Intern Emerg Med (2011) 6:23–28
DOI 10.1007/s11739-010-0410-9

IM - REVIEW

Rehabilitating chronic migraine complicated by medication overuse headaches: how can we prevent migraine relapse?

Ivano Farinelli · Ilaria Dionisi · Paolo Martelletti

Received: 15 March 2010 / Accepted: 28 April 2010 / Published online: 22 May 2010

Abstract Headache is among the most common neurological symptoms in clinical practice. In some cases of episodic migraine, the headache intensifies into a chronic form, defined as chronic migraine (CM) and such a condition encompasses a headache frequency of 15 days/month, with features similar to those of migraine attacks. The assessment of CM in the US general population ranges around 1.3–2%. Migraine progression from an episodic into a chronic form is realized through a period of time involving several months or years, during which an increase attack frequency occurs. Both Topiramate and Onabotulinum toxin A can be considered to be safe as well as effective medications, therefore, representing a treatment choice. Regarding drug abusers, the initial relief step always consists of drug interruption. Only after detoxification can a new prophylaxis therapy be commenced, which otherwise would be useless from the start. The feasible diagnostic setting for the tailored treatment of CM based on the application of pharmacogenomics will allow us in predetermining the efficacy of a single old and new drugs by avoiding abuse due to non-responsivity of the abused drug.

I. Farinelli (✉) · P. Martelletti
Department of Medical and Molecular Sciences,
II School of Medicine, Sant'Andrea Hospital,
Sapienza University of Roma, Via di Grottarossa,
1035, 00161 Rome, Italy
e-mail: paolo.martelletti@uniroma1.it

I. Farinelli · I. Dionisi
Department of Anaesthesia and Intensive Care Medicine,
II School of Medicine, Sant'Andrea Hospital,
Sapienza University of Rome, Rome, Italy

Keywords Chronic migraine · Medication overuse headache · Detoxification · Reprophylaxis

Introduction

Headache is the most common neurological symptoms in clinical practice. In Europe, about 51% of the general population is affected by a primary form of headache, of which 31% are tension-type headache and 14% are migraine sufferers. Patients with episodic forms can gradually develop a daily or almost daily form, possibly associated with drug abuse. In some cases of episodic migraine (EM), headache intensifies into a chronic form, defined as chronic migraine (CM) and such a condition encompasses a headache frequency of 15 days/month, with features similar to those of migraine attacks [1].

The assessment of CM in the US general population ranges around 1.3–2% [2]. In 2006, criteria for definition of CM have been revised by the Headache Classification Committee and such criteria implicate the presence of headache (tension-type or migraine) for over 15 days/month. A further criterion to be respected was the adherence for 8 days/month to features of migraine without aura as well as response to specific treatments for migraine (Table 1) [3].

The condition described represents a subset of chronic daily headache (CDH). 4–5% of general population suffers from a chronic form (CDH), with prevalence between 1.7 and 2.1% in men and between 2.8 and 6.8% in women. CDH is defined as a recurrence of headache for more than 15 days/month, for more than 3 months consecutively. Migraine progression from an episodic into a chronic form is realized through a period of time involving several months or years, during which an increase in attack frequency

Table 1 Revised International Headache Society criteria for chronic migraine

A. Headache (tension-type and/or migraine) on ⩾15 days/month for at least 3 months
B. At least five attacks fulfilling criteria for migraine without aura (ICHD-2 1.1)
C. On ⩾8 days/month for at least 3 months headache has fulfilled C1 and/or C2 below
1. Has at least two of a–d (below)
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 (below)
(a) Nausea and/or vomiting
(b) Photophobia and phonophobia

occurs and such escalation often produces a daily or almost daily pattern, with a more or less faded symptomatology depending in cases and such trend is often associated with an increase in drug intake and subsequent drug abuse. In some cases, symptom history becomes less typical of a classic migraine attack [4–6].

A progressive damage of the central nociceptive system is among the possible physiopathological considerations for the evolution of episodic headache into a chronic form. Activation of *N*-methyl-D-aspartate (NMDA) and non-NMDA receptors glutamate, released by central nociceptive terminations, induces calcium entry in dorsal horn neurons, as well as in the trigeminal nucleus caudalis. Calcium entry leads to the activation of nitric oxide (NO) synthetase causing NO synthesis. These neuromodulators produce the release of sensory neuropeptides, such as CGRP and substance P, which support the development of hyperalgesia and maintain central sensitization [7, 8].

In the chronicisation process, protracted stimulation of C-fiber nociceptors causes glutamate release, therefore, making NMDA receptors more responsive to both nociceptive and non-nociceptive imputs. Mechanisms, such as wind-up may be involved in broadening the message from peripheral to central structures. Wind-up consists of a frequency-dependent increase in spinal cord neuronal excitability, provoked by repeated electrical stimulation of afferent C-fibers and such mechanism is different from hyperalgesia, which reflects sensitization of peripheral terminations and compensation at the central level induced by a persistent afferent stimulus. Otherwise, wind-up can be defined as a processing of nociceptive information in the spinal cord [9].

In CDH patients, glutamate level in the cerebrospinal fluid is significantly higher than in the control group. Furthermore, there are no remarkable differences between abusers and non-abusers. In parallel, Gallai et al. [10] show an increase in NO end products as compared to the control group.

In headache pain, peripheral nervous structures surrounding meningeal vessels called the trigeminovascular system lead the pain stimulus to the trigeminal nucleus caudalis by activating *c-fos* gene transcription and subsequent release of neuropeptides, such as CGRP, substance P and neurokinin A. The trigeminal nucleus caudalis correlates with a descending analgesic network; namely, the periaqueductal gray matter (PAG), which plays a significant role in pain control. Patients affected by frequent headaches reveal iron deposits at this level that may represent an anatomic consequence associated with central sensitization. Among the risk factors for chronicisation, there are non-changeable factors, such as demography, age, and socio-economic status, as well as changeable factors such as obesity and a specific psychological pattern [11–13].

In chronic patients, the risk of abuse of pain killer medications increases among 30% of CDH sufferers in the general population, and 80% in patients under treatment in specialist centres [13, 14].

Medication overuse and subsequent medication overuse headache (MOH) have been described by the revised International Classification of Headache Disorders (ICHD)-IIR criteria as the use of each drug for at least 3 months, for a certain number of days per month (Table 2) [15].

Table 2 Revised criteria for medication overuse headache

The criteria for medication overuse headache [MOH (4)] have also been revised (MOH-R, A8.2) as the following (3)
A. Headache present on ⩾15 days/month
B. Regular overuse for >3 months of one or more acute symptomatic drugs
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 or opioids on ⩾15 days/month on a regular basis for >3 months without overuse (⩾10 days) of any single class alone
C. Headache has developed or markedly

All the drugs employed for headache treatment can cause MOH. In fact, the first definition for this particular headache form has been that of drug-induced headache in 1988 and such definition was later modified to emphasize the role of drugs of abuse in the development of headache. Classification of abuse is related to the pharmaceutical class applied during acute treatment, namely 15 days for analgesics and antiinflammatory medications, versus 10 days for triptans, ergotamines and opoids. Headache features differ from the original headache form since pain can vary according to the severity and location. Furthermore, the consumption of previously effective medication may develop or worsen the headache. Asthenia, nausea, anxiety, or gastrointestinal problems are associated with pain symptomatology [16].

In MOH sufferers, the only treatment of choice is drug withdrawal. Although there are no studies comparing gradual with abrupt interruption, the widespread opinion of expertise rulers is that abrupt interruption is more effective. A further step beyond drug interruption relies upon smoothing symptoms following interruption, through pharmacological support. The detoxification period is based on the use of various classes of drugs, among which corticosteroids certainly are the most frequently employed. Oral prednisone constitutes the most common treatment during detoxification; when compared with placebo, it reduces the duration of withdrawal headache [17–20].

In the follow-up period, the initial goal is to outline an effective prophylaxis therapy. Relapse percentages during the first year after withdrawal range between 22 and 44% [21].

Possible therapeutic agents in the reprophylaxis of CM after detoxification period are Onabotulinum toxin A and Topiramate.

Botox

Onabotulinum toxin A is a substance obtained from the gram-positive anaerobic bacterium *Clostridium botulinum*. Its action occurs through the block of peripheral acetylcholine release at the level of peripheral cholinergic nerve endings [22]. On travelling in the general vascular circulation, Onabotulinum toxin A reaches the extracellular space. The mechanism through which Onabotulinum toxin A exits from the vessels is unknown. At the level of the neuromuscular junction, Onabotulinum toxin A arrests spontaneous quantal release of acetylcholine via the cleavage of SNAP-25 protein (synaptosomal protein with a molecular weight of 25 kDa), producing muscular relaxation. Such mechanism of action can generate both the botulism disorder and the use of Onabotulinum toxin A as a therapeutic agent in clinical practice.

Paralysis at the muscular local level and reduced muscular contraction alone cannot explain Onabotulinum toxin A's pain relief. This suggests an indirect reduction in central sensitisation by inhibition of the peripheral sensitisation of nociceptive fibers, by inhibiting the release of neuromediators such as glutamate and substance P or *c-fos* gene expression [23].

Durham et al. [24] showed how Onabotulinum toxin A inhibit the release of calcitonin gene-related peptide (CGRP). In this study, CGRP was expressed in trigeminal ganglia neurons present in 1- to 3-day-old cultures, incubated afterwards with toxin. This incubation shows the reduction in secretory stimulation of CGRP neurotransmitter, with respect to control cultures. These data suggest a contribution of CGRP to migraine pathophysiology.

Opposite opinions exist in the literature for the mechanism of Onabotulinum toxin A therapy in primary headache disorders, according to ICDH-II criteria (1). Analysis of clinical trials with Onabotulinum toxin A in headache prophylaxis presents contrasting information. In 11-month, randomised, double-blind, placebo-controlled study, Dodick et al. [25] enrolled 355 CDH sufferers, of whom 228 were not under prophylaxis treatment and such patients received three treatment cycles (Onabotulinum toxin A or placebo) every 90 days. After the first month, Onabotulinum toxin A significantly decreased headache frequency, its effect lasts for 2 or 3 months. More than 50% of the patients reported diminished headache frequency after two Onabotulinum toxin A injection sessions, and the mean number of headache-free days per month was almost tripled (from 6 to 16 days). Furthermore, drug consumption was remarkably reduced. Mathew et al. [26] described similar results. Patients administered Onabotulinum toxin A report seven more (1 week) headache-free days with respect to their baseline. The initial difference between the groups consisting of 1.5 headache-free days was not statistically significant after 180 days [27].

Onabotulinum toxin A has also been tested in CM. In the PREEMPT clinical programme, 1,384 patients were randomized for a multicentre randomized placebo-controlled phase 3 trial. During a period of 24 weeks, two injection cycles were carried out. Onabotulinum toxin A (155 U) or placebo were administered through the fixed site method. Onabotulinum toxin A was remarkably more effective than a placebo in frequency reduction during headache days (primary endoint) as well as in the increase of health-related quality of life, measured through a specific questionnaire.

Adverse events proved to be mild and resolved without sequelae. The most frequent were neck pain (9.8%) and muscular weakness (5.2%) [28].

Topiramate

Topiramate is a sulfamate-substituted monosaccaride, presenting several mechanisms of molecular action, such as effects inhibition of voltage-dependent channels of calcium and sodium, signal enhancement of $GABA_A$ receptors, modulation of glutamate-mediated neurotransmission, and carbonic anhydrase inhibition. In migraine, such spectrum of actions may reduce nociceptive transmission at the central system level through trigeminovascular modulation and inhibition of the cortical spreading depression [29, 30].

In a 26-week randomized double-blind placebo-controlled study, Topiramate is effective in patients with a frequency of 3–12 migraine attacks per month. The mean ± SD monthly migraine days is considerably reduced for groups treated with Topiramate, 100 or 200 mg/day compared to placebo, but not for those treated with Topiramate, 50 mg/day. The mean ± SD monthly acute rescue medication days decrease significantly for patients treated with Topiramate, 100 or 200 mg/day versus placebo, but not for those treated with Topiramate 50 mg/day. [31].

In an open label study carried out on 64 patients affected by CM or probable CM, the use of Topiramate as a prophylaxis drug was evaluated at an average dose of 100 mg. The primary endpoint consisted of the number of patients with a reduction in headache frequency of >50–66% of patients showed such a response, with no difference in the response related to drugs of abuse [32].

Topiramate also is effective for prevention in chronic patients refractory to other therapies. A small study carried out on 11 patients shows Topiramate to be capable of reducing the number of headache days per week in 66% of patients. Furthermore, the intensity of analgesic intake is reduced by 64% at an average dosage of 100 mg [33].

In a randomized double-blind placebo-controlled trial, both Topiramate's efficacy and tolerance were investigated in the prevention of CM, with a dose target of 100 mg/day. Topiramate considerably reduces the mean number of monthly headache days (primary endpoint) from 15.5 ± 4.6 at baseline by 3.5 ± 6.3 when compared with placebo (−0.2 ± 4.7, $P < 0.05$). In the subgroup of patients with drugs of abuse, mostly triptans, Topiramate significantly reduces the mean number of monthly migraine days by 3.5 ± 7.1 from baseline [34].

In a randomized, double-blind placebo-controlled parallel group multicentre trial, Topiramate was tested for the prevention of CM. The titration period was 4 weeks with a maintenance period of 12 weeks, and the final mean Topiramate maintenance dose was 86 mg/day. Topiramate proved to be effective in reducing migraine headache days (Topiramate −6.4 vs. placebo −4.7, $P = 0.010$) and migraine headache days relative to baseline (Topiramate −5.6 vs. placebo −4.1, $P = 0.032$) [35].

Although from these studies, Topiramate is well tolerated, eventual adverse events are possible. Lainez et al. [36] analyzed three large multicentre studies, and found that therapy discontinuation occurred in 25% of patients administered Topiramate and in 1% of patients treated with placebo. The most common adverse events were paresthesias (8.0%), cognitive symptoms (7.3%), fatigue (4.7%), insomnia (3.4%), nausea (2.3%), loss of appetite, anxiety, and dizziness (2.1%). Paresthesia, due to the inhibition of carbonic anhydrase, is the most common side-effect although it does not constitute the main reason for therapy discontinuation. By cognitive symptom, one means having difficulty with concentration/attention and memory difficulties. The majority of adverse events appears during the titration period, generally within 6 weeks. These data suggest that in case patients do not present adverse events by the end of such period, they will by safe from such events.

In conclusion, migraine's preventative treatment with Topiramate is able to reduce the risk of transformation into a chronic form and such progression risk is extremely high in a subset of patients with elevated migraine frequency and frequent acute medication intake [37].

Botox versus Topiramate

In a single-center, double-blinded trial Mathew et al. compares Topiramate with Onabotulinum toxin A (Botox) in the prophylaxis treatment of CM. The study included patients diagnosed with CM without MOH, not undergoing further prophylaxis therapies and between 18 and 65 years of age. Sixty patients were enrolled and randomized in two different groups. One group was treated with Onabotulinum toxin A (Botox) injections up to a maximum of 200 U (100 U at fixed points and 100 U follow-the-pain methods) plus an administration of oral placebo both during first and third month of examinations. The latter group, assigned to Topiramate, was treated with a 4-week titration of 100 mg/day and an optional addition by the operator of up to 200 mg/day, as well as with placebo injections (physiological solution). Patients of the two groups received oral placebo or Topiramate with the same administration time and methods.

The primary endpoint was evaluated through the physician global assessment 9-point scale, with surveys at months 1, 3, 6 and 9. Both therapies produce moderate to marked improvements at all time points. No significant differences among the groups are found except at month 9, where the percentage of patients reporting marked improvements was 60.9% in the Topiramate group versus 27.3% in the Onabotulinum toxin A group. However, Botox injections occurred at months 1 and 3 while oral

therapy was continued until month 9. Both treatments showed a decrease from the baseline of 27–50% in headache days per month, at months 3, 6 and 9.

The main reason for discontinuation relied upon adverse events, in addition to the loss of follow-up. 53% of Topiramate patients abandoned the study because of adverse events, against 25% of the Onabotulinum toxin A group. The most common adverse event in the Onabotulinum toxinA group was weakness in the eyebrow/eyelids. In the Topiramate group, there were paresthesias, cognitive deficits, and weight loss.

The study reports no particular differences among treatments in terms of efficacy, but there is a significant difference for what concerns safety profiles, which is definitely in favor of Onabotulinum toxin A. In fact, adverse events due to Topiramate therapy result more often in abandoning the treatment itself [38].

Conclusions

The management of CM patients in reprophylaxis after detoxification of abuses still appears complicated. Both Topiramate and Onabotulinum toxin A can be considered safe as well as effective, therefore, representing a treatment choice. Regarding abusers, the first step always consists in drug interruption. Only after detoxification can a new prophylaxis therapy be commenced, which otherwise be useless from the start.

Furthermore, considering relapse frequency in chronic patients given symptomatic drugs, future studies on those two prophylaxis therapies associated with the treatment of refractory patients after detoxification are appropriate [39].

The future in relapse prevention of CM complicated by MOH consists in considering how drugs currently used such as triptans and emerging therapies present responsivity profiles related to well-defined genetic polymorphisms [40–43].

The feasible diagnostic setting for tailored treatment of CM based on the application of pharmacogenomics will allow us to predetermine the efficacy of single old and new drugs by avoiding abuse due to non-responsivity of the abused drug [44].

Conflict of interest None.

References

1. Headache Classification Committee of the International Headache Society (2004) Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain, 2nd edn. Cephalalgia 24:1–160
2. Scher AI, Stewart WF, Liberman J, Lipton RB (1998) Prevalence of frequent headache in a population sample. Headache 38:497–506
3. Headache Classification Committee, Olesen J, Bousser MG, Diener HC et al (2006) New appendix criteria open for a broader concept of chronic migraine. Cephalalgia 26:742–746
4. Stovner LJ, Zwart JA, Hagen K, Terwindt GM, Pascual J (2006) Epidemiology of headache in Europe. Eur J Neurol 13:333–345
5. Castillo J, Muñoz P, Guitera V, Pascual J (1999) Kaplan award 1998: epidemiology of chronic daily headache in the general population. Headache 39:190–196
6. Bigal ME, Lipton RB (2008) Concepts and mechanisms of migraine chronification. Headache 48:7–15
7. Harris JA, Corsi M, Quartaroli M, Arban R, Bentivoglio M (1996) Upregulation of spinal glutamate receptors in chronic pain. Neuroscience 74:7–12
8. Coderre TJ, Yashpal K (1994) Intracellular messengers contributing to persistent nociception and hyperalgesia induced by L-glutamate and substance P in the rat formalin pain model. Eur J Neurosci 6:1328–1334
9. Herrero JF, Laird JM, López-García JA (2000) Wind-up of spinal cord neurones and pain sensation: much ado about something? Prog Neurobiol 61:169–203
10. Gallai V, Alberti A, Gallai B, Coppola F, Floridi A, Sarchielli P (2003) Glutamate and nitric oxide pathway in chronic daily headache: evidence from cerebrospinal fluid. Cephalalgia 23:166–174
11. Mitsikostas DD, Sanchez del Rio M (2001) Receptor systems mediating *c-fos* expression within trigeminal nucleus caudalis in animal models of migraine. Brain Res Brain Res Rev 35:20–35
12. Welch KM, Nagesh V, Aurora SK, Gelman N (2001) Periaqueductal gray matter dysfunction in migraine: cause or the burden of illness? Headache 41:629–637
13. Scher AI, Midgette LA, Lipton RB (2008) Risk factors for headache chronification. Headache 48:16–25
14. 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
15. Silberstein S, Olesen J, Bousser MG et al (2005) The International Classification of Headache Disorders, 2nd edition (ICHD-II)—-revised of criteria for 8.2 medication-overuse headache. Cephalalgia 25:460–465
16. Diener HC, Limmroth V (2004) Medication-overuse headache: a worldwide problem. Lancet Neurol 3:475–483
17. Paemeleire K, Crevits L, Goadsby PJ, Kaube H (2006) Practical management of medication-overuse headache. Acta Neurol Belg 106:43–51
18. Obermann M, Katsarava Z (2007) Management of medication-overuse headache. Expert Rev Neurother 7:1145–1155
19. Pageler L, Katsarava Z, Diener HC, Limmroth V (2008) Prednisone versus placebo in withdrawal therapy following medication overuse headache. Cephalalgia 28:152–156
20. Krymchantowski AV, Barbosa JS (2000) Prednisone as initial treatment of analgesic-induced daily headache. Cephalalgia 20:107–113
21. Katsarava Z, Muessig M, Dzagnidze A, Fritsche G, Diener HC, Limmroth V (2005) Medication overuse headache: rates and predictors for relapse in a 4-year prospective study. Cephalalgia 25:12–15
22. Simpson LL (1980) Kinetic studies on the interaction between botulinum toxin type A and the cholinergic neuromuscular junction. J Pharmacol Exp Ther 213:504–508
23. Aoki KR (2003) Evidence for antinociceptive activity of botulinum toxin type A in pain management. Headache 43:S9–S15
24. 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
25. 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
26. Mathew NT, Frishberg BM, Gawel M et al (2005) Botulinum toxin type A (BOTOX) for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. Headache 45:293–307
27. Farinelli I, Coloprisco G, De Filippis S, Martelletti P (2006) Long-term benefits of botulinum toxin type A (Botox) in chronic daily headache: a five-year long experience. J Headache Pain 7:407–412
28. Silberstein SD, Blumenfeld AM, Cady RK (2009) Onabotulinum toxin A for treatment of chronic migraine: analysis of the PREEMPT chronic migraine subgroup who were overusing acute headache medication at baseline. IHS 14th Congress. Cephalalgia P049:31
29. Akerman S, Goadsby PJ (2005) Topiramate inhibits cortical spreading depression in rat and cat: impact in migraine aura. Neuroreport 16:1383–1387
30. Storer RJ, Goadsby PJ (2004) Topiramate inhibits trigeminovascular neurons in the cat. Cephalalgia 24:1049–1056
31. Silberstein SD, Neto W, Schmitt J, Jacobs D et al (2004) Topiramate in migraine prevention: results of a large controlled trial. Arch Neurol 61:490–495
32. Peres MF, Mercante JP, Tanuri FC, Nunes M, Zukerman E (2006) Chronic migraine prevention with topiramate. J Headache Pain 7:185–187
33. Mosek A, Dano M (2005) Topiramate in the treatment of refractory chronic daily headache: an open trial. J Headache Pain 6:77–80
34. Diener HC, Bussone G, Van Oene JC et al (2007) Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. Cephalalgia 27:814–823
35. Silberstein SD, Lipton RB, Dodick DW et al (2007) Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. Headache 47:170–180
36. Láinez MJ, Freitag FG, Pfeil J, Ascher S, Olson WH, Schwalen S (2007) Time course of adverse events most commonly associated with topiramate for migraine prevention. Eur J Neurol 14:900–906
37. Ruiz L, Ferrandi D (2009) Topiramate in migraine progression. J Headache Pain 10:419–422
38. Mathew NT, Jaffri SF (2009) A double-blind comparison of onabotulinumtoxin (BOTOX) and topiramate (TOPAMAX) for the prophylactic treatment of chronic migraine: a pilot study. Headache 49:1466–1478
39. Rossi P, Jensen R, Nappi G et al (2009) A narrative review on the management of medication overuse headache: the steep road from experience to evidence. J Headache Pain 10:407–417
40. Gentile G, Missori S, Borro M, Sebastianelli A, Simmaco M, Martelletti P (2010) Frequencies of genetic polymorphisms related to triptans metabolism in chronic migraine. J Headache Pain. doi 10.1007/s10194-010-0202-7
41. Di Lorenzo C, Di Lorenzo G, Sances G et al (2009) Drug consumption in medication overuse headache is influenced by brain-derived neurotrophic factor Val66Met polymorphism. J Headache Pain 10:349–355
42. Stovner LJ, Tronvik E, Hagen K (2009) New drugs for migraine. J Headache Pain 10:395–406
43. Farinelli I, De Filippis S, Coloprisco G, Missori S, Martelletti P (2009) Future drugs for migraine. Int Emerg Med 4:367–373
44. Simmaco M, Borro M, Missori S, Martelletti P (2009) Pharmacogenomics in migraine: catching biomarkers for a predictable disease control. Exp Rev Neurother 9:1267–1269