after detailed questions about her medical history she referred a very recent onset of parenthesis in the perineum region and also difficulties in the discharging of the bowel and of the bladder. She was submitted to extemporaneous catheterisation of the bladder with the notice of suggestive urinary stagnancy after urination. She, therefore, underwent urgent magnetic resonance of the lumbar and sacral medulla finding a huge extradural formation in the sacral region suggestive for meningeal cyst (Fig. 1), and she underwent surgical removal of the cyst. Following the surgical operation, she had mild urinary dysfunction that improved in the next weeks. After the operation, she is asymptomatic for headache at 5 months follow-up.

## Discussion

Patients with lumbar and sacral cysts usually present low-back pain, bowel and bladder dysfunction, sensory loss or motor weakness of the lower limbs. Symptoms are often intermittent and exacerbated by Valsalva manoeuvre.

Our patient had a long history of headache with the features of migraine [3] and progressive worsening during the years with severe and daily headache in the last month.

We hypothesise that in our patient the headache was caused by changes in the hydrostatic pressure of the cerebrospinal fluid. A support to this hypothesis is the sudden improvement of the headache after the lumbar puncture and the disappearance of headache after the surgical intervention. Moreover, the worsening of headache in the last month coincides with the onset of the symptoms suggestive for spinal compression.

We search in the literature and we did not find report of spinal meningeal cyst presenting with headache.

The mechanism proposed here for enlargement of the cysts are active fluid secretion from the cyst wall, passive osmosis of water and hydrostatic pressure of cerebrospinal fluid [4].

The fluctuation of symptoms, such in the case described, may be correlated to a valve mechanism in the communicating pedicle, as proposed by some authors [5].

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

## References

1. Cloward RB (1968) Congenital spinal extradural cysts: case report with review of literature. Ann Surg 168:851–864
2. Mc Crum C, Williams B (1982) Spinal extradural arachnoid pouches. Report of two cases. J Neurosurg 57:849–852

3. Headache Classification Subcommittee of the International Headache Society (2004) The International Classification of Headache Disorders, 2nd edn. Cephalalgia 24(Suppl 1):1–160
4. Gortvai P (1963) Extradural cysts of the spinal canal. J Neurol Neurosurg Psychiatry 26:223–230
5. Rohrer DC, Burchiel KJ, Gruber DP (1993) Intraspinal extradural meningeal cyst demonstrating ball-valve mechanism of formation. Case report. J Neurosurg 78:122–125

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CASE REPORT

# Migrainous infarction: association with vascular risk factors in a male subject

**D. Decima · M. Cavallo · M. R. Leotta · A. Gaballo**

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**Abstract** Migraine with aura (MA) is associated with an increased risk of ischemic stroke, especially in young women with vascular risk factors (smoke, contraceptive pill). Patent foramen ovale (PFO) has also been associated with MA. We describe a 41-year-old man, in good health, with MA since 16, familiar history of diabetes, heavy smoker (30 cigarettes/day). Frequency (1–2 attacks/year) and clinical features of migraine have been unchanged since the onset. A few days before our examination he suffered a typical migraine attack. In the following hours, however, the headache became more and more throbbing and the aura symptoms (regressed as usual in 30 min) reappeared and persisted, so he went to an Emergency Department. The CT-scan (without contrast) was normal. The following days he had visual disturbances and spatial disorientation. We found a normal neurological examination and fundus oculi. He referred persisting visual troubles. We prescribed MR + angioMR which confirmed a migrainous infarction and ruled out others pathological conditions. Further tests found out dislipidemia, hyperhomocysteinemia, impaired glucose tolerance. Transcranial Doppler showed right to left shunting. We also prescribed the screening tests for vasculitis (normal). In our opinion this case highlights the relevance of vascular risk factors in MA complications also in male subjects.

**Keywords** Migrainous infarction · Migraine with aura · Ischemic stroke · Vascular risk factors

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## Introduction

According to the 1998 IHS classification, updated in 2004, the definition of migrainous infarction is as follows:

One or more migrainous aura symptoms associated with an ischemic brain lesion in appropriate territory demonstrated by neuroimaging.

Precise criteria are requested for this diagnosis.

1. The present attack in a patient with 1.2: Migraine with aura is typical of previous attacks except that one or more aura symptoms persists for >60 min;
2. Neuroimaging demonstrates ischemic infarction in a relevant area,
3. Not attributed to another disorder.

Along with the definition and the diagnostic criteria the following comments are written:

An ischemic stroke that occurs in a migrainous patient may be categorized as:

1. Cerebral stroke resulting from other causes and coexisting with the migraine,
2. Cerebral stroke resulting from other causes presenting with symptoms resembling migraine with aura,
3. Cerebral stroke occurring during a typical migraine with aura attack. Only this fulfills criteria for 1.5.4.: Migrainous infarction.

Many studies looked upon the correlation between migraine, vascular risk factors and increased risk of stroke particularly in young women, with MA, taking oral contraceptive. The correlation seems to exist for older women too [1–3] and recent works looked upon it even in men, especially related to other vascular risk factors [4]. The association with patent foramen ovale (PFO) is well known, even if the mechanism of this association is only supposed and not yet demonstrated [1].

## Case report

We describe here a 41-year-old man, in good health, with familiar history of diabetes, heavy smoker (30 cigarettes/day), with no history of migraine who suffered migraine with aura since 16 (typical aura with migraine headache, 1.2.1) [5]. The frequency and clinical features of migraine have been unchanged since the onset.

A few days prior to our examination he suffered a typical migraine attack. The aura symptoms regressed as usual after 30 min and then started a headache that became more and more throbbing in the following hours; the aura symptoms reappeared and persisted, so he went to an Emergency Department.

The CT-scan (without contrast agents) was normal. The following days he had visual disturbances (flashes and blurred vision in the upper visual field) and spatial disorientation (he did not recognize the rooms of his home), so he came to our examination.

We found a normal neurological examination and fundus oculi. He referred persisting visual troubles.

We prescribed MR + angioMR which evidenced an ischemic lesion in the occipital cortex (confirming the diagnosis of migrainous infarction) and ruled out others pathological conditions.

Further tests found out hypercholesterolemia (246 mg/dl), (HDL 29) hyperhomocysteinemia (18.2 μmol/l) (VN < 15), impaired glucose tolerance.

Transcranial Doppler showed right to left shunting (the patient refused transesophageal echocardiogram). Color-coded duplex ultrasonography (DUS) was normal.

We also prescribed the screening tests for vasculitis consisting in PT, PTT, antithrombin III, fibrinogen, d-dimer, clotting factors II, VII, Protein C, Protein S, C3, C4 organ and not organ-specific antibodies (anticardiolipin, antithyroglobulin, antiparietal gastric cells, antismooth muscle, antimicrosomes, antimitochondrion, Lupus anticoagulant).

## Discussion and conclusion

We considered that the diagnostic criteria listed above are all respected:

1. The patient has been suffering of MA for many years. The episode that we described started with typical symptoms, but the visual disturbances persisted for many days.
2. The magnetic resonance imaging (MRI) showed an ischemic area in the occipital cortex and excluded other brain pathologies.
3. Further examinations ruled out vasculitis and cervical vessels pathology.

However, the patient shows numerous vascular risk factors (smoke, impaired glucose tolerance, hypercholesterolemia, hyperhomocysteinemia) along with that PFO might have determined the migrainous infarction.

**Conflict of interest statement** The authors declare that they have no conflict of interest related to the publication of this manuscript.

## References

1. Sacco S et al (2008) Comorbid neuropathologies in migraine: an update on cerebrovascular and cardiovascular aspects. J Headache Pain 9(4):237–248
2. Etminan M et al (2005) Risk of ischemic stroke in people with migraine: systematic review and meta-analysis of observational studies. Br Med J 330:63–65
3. Moskowitz MA, Kurth T (2007) Blood vessels, migraine abd stroke. Stroke 38:3117–3118
4. Kurth T et al (2007) Migraine and risk of cardiovascular disease in men. Arch Int Med 167:795–801
5. Headache Classification Committee of the International Headache Society (2004) The International Classification of Headache disorders, 2nd edn. Cephalalgia 24 (Suppl 1):1–160

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POSTERS

# 6th International Headache Seminary

## SUNCT: a rare or underestimated pathology?

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**Introduction:** SUNCT syndrome is known as a rare form of unilateral neuralgiform pain associated to ipsilateral conjunctival injection and tearing. Until today, literature formally reports just about 80 cases describe and correctly diagnosed, even if experts presume that this pathology is actually more common.
**Patients and methods:** During the last year three patients came to our observation: A.V., male, 53 years old, admitted for episodical stabbing pain localized to the right periorbital area irradiated to the frontal regions, related to conjunctival injection and tearing; the episodes lasted few seconds but recurred many times a day. The subject complained of similar events in the past. The only relevant comorbidity was essential hypertension. P.P., male, 71 years old, with stabbing and burning pain in the right eye and periorbitary region irradiated to the nasal wing; these events were short-lasting, often triggered by chewing and yawning, associated to rhinorrea, tearing and conjunctival hyperemia in the affected eye. Relevant comorbidities were essential hypertension, chronic ischemic cardiopathy and stroke. C.E., male, 19 years old, was admitted for the diagnostic definition of an electric shock-like pain localized to the superior right mandibular hemiarch and hemiface; the pain was short-lasting, sometimes triggered by chewing, always associated to rhinorrea and tearing with conjunctival hyperaemia in the right eye; no significant comorbidities.
**Results:** The three patients were studied with the same diagnostic pathway: anamnesis, neurological visit, hematic exams, ECG, EEG, brain MRI. All these findings resulted normal, and the MRI scan excluded neurovascular conflicts or neoformations. Subjects were treated with lamotrigine, amytriptiline, gabapentin, carbamazepine in different combinations with good results.
**Discussion:** All these three patients satisfy the 2004 IHS criteria for the diagnosis of SUNCT. Thus, we speculate if the diagnosis is based on too non-specific criteria or if, on the contrary, this pathology should not be deemed as "rare".
**Conclusions:** International literature, in the last years, argues that SUNCT syndrome is not rare but often underdiagnosticated; with this brief case series, we want to add our contribution to enforce this hypothesis, recommending to apply the 2004 HIS criteria to diagnosticate SUNCT in patients with suggestive symptoms.

## Hormonal contraception and migraine-associated allodynia

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**Background:** Cutaneous allodynia is complained by about two-thirds of patients during migraine episodes. Among migraineurs, allodynia is thought to be caused by the headache: the persistence of pain sensation seems to be able to induce central sensitization in the caudal nucleus of the trigeminal nerve by lowering the neuronal pain threshold. A significantly higher prevalence of cutaneous allodynia in women has been found. An estrogen-dependent modulation of pain is known and extremely complex. Central sensitization alone cannot presumably explain the occurrence of allodynia in migraine and a susceptibility to allodynia seems to be necessary. This susceptibility is probably related to a particular genetic combination on which environmental and hormonal elements co-work with pain persistence.
**Objective:** To compare prevalence of allodynia among female migraineurs grouped by use of hormonal contraception.
**Population and methods:** 150 female migraineurs consecutively evaluated in the Headache Center of the L. Sacco Hospital in Milan: 89 had only attacks of migraine without aura (MO) and 61 had also attacks with aura (MA). 43 out of these 150 patients used hormonal contraception. Presence of cutaneous allodynia was investigated by a semistructured interview. Statistical analysis was performed by chi square.
**Results:** Allodynia during headache episodes was complained by 88 out of 150 migraineurs (58,6%): 26 out of 43 patients using hormonal contraceptive were allodynic (60,4%). Among the 107 patients free from hormonal contraception 62 complained allodynia (57.9%). No difference was found in prevalence of allodynia between patients with and without hormonal contraception. With regard to the MO subgroup, allodynia was complained by 13 out of 28 patients with oral contraceptive (46.4%) and 28 out of 61 without hormonal therapy (45.9%). In the MA group, allodynia was present in 13 out of 15 patients with hormonal treatment (86%) and in 34 out of 46 subjects free from hormonal intake (74%). Also in these diagnostic subgroups no difference emerged with regard to allodynia prevalence.
**Conclusions:** Allodynia complaint seems not to be influenced by use of hormonal contraception, reinforcing the observations that persistence of pain and predisposition are the main elements in allodynia pathophysiology, independently by external factors.

## A new option for migraine treatment in young age: preliminary results

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**Background:** Although recurrent headaches are common in children and adolescents, effective pharmacological treatment(s) without side effects are still lacking. Most of current non-pharmacological investigations modalities have employed (either medication or behavioral) often with unsatisfactory results. Few pharmacological studies have included treatment comparisons. One of the most urgent and important problems with this kind of patients is to have therapeutic

possibilities without side effects, so common with pharmacological treatments. Ginkolide b, an herbal constituent extract from ginko biloba tree leaves, is a natural anti-platelet activating factor (PAF). PAF is a potent pro-inflammatory and nociceptive agent released during the inflammation process. In addition ginkolide b modulates the action of glutamate acid, the main excitatory neurotransmitter of CNS. It is known that abnormal levels of glutamate may cause spreading depression and migraine aura in the susceptible individuals and the PAF, released from platelets and leukocytes during the first phase of migraine without aura attacks, sensitizes the trigeminal-vascular endings and induces pain. Therefore ginkolide b can be considered a promising not pharmacological tool for treatment of migraine.

**Objective:** On the basis of this background we tested the efficacy of ginkolide b in a group of young patients suffering from migraine without aura. All patients were recruited at the headache center of Besta neurological institute.

**Methods:** A small sample of 8 young patients suffering from migraine without aura were treated with ginkolide B and magnesium twice per day, in oral administration, for 3 months. Number, duration and severity of migraine attacks were assessed in a diary card one month before the starting of the trial and during the treatment period. After 3 months, all patients were checked with their daily card for number, duration, severity headache episodes and analgesic consumption.

**Results:** Seven patients referred a significant clinical improvement (days of headache per month pre $13.7 \pm 11.5$ post $5 \pm 2.7$) with a decrease of number of analgesics used for the attacks (pre-treatment $6.3 \pm 3.7$ post $4 \pm 3$). The treatment was well tolerated and the compliance was good (from patients and parents too).

**Conclusion:** Although the results are very preliminary, this treatment could be a good option for patients suffering from migraine in particular for young patients where therapies without side effects are needed.

## Migraine with medication overuse and disability out-patient versus day-hospital withdrawal for chronic assessment: preliminary results

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**Background:** Patients with chronic migraine and medication overuse are particularly difficult to treat, with no one approach being universally accepted. Some type of withdrawal program, however, is typically implemented before beginning a pharmacological prophylaxis treatment.

Different withdrawal modalities have been performed for managing these patients at first step; in-patient withdrawal has been confirmed effective in preceding clinical experiences. In recent years new modalities for withdrawal have been developed as day-hospital setting and out-patient withdrawal.

**Objective:** Purpose of this study was to determine the clinical course of 2 samples of chronic migraine patients with medication overuse 3 months following different treatment interventions: day-hospital or out-patient withdrawal.

**Methods:** Two groups of patients were treated. Patients were suffering from chronic migraine with medication overuse according with HIS criteria. In Group A, 9 patients were treated by out-patient withdrawal. In Group B, 25 patients were treated by day-hospital withdrawal.

**Results:** Patients of both groups clinically improved at the 3 months follow up: in fact days of headache per month decreased significantly (group A: 18.4 vs 8.6; group B: 22.4 vs 8.1), medications/month decreased significantly too (group A: 25 vs 10.7; group B: 25.4 vs 8.1).

**Conclusions:** From these results the out-patient withdrawal followed by periodic clinical meetings seems to be effective for this category of patients, in particular for high-motivated patients, as day-hospital withdrawal. Nevertheless the follow-up period is too short and our data are too preliminary for having definitive conclusions.

## Efficacy of duloxetine in patients with comorbidity of depression and chronic migraine with medication overuse

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**Background and objectives:** Antidepressants are often used to treat chronic daily headache (CDH) disorders mainly because of the high prevalence of associated mood disorders. Among CDH, chronic migraine with medication overuse (Silberstein and Lipton criteria) is the most frequent form. Some chronic migraine patients do not improve with current drug prophylaxis. New therapeutic strategies are needed in such cases. Duloxetine hydrochloride, a new antidepressant, is a selective serotonin and norepinephrine reuptake inhibitor. Aim of this study was to evaluate the efficacy and tolerability of duloxetine treatment in chronic migraine patients with medication overuse and concomitant depression.

**Patients and methods:** Fifty patients, 40 women and 10 men, aged 20–65 years (mean 39.4) fulfilling the Silberstein and Lipton criteria of chronic migraine with symptomatic medications overuse were included in the study. These patients had a Hamilton depression rating scale (HDRS) score between 20 and 35 and a migraine disability assessment scale (MIDAS) $> 20$ (grade IV).

Duloxetine was administered at a daily dose of 60 mg for 12 weeks. Patients had a baseline 1-month period; hence, duloxetine was started and they were assessed after 4, 8 and 12 weeks. The following parameters were employed to measure outcome (clinical end-points): number of headache days per month, headache intensity, analgesic consumption, Hamilton Depression Scale and MIDAS. Number of responders (=headache frequency reduction $\geq 50\%$ in the treatment period vs baseline) were also evaluated.

**Results:** All patients completed the study; the drug was well tolerated. In our patients, number of headache days per month, analgesic consumption, headache intensity, HDRS and MIDAS were significantly reduced after duloxetine treatment (mean $\pm$ SD before and after treatment $20.6 \pm 1.8$ vs $11.0 \pm 1.3$; $20.0 \pm 1.8$ vs $10.5 \pm 1.3$; $2.7 \pm 0.5$ vs $1.9 \pm 0.4$; HDRS $26.3 \pm 2.0$ vs $14.8 \pm 1.1$; MIDAS $85.66 \pm 21.4$ vs $6.7 \pm 2{,}05$; $P < 0.0001$). Twenty-seven of the fifty (54%) patients were responders.

**Discussion and conclusions:** Migraine causes significant lost productivity and decreases quality of life. Part of the burden of migraine is produced by the psychiatric conditions that often coexist, such as depression or anxiety. Similar neurochemical alterations may explain comorbidity between migraine and psychiatric disorders.

Amitriptyline is a tricyclic antidepressant consistently shown to prevent migraine. Unfortunately it commonly causes side effects (such as cognitive impairment, orthostatic hypotension and cardiac abnormalities) that may limit its utility. This study shows that chronic migraine patients significantly improved after duloxetine

administration. We have observed a good tolerability profile during the treatment period. Duloxetine does not bind to receptors originating tricyclic-induced side-effects and this could explain the good tolerability. Duloxetine efficacy in our patients may be explained either as a direct effect on migraine or an improvement in depression.

## Disability in migraine patients: the role of muscle tenderness and psychometric correlates

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A relationship between pericranial muscle tenderness and psychiatric disorders was described in migraine patients, in particular when associated with chronic tension type headache (CTTH). The aim of the study was to evaluate the temporomandibular system and cervical spine function, the tenderness of pericranial, cervical and body muscles, and their relationship with personality profile and psychiatric symptoms in a population of migraineurs with and without CTTH.
**Methods:** Healthy subjects and migraineurs with and without CTTH (according to IHS-2004 criteria) were consecutively recruited. All subjects were submitted to a clinical investigation of the temporomandibular system according to "Craniomandibular Index" (CMI), of pericranial and body muscles respectively according to "tenderness total score" (TTS) and "Fibromyalgia tender points" (TP), and of the cervical spine (PECS). Personality profile and psychiatric symptoms were assessed with tridimensional personality questionnaire (TPQ), toronto alexithymia scale—20 items (TAS-20), state and trait anxiety inventory (STAI 1-2), and beck depression inventory (BDI). All migraineurs underwent migraine disability assessment (MIDAS) and Headache Impact Test—6 items (HIT-6) to assess migraine disability.
**Results:** 47 migraineurs (mean age $37 \pm 12$), 40 migraineurs with CTTH (mean age $32 \pm 10$) and 40 healthy controls (mean age $35 \pm 12$) were admitted to the study. All migraineurs have showed a significant higher scores in CMI, TTS, PECS, TP and in BDI, STAI, Harm Avoidance dimension of the TPQ and TAS-20 than healthy controls ($p < 0.05$). All the clinical and psychometric findings were more evident in migraineurs with CTTH ($p < 0.05$). Duration of illness, frequency of attacks as well as MIDAS and HIT-6 scores were positively correlated with the total number of craniomandibular and cervical tender points ($p < 0.05$).
**Conclusion:** Migraine patients present subclinical temporomandibular and cervical spine disorders, with high muscle tenderness. These clinical findings are more evident in migraineurs with CTTH and are associated with psychiatric symptoms and with a peculiar personality profile. It might be important to point out these clinical features not only for the therapeutic implications, but also to prevent and better understand the physiopathological mechanisms that may lead to chronic migraine.

## Processing visual stimuli in cluster headache: a combined functional and tractography MRI study

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**Background:** Morphological and functional imaging studies have indicated that a primary hypothalamic dysfunction might be involved in the pathogenesis of cluster headache (CH). However, a few neurophysiological and metabolic studies have suggested a more global dysfunction of central modulation of peripheral stimuli in these patients.
**Objective:** To define the structural and functional magnetic resonance imaging (MRI) abnormalities of the visual network in patients with CH.
**Methods:** Dual-echo, diffusion tensor (DT) and functional MRI (during visual stimulation with a 2 Hz checkerboard) were acquired from 18 patients with chronic CH and 18 sex- and age-matched controls. Using DT MRI tractography, probability maps for the major brain white matter (WM) fiber bundles were constructed from controls and applied to patients' data to calculate mean diffusivity (MD) and fractional anisotropy (FA) values. FMRI data were analysed using SPM2 software.
**Results:** No difference was found for any of the WM fiber bundles metrics analyzed between controls and CH patients. Compared to controls, CH patients showed a decreased activation of the right (R) middle occipital gyrus, the R dorsolateral prefrontal cortex (DLPFC) as well as an increased deactivation of the R postcentral gyrus. No correlation was found between fMRI changes and patients' clinical characteristics.
**Conclusions:** A central dysregulation of top-down modulation of antinociceptive system occurs in CH patients. Such a dysfunction tends to involve also other systems, including the visual one, and does not have corresponding structural abnormalities, measured using DT MRI. The lack of a correlation between fMRI changes and patients' clinical characteristics suggest that they might reflect congenital abnormalities.

## Cerebral transverse sinus asymmetry in chronic daily headache

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**Aims:** Large venous cerebral sinuses are pain-sensitive structures richly innervated by branches of the ophthalmic division of the trigeminal nerve, involved in the pathophysiology of head pain. Our aim was to investigate the correlation between alterations of cerebral venous sinuses morphology on neuroimaging and chronic headache.
**Subjects and methods:** We studied 70 consecutive patients affected by CDH with medication overuse (mean age $47.1 \pm 15$; sex M/F: 6/64; mean duration of headache $26.3 \pm 14.3$ years) admitted to our Unit from November 2006 to May 2008. According to ICHD- II, 48 had a diagnosis of EC, 2 of CTTH, 2 CCH and 17 EC with abuse of analgesics. Clinical features of headache were assessed by means of a structured questionnaire. All patients underwent a cerebral MRI and MRV (phase contrast sequence) to investigate venous sinuses morphology.
**Results:** In 48.5% (34/70) of patients the MRV showed a transverse sinus asymmetry with predominant right transverse sinus (right 80%; left 20%). Moreover, two-thirds of asymmetric patients had an unilateral side of pain, while only a bit more of 50% of symmetric patients had bilateral pain.
**Discussion and conclusion:** Our data suggest an increased prevalence of cerebral sinuses asymmetry, mainly the transverse sinus, in patients with CDH (48%) compared to that reported in both episodic headache (31%) and general population (24%). We

hypothesize that cerebral transverse sinus asymmetry could have a role in the pathophysiology of CDH. Our data need confirm in a larger population.

**References**


1. Ayanzen RH, Bird CR, Keller PJ, McCully FJ, Theobald MR, Heiserman JE (2000) Cerebral MR venography: normal anatomy and potential diagnostic pitfalls. AJNR Am J Neuroradiol 21:74–78
2. Alper F et al (2004) Importance of anatomical asymmetries of transverse sinuses: an MR venographic study. Cerebrovascular Dis 18(3):236–239
3. Castillo et al (1999) Epidemiology of chronic daily headache in the general population. Headache 39:190–196
4. Bono F et al (2003) Cerebral MR venography of transverse sinuses in subjects with normal CSF pressure. Neurology 61:1267–1270


## On prophylaxis therapy of pediatric migraine with magnesium, l-triptophan and niacin


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**Aim:** To evaluate the efficacy and tolerability of magnesium, l-triptophan and niacin in prophylaxis therapy of pediatric migraine.
**Methods:** 12 outpatients, (7 F, 5 M) mean age 7.9 years (SD 1.2), range 6–10 years, suffering from migraine without aura (ICDH '04 criteria) were enrolled. The mean duration of disease was 1.8 (SD 0.8) years, range 1–3 years. At baseline the mean frequency of attacks was 7.8/month (SD 2.3), range 4–12; the mean number of drugs intaking for acute attacks was 6.6 tablets/month (SD 1.4). During the 6-month evaluation period magnesium, l-triptophan and niacin were administered (at dose 90 mg, 350 mg, 25 mg/day respectively). All patients filled a headache-diary card during the evaluation.
**Results:** The basal frequency of attack was 7.8 (SD 2.3) and 4.4 (SD 2.3), 3.4 (SD 2.2), 2.4 (SD 2.6), after 1, 3 and 6 months, respectively ($p = 0.002$; $p < 0.0001$; $p < 0.0001$). The basal value of intaking drugs for acute attacks was 9.2 (SD 2.9) and 5.2 (SD 2.6), 3.6 (SD 2.7), 2 (SD 2.6) after 1, 3 and 6 months, respectively [$p = 0.002$; $p < 0.0001$; $p < 0.0001$] ($t$ test analysis). Magnesium, l-triptophan and niacin was well tolerated (4 patients complained somnolence, diarrhea and gastralgia but none of the patient withdrew the study).
**Conclusions:** These data showed a good efficacy in reduction of frequency and intensity of headache attack, a good tolerability and a very good reduction of drugs intaking for acute attacks. Our study suggests that magnesium, l-triptophan and niacin could be an alternative therapy for pediatric migraine prophylaxis.

## Zonisamide in refractory patients with episodic cluster headache: an open study


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**Background:** The prophylactic therapy of the cluster headache (CH) is based on verapamil and carbolithium. Besides several patients are not responders at this drugs.
**Aim:** To evaluate the efficacy and tolerability of zonisamide in prophylaxis therapy of refractory episodic cluster headache.
**Methods:** 8 patients, (2 F, 6 M) mean age 42.6 years (SD 6.6), range 36–56 years, suffering from episodic cluster headache (ICDH '04 criteria) were studied. The mean duration of disease was 9.6 (SD 7.3) years, range 3–26 years. In all patients prophylaxis therapy with verapamil, carbolithium and valproic acid was failed in the past. During the 3 months evaluation period zonisamide was administered (starting dose 25 mg/day, target dose 100 mg/day). All patients filled a headache-diary card during the evaluation.
**Results:** The basal frequency of attack/days and 1, 2, 3 months respectively was 4.2 (SD 1.9): 2.4 (SD 0.9), 1.6 (SD 0.9), 0.8 (SD 1.1) [$p < 0.03$; $p < 0.004$; $p < 0.0001$] ($t$ test analysis). Zonisamide was well tolerated (2 patients complained somnolence, lack of concentration, vertigo and nausea but not withdrew the study).
**Conclusions:** These data showed a good efficacy in reduction of frequency of attacks. Still, the drug is tolerable, in fact none of the patients withdrew the study. Our study suggests that zonisamide could be an alternative prophylaxis therapy for episodic CH.

## New mechanisms of migraine with aura revealed by NIRS


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**Background:** Leao first suggested a relationship between cortical spreading depression (CSD) and migraine aura, based on the uniquely slow spread of clinical and electrophysiological events. Some human neuroimaging studies have indirectly suggested that CSD underlies migraine and cerebral hypoperfusion associated with spreading depression was a result of decreased metabolic demand. During migraine with aura some studies performed by Transcranial Doppler (TCD) showed a decrease in blood flow velocities and increase of the pulsatility index (PI) suggestive of hypoperfusion of cerebral microcirculation. Innovative near-infrared spectroscopy (NIRS) can measure Cerebral Tissue Oxygen Saturation ($StcO_2$), and the arterial pulse wave in cerebral microcirculation (APWCM) that reflect cerebral function and regional cerebral bood flow (CBF).
**Objective:** To study cerebral microcirculation during spontaneous prolonged migraine aura, to compare the results with headache-free periods, to identify new mechanism of migraine aura.
**Patient and methods:** We studied 8 subjects (3 M and 5 F, age range 12–41) by innovative continuous-wave NIRS system (portable, 760 and 850 nm as source, 4 cm source-detector separation) and TCD during spontaneous prolonged aura of migraine attacks and after 2, 4, 6 h the end of aura.
**Results:** During aura of migraine attack NIRS showed significant decrease of amplitude APWCM (35%) $p < 0.002$, and increase of $StcO_2$ (15%) $p < 0.008$ ipsilateral to the headache pain and contralateral to the symptoms of aura compared with headache-free periods, TCD showed a significant increase of PI (38%), $p < 0.001$ and decrease of diastolic velocity in the posterior and middle cerebral artery ipsilateral to the headache pain compared with headache-free periods. NIRS and TCD parameters normalized only after 4–6 h the end of migraine aura.
**Conclusion:** These findings suggest that hypoperfusion of cerebral microcirculation associated with spreading depression during migraine aura was a result of decreased metabolic demand and normalized later the end of migraine aura.

## A "quality path" for the assessment of headaches in cases of civil invalidity

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Due to the considerable aetiological complexity and range of clinical variations which characterize them, headaches are particularly difficult to assess. The highly subjective nature of headaches often makes it very difficult to confirm and assess them in terms of severity, frequency, and level of invalidity, which in turn often leads to medico-legal disputes. Nevertheless, such a pathology is of great interest both in terms of civil invalidity and in issues of liability claims, as cephalalgic situations may be the result of a variety of factors such as, for example, cranial or neck trauma, exposure to toxic factors in the workplace, the use of video-terminals, or they may be triggered by workplace mobbing (harassment). At the present time, there is an almost total lack of standardized criteria designed to establish suitable percentages of invalidity for each sub-category of headache. The aim of the present paper is to provide a series of parameters that will correspond as fully and realistically as possible to the needs of the invalid, while taking account of both current legislation and its benefits and of the nosological framework, with particular reference to episodic and chronic headaches and their relative impact on the subject's ability to work, while also considering the assessment in relation to repercussions of the headache on the subject's mental and physical capabilities in the widest sense (biological damage). Further, given that the pathology in question presents a strongly heterogeneous clinical and temporal component, we also propose the necessary prerequisites for establishing a medico-legal assessment in terms of intensity, frequency, duration, response to treatment in connection with the types of pharmaceuticals used and their side-effects, indicating the appropriate bodies/agencies for the issue of relative certifications as well as the required clinical and/or instrumental tests. The aim of this "path" is to focus greater attention on a clinical situation which has wide-ranging impact on society, with a view to contributing to the definition of a common assessment procedure on a national scale which will have a concrete impact on the new civil invalidity tables that are currently being prepared.

## Migraine with aura in two patients with arteriovenous malformation and intrapetrosal carotid dissecation

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A 42-year-old woman came to our observation for migraine attacks preceded by visual symptoms from the adolescence. More in detail, a hazy spot was followed after 2–15 min by a star-shaped figure and then by a semicircular zigzag line. Sometimes, the pulsating headache was also preceded by sensory symptoms and it was associated to photophobia, phonophobia, nausea and vomiting. The mother's and the sister's patient had similar migraine attacks, with a complete resolution after non-steroidal anti-inflammatory therapy. On the basis of her familial history, diagnostic investigations were never performed even if the patient underwent to several neurological examinations. In our Department, Angio- and Brain Magnetic Resonance Imaging (MRI) were performed and they revealed a large left artero-venous malformation, extended from the occipital to the frontal left lobe.

One month later, a 32-year-old man came to our observation for a third throbbing headache attack preceded by visual symptoms and followed by right hand weakness accompanied by sensory symptoms, dysarthric speech disturbance, nausea and vomiting. The patient's familial history was positive for migraine with similar characteristics and in the past a MRI of the brain had been performed and it was normal. In our Department, we decided to perform another brain magnetic resonance imaging (MRI) because the patient referred, from the last attack, dizziness during the day. The neuroradiological investigation revealed a left intrapetrosal carotid dissecation.

Our experience confirm that, even if every patient with migraine with aura, in our opinion, would undergo to at least a MRI of the brain, the clinician has to consider every migraine attack with particular characteristics as the possible manifestation of a new underlying disease.

## The creation of a biobank for patients affected by familial and sporadic hemiplegic migraine

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Familial Hemiplegic Migraine (FHM) is a rare subtype of migraine with aura inherited with an autosomal dominant pattern. We created in our laboratory a BioBank sampling the DNA of patients affected by Familial and Sporadic Hemiplegic Migraine, diagnosed according to the International Headache Society criteria (2004). When these patients come to our Department, they undergo a neurological examination and all the instrumental investigations that can confirm the absence of other diseases. After obtaining written consent, we purify DNA from blood of all affected individuals and some of their healthy relatives by using the IsoQuick Nucleic Acid Extraction kit (ORCA Research, Bothell, WA, USA). Our genetic analysis is made in order to search for mutations in the three genes associated to the disease. The majority of the families (50–75%) is linked to chromosome 19p13 and carry mutations in the gene *CACNA1A* (FHM1) encoding the Cav2.1 calcium channel subunit (Ophoff 1996; Ducros 2001), so this is the first gene that we generally investigate. However, even if only a smaller proportion of FHM families is linked to chromosome 1q23 (FHM2) (Ducros 1997; Gardner 1997), with mutation in the *ATP1A2* gene encoding the alpha-2 subunit of $Na^+/K^+$-ATPase (De Fusco 2003), sometimes, according to the patient's clinical features, this is the first gene that we examine. Finally, if we have not found mutations in the CACNA1A and in the ATP1A2 genes, we also analyse the *SCN1A* gene (FHM3), recently identified, located on chromosome 2q24 and encoding a $Na_v2.1$ sodium channel subunit already known to be associated to different forms of epilepsy (Escayg, 2000, Claes, 2001). In the past 2 years we have found new mutations in the ATP1A2 gene, never described in literature. Recently, we created a network with other Neurological Departments in order to collect as many patients as possible. This fact could facilitate the discovery of new genetic mutations, the characterization of the genotypic/phenotypic correlations and possibly it could contribute to understand the pathogenesis of Hemiplegic Migraine and probably of migraine of aura. In fact, according to the main

hypothesis, mechanisms underlying attacks of Hemiplegic Migraine are thought to be closely related to those of migraine with typical aura. More in detail, Moskowitz et al. (2004) have recently suggested that FHM mutations render the brain more susceptible to prolonged cortical spreading depression (CSD) caused by either excessive synaptic glutamate release (FHM1) or decreased removal of glutamate and $K^+$ from the synaptic cleft (FHM2).

## Prevalence of migraine in essential tremor: a case–control study

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**Background:** Essential tremor (ET) and migraine (M) are common neurological disorders sharing (1) a strong genetic background, (2) benefit form identical therapeutic options (B-blockers) (3) a similar pattern of bilateral activation of the red nucleus (Bold fMRI).
**Objective:** To determine the prevalence of M in ET in a case–control study.
**Methods:** We investigated the presence of M (ICHD-II criteria) in 100 consecutive ET patients (AAN criteria) (mean age 70 ± 11 years) and in 100 sex- and age-matched healthy controls (HC). Current and lifetime M and its clinical features were assessed by means of a structured questionnaire in a face-to-face interview.
**Results:** The prevalence of lifetime M and current M was similar in ET patients and HC. Among ET patients, 25 had lifetime M (M/F: 7/18; mean age 68.9 ± 13 years; M without aura 24, M with aura 1; mean duration of tremor 16.7 ± 15 years) and 10 had current M (M/F: 2/8, mean age 66 ± 9,4; M without aura 9, M with aura 1; mean duration of tremor 18.4 + 15.6 years). Among HC, 22 had lifetime M (M/F: 6/16, mean age 67 ± 15 years, M without aura 20, M with aura 1, CDH 1) and 14 had current M (M/F: 4/10, mean age 62.3 ± 16 years, M without aura 13, CDH 1). ET patients with M did not differ from ET patients without M in age, familiarity for tremor, age at onset of tremor, duration of tremor, severity of tremor in the upper limbs or in the head.
**Conclusion:** In contrast with previous open studies, we demonstrate that the prevalence of M is similar in patients with ET and in HC.

## Headache and carotid-cavernous fistula: a case report

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Carotid-cavernous fistulas (CCF) are an uncommon pathology consisting a vascular anomaly in which blood flows from meningeal branches of the internal and external carotid arteries, or directly from the internal carotid artery, into the venous circulation around and in the cavernous sinus.

We describe a case of a 26-year-old woman who presented a 7-day history of severe temporo-occipital headache and a right retro-orbital pain. This cephalalgia did not respond to any abitually analgesic drugs. She arrived at the Emergency Department for a worsening of the headache and for the sudden onset of diplopia caused by VI cranial nerve palsy; the patient presented also nausea and vomiting, conjunctival injection and chemosis. The patient had a medical history of catamenial migraine. A cerebral CT scan was normal while angio-CT study showed a bilateral cavernus sinus dullness (>dx). For this finding, an urgent cerebral angiography was performed which revealed the presence of a high flow carotid-cavernous fistulae (CCF). Also a transcranial doppler performed trough the right temporal window showed a turbulent flow at the deep of 7 cm. After neurosurgeon and neuroradiologist counselling the patient underwent transarterial embolisation procedure.

Headache can be the first clinical manifestation of the CCF: this vascular disease generally causes periorbital aching with ocular symptoms due to high venous pressure in the cavernous sinus. According to the II edition of the International Headache Classification (HIS 2004), the diagnostic criteria for the headache attributed to dural arterio-venous fistula are the follows: A. Any new acute headache fulfilling criterion C; B. Neuroimaging evidence of dural arteriovenous fistula; C. Evidence exists of causation by the fistula; D. Subarachnoid haemorrhage, intracerebral haemorrhage and other causes of headache ruled out by appropriate investigations. Sometimes the carotido-cavernous fistulae may arise as painful ophthalmoplegia. Most CCF are considered benign lesions; however, acute neuro-ophthalmologic changes due to the rare incidence of rupture (risk depending on size) may warrant immediate therapy. Although surgical management of CCF is possible, endovascular therapy is the mainstay of modern therapeutic options.

## Migraine and mitochondrial dysfunction: a review

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The central nervous system (CNS) is, after the peripheral nervous system, the second most frequently affected organ in mitochondrial disorders (MCDs). CNS involvement in MCDs is clinically heterogeneous, manifesting as epilepsy, stroke-like episodes, migraine, ataxia, spasticity, extrapyramidal abnormalities, bulbar dysfunction, psychiatric abnormalities and neuropsychological deficits. Several lines of evidence suggest that at least some subtypes of migraine may be related to a mitochondrial defect. Skinoj, in 1973, was the first to demonstrate that lactate levels are increased in the CSF during migraine attacks. Migraine is a prominent feature particularly of Mitochondrial Encephalomyopathy, LActacidosis, Stroke-like episodes (MELAS) but may also occur together with other nonsyndromic or syndromic MCDs, such as Myoclonic Epilepsy and Ragged Red Fibers syndrome (MERRF), LS (leigh syndrome), KSS (Kearns Sayre syndrome) and PEO (Progressive External Ophtalmoplegia), in which migraine can precede ocular involvement and ataxia by many years. Along with other inherited factors, such as disturbances in calcium channelopathies, an abnormality of mitochondrial oxidative metabolism increases neuronal excitability and reduces the threshold for triggering migraine attacks. On the other hand, exogenous stimuli may, in cortical areas characterized by a reduced mitochondrial energy reserve, create an imbalance between neuronal energy supply and energy consumption that can accelerate the rise in lactate concentration normally occurring with stimulus-induced neuronal activity. The resulting imbalance of the brain metabolic homeostasis might activate the trigeminovascular system, triggering a migraine headache (Schooenen et al. 1996).

In conclusion, an impairment of oxidative metabolism may explain the "threshold character" of migraine attacks and migraine is probably associated with unidentified mutations of the mtDNA or of nuclear genes which may equally affect the energy production of the mitochondrial machinery (Sparaco et al. 2005).

## CNS dysregulation extends beyond the pain-matrix network in cluster headache: a study of resting state networks

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**Background:** The assessment of low-frequency (<0.1 Hz) fluctuations in functional magnetic resonance imaging (fMRI) data at rest has demonstrated the presence of high temporal coherence between spatially distinct, functionally related brain regions, which characterizes the resting state networks (RSN) of the human brain.

**Objectives:** To investigate abnormalities of brain RSN in patients with episodic cluster headache (CH), outside the bout phase, in comparison with healthy individuals.

**Methods:** RS fMRI data were acquired from 13 CH patients and 15 matched healthy controls. Independent component analysis (ICA) was used to decompose RS fMRI data into spatially independent maps and time courses using the GIFT software. SPM2 was used to assess within- and between-groups activations (one-sample *t* test and ANOVA).

**Results:** Our analysis detected 11 RSN with potential functional relevance. Significant between-groups difference were found for the sensorimotor network (decreased fluctuation in the primary sensorimotor cortex and supplementary motor area, bilaterally in CH patients), and the primary visual network (decreased fluctuation in V1 in CH patients) ($p$ ranging from 0.03 to 0.007). No differences were found in the default mode network. RSNs abnormalities were significantly correlated with disease duration.

**Conclusions:** RSN analysis reveals abnormalities of the visual and motor networks in CH patients outside the acute attack. These findings suggest a diffuse dysfunction of functional connectivity which extends beyond the antinoceptive system.