# 16th Marcia Wilkinson Lecture: Behaviour counts in migraine prophylaxis

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## Introduction

It is with great pleasure that I accepted the invitation to present the 16th 'Marcia Wilkinson Lecture' (MWL) of the Anglo Dutch Migraine Association. At last years annual scientific meeting Tim Steiner, who staged the 13th MWL in 2005, concluded from the state of clinical headache research that current empirical evidence to guide optimal headache management is weak[1]. Two reasons mentioned were that outcome research is focused on symptoms, while headache disorders do also affect health, well-being and quality of life, and that calls for better pharmaceutical prophylaxis were ignored until recently[1]. Preventive treatment of migraine is important, however, given recent evidence calculated for the United States that 75% of the patients suffer from 1 to 2 attacks per month[2].

Migraine holds the 19th position - and in women moves to position 12 - on the top-twenty list for 'years lost to disability' for *all* diseases as established by the World Health Organization (WHO)[3]. According to a recent WHO report the problem of headache is trivialized among the prominent neurological disorders worldwide, while migraine holds the second position in terms of one-year prevalence (13% aggregated for Europe and the United States), is third in terms of burden calculated in DALYs, (the life years affected by disability due to the disease), and is expected to maintain both positions to the year 2015[4]. If migraine is such a problem, all means should be employed to support optimal management, relieve the suffering in patients, and reduce the burden that migraine inflicts on society. In this respect I underscore that behaviour counts in migraine management.

My focus is on behavioural management of migraine. Behavioural methods offer no acute treatment. The primary target is attack prophylaxis, and secondary goals are strengthening a sense of internal control and self efficacy in attack prevention, decrease of functional disability, and improvement of quality of life as well as depression or anxiety if indicated[5-9]. Behavioural methods for migraine management share a common aim, that is, to support attack prevention[8,9].

In this paper I will present points of attention for health education, describe current methods for behaviour change in migraine management, and explain why these methods are supposed to work. I will then portray the present position of behavioural migraine management. I will consider the international guidelines for clinical practice in headache as well as examples of increasing the outreach of these methods by bringing them closer to the patients, and I will briefly draft a stepped care perspective for these methods in the Netherlands.

## Health education in behavioural migraine management

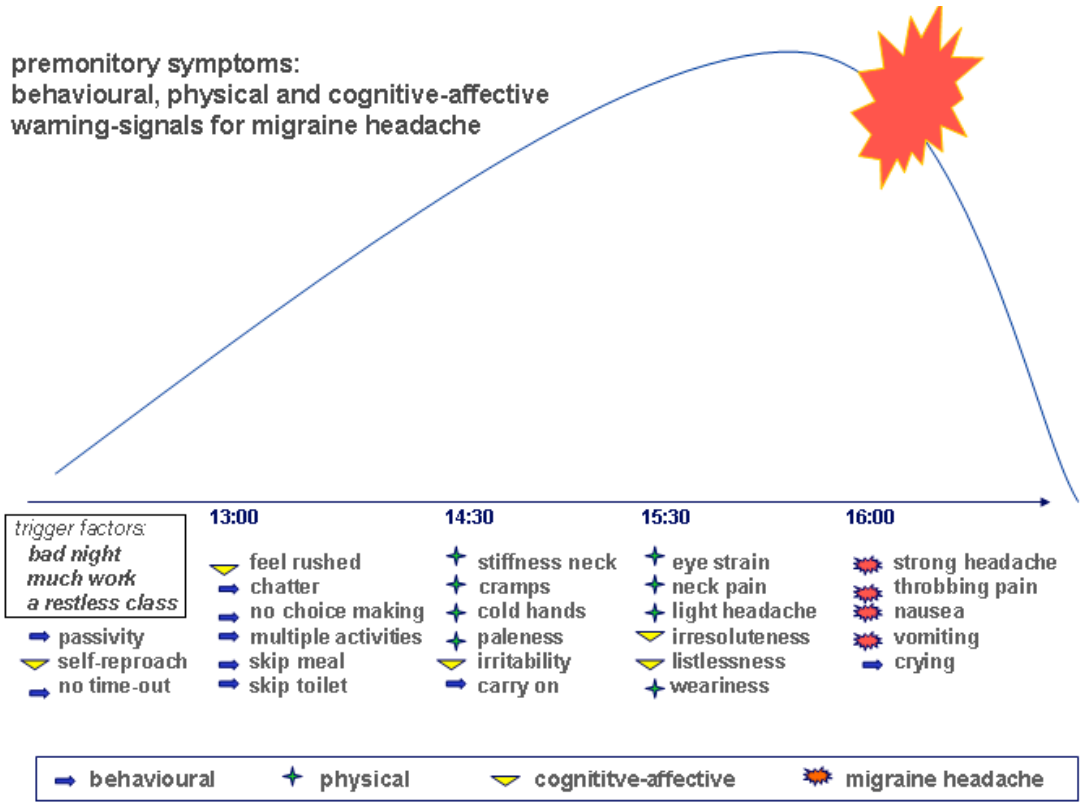
In training patients to manage their migraine health education always is an essential component. Let me first elucidate what we encounter as two related and relatively typical responses in migraine patients. (1) Many patients tend to focus on the hell of the migraine headache that draws all of their attention, while trigger factors and premonitory symptoms are relatively ignored. The latter in particular are often not clearly distinguished since these symptoms are elusive and may not be perceived as warning-signals. Premonitory symptoms can be recognized, however, given that spouses or other intimates often see in the patient's behavior, eye gaze and verbal responses

warnings of an attack emerging. (2) When patients finally realize that they are on the verge of imminent headache they tend to increase effort and exertion to get things done before the pain strikes. This second response is comprehensible but counterproductive, because this effort spurs the sensitivity to external stimuli instigated by brain dysfunction in the premonitory stage, and it may intensify the impending attack. With health education the patient learns to see that premonitory symptoms are part of the attack and that the susceptibility to external triggers is increased in the premonitory phase. Knowledge of these symptoms and triggers is essential, as is the taking of immediate action and behaviour change to counteract the susceptibility to external stimuli and strain by voluntary self-relaxation, adapted goal-setting, slowing down, time-out or rest.

Behaviour change requires markers signifying exactly when the new behaviour is required. In migraine trigger factors and premonitory symptoms constitute these markers, and their early detection is essential. Both aspects gained relatively little attention in scientific research thus far. In addition, these are not properly defined in the literature since the same phenomenon - say: irritability - may be presented as a trigger or as a premonitory symptom[10]. In 2006 we analyzed 51 publications on these issues (data from questionnaires or patient files: 33%, general descriptions: 30%; research or clinical presentation regarding specific trigger factors: 25%; diary studies: 12%)[1], extracted >100 factors distributed almost equally between more external aspects (such as whether conditions or menstruation) and internal aspects (such as neck stiffness or eye strain), and we grouped these factors into clusters [10]. We consider it important that migraine patients learn to distinguish between external factors or migraine triggers (which they can not change but have to account for) and internal factors or premonitory symptoms (which they may be able to influence with psycho-physical and cognitive-behavioural means). The four categories of *triggers* are: (1.1) menses-related hormonal changes in women, particularly the premenstrual days; (1.2) taxing incidents or life conditions; (1.3) weather and sensory stimulation, and (1.4) consumables and eating habits. Patients often refer to 'stress' as the number-one trigger. This statement is not sufficiently specific or descriptive. You have to ask your patient whether this concerns 'stressors' (taxing incidents such as daily hassles or a major life event), or 'stress responses' (emotional or physiological reactions) [11], or whether so-called rebound headache is at issue, which can result from tension release after a stressful experience[12]. In addition, it is important for the patient to realize that the brain dysfunction in the premonitory stage of the attack amplifies responses that may be taken to reflect 'stress', while these responses would not have occurred under 'normal' or non-migraine conditions. This brings us to the premonitory symptoms. Premonitory symptoms are responses intrinsic to the individual patient, which may be (2.1) behavioural, (2.2) physical or (2.3) cognitive-affective. Figure 1 shows an example of an individual migraine attack in progression, reported by a 43 year old female primary school teacher. In the morning three triggers were present: a night with bad sleep due to worry about her daughter (1.2), much work to do (1.2) and a class of restless and noisy children (1.2). The figure displays all of the premonitory or warning symptoms that mrs. B. experienced that particular day. There are behavioural (2.1), physical (2.2) and cognitive-affective (2.3) symptoms. Accumulation occurs of particularly the physical symptoms, which develop into more headache-related warnings. With proper education and support, and when adequate means of self-monitoring are used[13-15], migraine patients can learn to identify external triggers and internal warning symptoms, which are the cues to change behaviour and employ self-care in the service of attack prevention.

[1] We also identified a 'top-five' prevalence list of factors based on 15 studies with percentages of trigger or symptom occurrence in migraine. (1) Menstruation or premenstrual changes in the two days before menstruation onset in women only; 2. 'stress' reflected by for example (time)pressure, hard work or irritability, and a shared third position for 3a. severe fatigue, sleep problems or changes in sleep pattern; 3b. change in whether conditions; and 3c. sensory sensitivity to light, noise and odours.

Figure 1. Example of the course of behavioural, physical and cognitive-affective premonitory symptoms preceding the migraine headache of a given patient.




The term behaviour change was used straightforwardly thus far - as if this is easily achieved. But we know better, of course: just regard our own intents for a healthy lifestyle. Behaviour change is threatened by external temptations and by the strength of habituation, which easily overrules good intentions. This holds particularly when we feel weary and experience life as demanding, a state that typifies the preface of the migraine attack. Therefore the need for motivation, support, self-reinforcement and acceptance of temporary relapse must be emphasized. Also important is the acknowledgement that behaviour change for our own good requires that we feel the right to make choices in the interest of our health, which may be experienced as running against other interests - that of our children, of deadlines in our work, or of friends in need of help. The option of this conscious choice, and its existence on a daily basis, is not self-evident for many migraine patients. Other points in health education concern the importance of a focus on own resources instead of on failure and disability, and relieving the idea that migraine attacks are the patients' own fault, that they are making themselves sick, so to speak[16]. Last, the patient has to know and accept that behavioural management of migraine requires active participation, self-monitoring of migraine, medication-use and training progress, as well as compliance with regular homework exercises. The behavioural methods for migraine management are psycho-physical and cognitive-behavioural.

## Current methods for behavioural management of migraine

Prevention of migraine attacks with behavioural means is pursued by teaching the patient skills in migraine self-regulation. This involves a better *view* and a better *grip* on the precursors of the migraine headache. It entails that the patient can identify factors that trigger attack occurrence as well as recognize its premonitory symptoms in time (view), and that he/she adapts own behaviour immediately to counteract the brain dysfunction in the premonitory stage of the migraine attack (grip) [17-21]. Psycho-physical intervention consists of relaxation training with or without biofeedback. Cognitive-behavioural and psycho-physical training require approximately 8 to 10 sessions each and is often combined.

Relaxation training[17-21] aims at reducing physical arousal of the nervous system and at soothing the proneness to overstimulation and sensory receptivity of the migraine patient[17,20]. The training pursues the acquisition of the 'relaxation response', the skill to voluntarily slacken attention and vigour, harmonize breathing and ease muscle tension under various conditions of daily living. In 'autogenic training', relaxation is induced through focussing on sensations of heaviness, of warmth or pleasant coolness and of rest in the body, and through exercises for breathing and body posture. 'Progressive muscle relaxation' includes exercises to tighten and loosen various muscle groups. Training to loosen neck and shoulders is commonly included. Daily practice is required and exercises gradually become more difficult. Usually skill acquisition in the first half of training is distinguished from guided application of the relaxation skills in daily life and under migraine-provoking conditions.

Biofeedback training[17-21] uses sensors or electrodes to detect involuntary physical responses, such as electromyographic measures of muscle tension (EMG feedback), peripheral temperature mostly derived from the dominant index finger (TEMP feedback) or the blood volume pulse of the cranial artery (BVP feedback), of which BVP-feedback tends to be most effective[22]. Newer applications involving feedback on Doppler echographic measures of cerebral blood flow, as well as electro-encephalography in so-called neurofeedback, are highly experimental and lack strong empirical evidence[20-22]. The bodily response is transformed to a visual graph or auditory signal, and the patient is instructed to influence the slope of this graph or pitch of the signal, which happens through some sort of self-relaxation that may be supported by peaceful images on a screen. Therefore biofeedback is often combined with relaxation training. Biofeedback is not clearly superior and shows a gap in utilization compared to relaxation training alone, due in part to the greater technical sophistication and costs involved[22].

Cognitive-behavioural training[17-21] is more complex and thus requires more professional expertise than the psycho-physical methods. The advantage is that it also can influence habitual negative thinking and affect, which characterize depression or anxiety[21]. Patients learn to acknowledge aspects in their personal functioning and attitude, which reinforce the vulnerability to external migraine triggers. The main training elements are the structured analysis of risk conditions for attack occurrence, self-monitoring of triggers, premonitory symptoms and stress responses, cognitive restructuring to improve realistic appraisal, choice making and pacing of activities, as well as step-wise behavioural training to optimize time-management and adaptive coping tailored particularly to the premonitory stage of the migraine attack.

## Why do behavioural methods work in migraine?

We will now review aspects of the pathology of migraine[11,23-29] relevant to the question why the behavioural methods are supposed to work. The pathology of migraine involves abnormal cortical activity and cortical spreading depression in the case of migraine with aura. The trigeminal sensory system, with its cell bodies in the trigeminal ganglion, provides pain-sensitive innervation of the cranial vasculature: it innervates cranial vessels and dura mater via its first ophthalmic division and thus constitutes a vasodilator pathway[24]. This trigeminovascular system is central to the pathology

of migraine headache, which may be reinforced by neurogenic inflammation[23]. In addition to this comes central sensitization of nociceptive trigeminovascular neurons of the medullary dorsal horn that receive converging sensory input.[27,28]. These neurons exhibit increased excitability, increased synaptic strength and enlargement of their receptive fields beyond the original site of the pain. The central sensitization is expressed by allodynia, which refers to the patients' irritation during an attack of migraine with mundane mechanical or thermal stimulation of the scalp and face such as in combing, shaving, breathing cold air and wearing contact lenses or eye glasses[2]. In addition to this there is peripheral sensitization, which induces pain hypersensitivity. Common migraine symptoms worsened by peripheral sensitization are the throbbing pain and its aggravation during routine physical activity that includes walking, climbing stairs, bending over, sneezing or coughing, and rapid head shake[25]. But it is predominantly central sensitization, which fortifies the impact of the trigeminovascular system on migraine headache. And there is another factor - abnormality in brain stem function[27,28] that does so also.

Although there remains controversy regarding a central versus a pontine generator in migraine pathogenesis, these two are not necessarily mutually exclusive[29]. Abnormal brainstem function at least partly generates the pathophysiology that drives migraine pathogenesis. Particularly involved in this are three areas, which are relevant to pain transmission, but which also modulate mood, agitation versus quiescence, and responses to stress. These are the locus caeruleus, the raphe nuclei and the periaqueductal gray[27]. The locus caeruleus (Latin for 'the blue spot') is an important homeostatic control center of the body, responsible for mediating many of the sympathetic effects during stress. It is the principal site for synthesis of norepinephrine, and its projections reach far and wide through the brain. This brain stem nucleus is involved with physiological responses to stress and to panic in particular. The raphe nuclei too have interactions with almost every portion of the brain. The main function of this cluster of brain stem nuclei is to release serotonin (5-HT) to the rest of the brain, and this neurotransmitter seems to be an important wrongdoer in problems of depression and sleep disorders. In addition, projections from the raph nuclei terminate in the dorsal horn of the spinal gray matter, where they regulate the release of enkephalins, which inhibit pain sensation. And third there is the periaqueductal gray, which in fact is the midbrain gray matter. Its stimulation activates enkephalin releasing neurons that project to the raphe nuclei. The periaqueductal gray is a crucial agent in the 'gate control theory of pain', and plays a role in the descending modulation of pain. Stimulation of its dorsal and lateral parts (in the rat) was shown to provoke so called 'defensive responses', such as freezing immobility, running, jumping, tachycardia and increased muscle tonus and blood pressure. Conversely, however, stimulation of the caudal and ventrolateral part could result in an immobile, relaxed posture known as quiescence.

If the brain stem operates as migraine generator, then it seems plausible that behavioural methods aiming at stabilizing arousal in the premonitory phase could be of importance to attack prevention. Additional evidence for this concerns dysfunction of the autonomic nervous system in migraine. This evidence is inconclusive thus far, because sympathetic hyper and hypofunction was found to play a role[30]. However, autonomic dysfunction also is an aspect of the physical response to stress. Relevant here is that chronic exposure and poor adaptation to repeated stressors predispose to disease, and this predisposition may interact with the pathophysiology of migraine. For a healthy state, homeostatic processes, such as body temperature or blood oxygen level, must be maintained within narrow ranges[11]. An 'allostatic state' occurs when bodily systems responsible for maintaining homeostasis are elevated in a sustained manner: examples are hypertension or chronic sleep deprivation. Migraine patients are likely to profit from preventing allostatic state and autonomic dysbalance, and the psycho-physical methods presented aim to contribute to this goal. Another point of their action is to buffer the patients' susceptibility to sensory and other stimulation. This is crucial

[2] It is of interest that the sensitization of the central neurons may remain dependent on incoming input (activity dependent), or it may become self-sufficient (activity independent). According to Burstein, triptans do abort the pain of a migraine attack successfully as long as sensitization still depends on incoming peripheral signals, but not after central sensitization becomes self-sufficient[17], that is: *in*dependent of incoming peripheral stimulation.

when attacks are close, but also seems relevant to the patients' state in between attacks. Evoked and event-related potential studies showed that migraine patients with and without aura are characterized by an interictal lack of habituation of the sensory cortices, which was shown to be a reproducible central nervous system dysfunction[31].

"The world shouts at the migraine patient" said Peter Goadsby at the 11th Conference of the International Headache Society in 2003. This seems the case interictally but especially in the hours preceding the headache in migraine. The behavioural methods aim to soothe this shouting by helping the patient - particularly in the prodromal stage - to mitigate the hyper-excitability and sensory sensitivity through conscious behaviour change aimed at psycho-physical quiescence. Therefore means of behavioural management do count in migraine prophylaxis.

## Position of behavioural migraine management in current health care

Tabel 1 presents an overview of current guidelines for neurological practice in headache care published in the United States and three European countries with a focus on the importance of behavioural management[7,32-36]**.** The guidelines of the American Academy of Neurology and the US Headache Consortium published in 2000 were the first to recommend behavioural treatments for adult migraine patients. Physical treatments as, for example, acupuncture or forms of physical therapy where also considered but not recommended[32,33]**.** According to this guideline relaxation training, THERM feedback with relaxation training, EMG feedback and cognitive-behavioural training may be considered as evidence-based methods for attack prevention in migraine. Grade A signifies that the recommendation is based on multiple well-designed trials with consistent results. Table 1 shows that there is progression in the guidelines published between the years 2000 and 2007. Consecutively included are behavioural methods for adults *and* children, and this is considered separately for the treatment of migraine and tension-type headache.

Table 1. Acknowledgement of the preventive usefulness of behavioural management methods in professional guidelines for headache care.

| | USA 2000 | | Germany 2005 | | United Kingsdom 2007 | | The Netherlands 2007 | |
|---|---|---|---|---|---|---|---|---|
| | adults | children | adults | children | adults | children | adults | **children** |
| migraine | ✓ | | ✓ | ✓ | ✓ | **(✓)** | ✓ | ✓ |
| tension-type headache | | | ✓ | | ✓ | | ✓ | ✓ |

The Dutch guidelines, published in 2007 by the Netherlands Society for Neurology[7], were the first to devote a distinct chapter on behavioural and physical treatments, separately for adults and for children with, respectively, migraine or tension-type headache based on the studies reviewed for the American guidelines[32,33] as well as the studies published since. We limit this brief review to the behavioural methods for migraine, which again received a grade A recommendation to acknowledge their use as a preventive option in headache care. Table 2 shows the mean percentage improvement per method and the effect sizes (ESs), a statistical measure indicating the strength of the findings. The psycho-physical methods produce an average improvement of 32 to 40% in attack frequency, and cognitive-behavioural training yields 49%. ESs are of medium strength and usually the

effects are maintained for several months to years. It is of interest that the averaged effect measured in waiting-list control groups was 5%[33], and that measured for attention control 9%[7,33]**.** In comparing these methods for migraine we consider again that cognitive-behavioural training is more complex, requires more professional expertise and therefore is less easily offered in a group or self-help format. Relaxation training and biofeedback training, on the other hand, are quite comparable regarding the level of professional expertise needed and the working of physical self-relaxation as active ingredient. Biofeedback training requires more equipment, however, and thus is more costly. Therefore, relaxation training deserves preference as a primary behavioural intervention with a preventive purpose.

Table 2. Mean percentage improvement in migraine attack frequency and effect sizes for methods of behavioral management in migraine.

| | mean % improvement | effect size **(ES)*** |
|---|---|---|
| relaxation training | 32% | **0.55** |
| biofeedback TEMP | 37% | **0.52** |
| EMG | 40% | **0.50** |
| BVP | 40% | **0.68** |
| cognitive-behavioural training | **49%** | **0.54** |

* Effect sizes (Cohen's *d*) are defined as "small, *d* = 0.2", "medium, *d* = 0.5", and "large, *d* = 0.8"[37]

Basic cognitive behavioural techniques, such as goal setting and time-management, can be made available flanking a relaxation training protocol. Based on evidence-based protocols for behavioural intervention in migraine[17,38,39] we developed a self-management training along these lines, which consists of seven two-hour sessions for small groups of up to four patients. The training employs patient education, detailed self-monitoring, guided detection of premonitory symptoms and triggers of attacks, relaxation training and a limited dose of cognitive-behavioural training. It is suitable for migraine patients with one to six attacks but less than 15 migraine (or headache) days per month[40], who do not present with medication overuse, evident psychopathology or complex comorbidity.

This self-management training for behavioural attack prevention was very well received by migraine patients. To bring it closer to the patients, we were interested whether trained patient trainers under professional supervision could provide it to their fellow patients[41]. The efficaciousness of this self-management format was recently tested in a Dutch randomized controlled trial[8,41]**,** with 95 migraine patients who completed the training and a 6-months follow-up measurement. Results were stable from post-training to follow-up and then yielded a significant decrease in attack frequency (-23%, ES=0.57) and very strong improvements in perceived control over and self-efficacy in attack prevention (ESs=0.81 and 1.14)[9,41]. In principle this sets the stage to actively engage headache patient organisations to provide aids in behavioural self-management for their members. It could also be the start to involve headache nurses to offer migraine self-management in the context of headache centre services.

In order to further increase easy availability and outreach of this type of support we then developed an Internet training aid for migraine self-management, which was under construction when presenting this MWL. At the moment of submitting this paper for publication in volume 11 of the ADMA series *Headache and Migraine*, however, the Internet training is completed and it's acceptance and usability is established successfully, which also pertains to a supplementary application designed for direct online support of migraine self-management through mobile devices and cellular phones[42,43].

This brings me to sketch a stepped-care perspective for the behavioural treatment of migraine. In the Netherlands health care is distributed over three levels or echelons according to the degree of specificity and complexity of a given health problem, and the costs for diagnosis and treatments involved. In Dutch health care, headache patients are seen by general practitioners (1st echelon), but presently also in about 30 specialized headache centres, operating in the 2nd echelon, given that a neurologist is the key provider of care with the support of headache nurses. In addition, a few centres offer multidisciplinary treatment arrangements offered in a day care format (3rd echelon).

We developed protocols for behavioural treatment of migraine that fit in with the 2nd to 3rd echelon of specialist Dutch headache care [17,38,39]. These protocols cover a relaxation training and a cognitive-behavioural training for migraine patients with accompanying diagnostic, assessment and evaluation procedures, which are suitable for individual psychological treatment offered by a psychologist with a two-year professional licence in health care, or by a cognitive-behavioural psychotherapist to serve the more complicated patient. The self-management training developed more recently offers a lower threshold for participation and a larger outreach, is designed more as training than as a treatment programme, and involves participants very actively in promoting self-care and control in daily life over the occurrence of their attacks. The self-management training for small groups offered in the home of an associated patient trainer[8,9,41] operates at the interface between self-care and primary care in the 1st echelon. This protocol can also be delivered individually to patients in need of more care and attention. If participants are carefully selected both the group and individual application of the self-management training could in principle be provided by a junior psychologist or by trained headache nurses and lay trainers under professional supervision. The application is currently offered in the day clinic of the Utrecht University Faculty of Social and Behavioural Sciences.

The internet training for migraine self-management[42,43] must first be subjected to a randomized controlled trial to establish its efficaciousness (to be started in 2010). But if this trial is successful, we will have a guided format for behavioural self-management in migraine, which may operate in the so-called '0st echelon' of self-care with minimal professional support that also is provided through the Internet.

Thus, we are getting ready to contribute to the health-care service for migraine patients at various levels of the Dutch health care system. A problem that is not easily resolved, however, is financing this type of service. At present the Dutch health insurance policy covers methods of behavioural management in migraine only as part of regular mental health care and psychotherapy. Migraine patients may be reluctant in seeking this type of care, however. We agree that many migraine patients are not in need of specialized mental health care, and we think that behavioural management of migraine should be part of the basic Dutch health care services for migraine.

## Conclusions

To conclude this paper I draw the following conclusions. *First*, antecedent conditions of the migraine attack, e.g. triggers and premonitory symptoms, deserve more attention in migraine research and treatment. *Second*, behaviour counts in migraine, and behavioural management of attacks is important. Its utility and relevance is acknowledged in international guidelines for clinical practice, which now extend to other primary headaches, and to the treatment of children. *Third*, attack prevention deserves sound attention in migraine treatment, as does the explicit employment of stepped care. I truly hope that the recent focus on prophylactic pharmaceutical treatment may promote the consideration of combined medical and behavioural preventive measures in migraine. *Fourth*, self-care and proper health education is at the basis of good health services for migraine. And I am convinced that, if handled safely and professionally, the Internet is a promising tool to support these goals.

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