Migraine disability and its recognition and assessment

Herkennen en boordelen van beperkingen door migraine

Thesis

to obtain the degree of Doctor from the Erasmus University Rotterdam
by command of the
rector magnificus

Prof.dr. S.W.J. Lamberts

and in accordance with the decision of the Doctorate Board

The public defence shall be held on

Wednesday 9th November* 2005 *at 09.45 hrs

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Acknowledgements

I am very pleased to acknowledge the co-authors of the papers that have been edited for inclusion in this thesis: Drs Shaun Kilminster, Michele Peters, Susan Lipscombe, Trevor Rees, Frances Carter, Stan Darling, Stewart Tepper, Carl Dahlöf, Matthew Clark, Michael Bundy, Vicente Baos, Francis Baudet, and Domenico D'Amico, and Ms Rebecca Salt, Ann Turner, and Christine Glover. All gave their permission freely for the editing and publication of the papers in this format. I am also indebted to the members of the Migraine in Primary Care Advisors (MIPCA) and the Migraine Action Association (MAA), for their input to several of the projects contained here, particularly Drs Susan Lipscombe, Trevor Rees, Frances Carter, Stan Darling, David Watson and Jerome Sender (MIPCA), and Ms Ann Turner (MAA).

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Introduction

Summary

General introduction: This section reviews the classification, epidemiology and burden of illness associated with headache disorders. The discussion concentrates on the common benign disorders of tension-type headache (TTH), migraine and chronic daily headache (CDH), these being the main types of headache seen in everyday clinical practice. The methodology of assessing headache burden is discussed, concentrating on disability and impact tools. Migraine and CDH are both disabling conditions, leading to significant impairment of daily activities in sufferers.

Primary care: Population-based studies show that migraine is under-estimated, under-diagnosed and under-treated in the clinic. Many patients never consult for headache, and drop out rates are high even among those who do. A study conducted by the author in primary care showed that patients who consulted with episodic headaches almost always had migraine. Patients with TTH hardly ever consulted. The conclusion was that migraine should be the default diagnosis for patients presenting to primary care with episodic headaches.

Specialist care: A second study conducted by the author showed that the headache pattern is very different for patients who consult for specialist care. Sixty percent of patients presenting to a UK specialist clinic had CDH, while only 33% had migraine. Other types of headache were seen infrequently.

Commentary: New methods are required to deal with the variable pattern of patients seen with headache in clinical practice. Innovative diagnostic and evaluation tools have been developed recently that utilise assessments of disability.

Shortcomings in available knowledge: Headache remains a generally unrecognised disorder, with its epidemiology and burden still not fully characterised. It would be particularly useful to identify the factors that predict medical need in patients. Assessments of disability have the potential to aid the diagnosis, evaluation of medical need and assess outcome in studies.

Objectives of the thesis: The thesis is based on a series of studies conducted in primary care to evaluate the evidence base of disability assessments and their potential in aiding diagnosis and management of headache.

1.1 General introduction

Headache is the most common neurological condition, and due to this is the neurological condition most likely to be seen in primary care. However, UK medical training typically provides less than one day of education on headache management. Primary care physicians may therefore be unprepared for the everyday management of headache, and many patients end up being referred to secondary care, with the inevitable delays this entails. The paradox is that most types of headache are eminently suitable for treatment in primary care. In addition, there has been an explosion of research on headache over the past 15 years or so, and guidelines for managing common headache subtypes have been published in several countries.

Historically, research on headache was conducted on an *ad hoc* basis, with no common diagnostic criteria used. This makes it difficult to apply studies conducted before 1990 to the present day. Year zero for headache was 1988, the year of publication of the *International*

Headache Society (IHS) classification criteria for headache subtypes.[1] Since its inception, it has become possible to diagnose patients accurately and consistently. The criteria have since been revised, and new classification criteria were published in 2004.[2] Guidelines on how to conduct studies with acute medications were first put forward by Glaxo in 1991,[3] followed by IHS-recommended guidelines a few years later.[4] These initiatives have transformed research in headache, providing consistent methodology for diagnosing patients, designing studies and defining endpoints. We are now able to use evidence-based criteria to evaluate headache research, which has greatly expanded our understanding of the subject. Due to commercial considerations and clinical importance, most recent headache research has concentrated on migraine, but increasing amounts of data are now emerging on other headache subtypes.

Most recent research on headache has been conducted in secondary care centres, resulting in guidance being produced for the specialist physician. Only in the past few years have evidence-based guidelines been produced for the primary care physician. In addition, little research has been conducted in the primary care setting. The studies included in this thesis are an attempt to rectify this situation, involving naturalistic clinical studies on the types of patients seen in everyday clinical practice and the development of new, simple to use questionnaires that are applicable to primary care. In this section, I review data on the epidemiology, illness burden and clinical management of the common headaches, and analyse the strengths and weaknesses of the methodology used.

1.2 Headache classification

Headaches can be classified into three major types: primary (benign) headaches, secondary (possibly sinister or worrisome) headaches, and the cranial neuralgias and facial pain syndromes (Table 1).[2]

Table 1. Classification of the common headache disorders.[2]

Primary headaches	Episodic migraine (with or without aura) Chronic migraine Rare migraine variants (e.g. familial hemiplegic migraine, basilar migraine, retinal migraine) Episodic tension-type headache (TTH: infrequent or frequent) Chronic TTH Cluster headache (episodic or chronic) Other trigeminal autonomic neuralgias Other primary headaches (stabbing, cough, exertional, sexual activity, hypnic, thunderclap, hemicrania continua and new daily-persistent headache (NDPH)
Secondary headaches	***Related to:*** Head/neck trauma *(e.g. whiplash, post-traumatic disorder)* Cranial/cervical vascular disorder *(e.g. stroke)* Non-vascular intracranial disorder *(e.g. brain tumour)* A substance or its withdrawal *(e.g. medication overuse headache [MOH])* Infection *(e.g. meningitis, systemic bacterial or viral infection)* Disorder of homeostasis *(e.g. hypertension)* Disorder of cranial structures *(e.g. neck, eye, nose, ear, jaw disorders)* Psychiatric disorder *(e.g. somatisation, psychotic disorders)*
Cranial neuralgias and facial pain syndromes	Trigeminal neuralgia and other neuralgias Compression headaches Cold-stimulus headache Eye-related headaches Headaches related to Herpes zoster Central causes of facial pain.

The most frequently reported headaches are the benign primary headaches of episodic tension-type headache (TTH), episodic migraine and chronic migraine/ chronic TTH. Several types of headache are commonly and arbitrarily grouped into the term ‘chronic daily headache’ (CDH). CDH comprises daily or near-daily headaches that last for more than 4 hours on average and are often thought to be linked to medication overuse. They usually arise from a primary, episodic headache disorder. These headaches are included in the primary disorders of chronic migraine, chronic TTH, hemicrania continua and new persistent-daily headache (NPDH) and the secondary disorder of medication overuse headache (MOH) in the new IHS criteria.[2] Table 2 illustrates the differences in presentation in CDH disorders.[5]

Table 2. Presentation of CDH disorders.[5]

Headache subtype	Frequency	Presentation
Chronic migraine	≥ 15 d/mo for > 3 mo	Primary headache is migraine May present with migraine or TTH-like features
Chronic TTH	≥ 15 d/mo for > 3 mo	Primary headache is episodic TTH Presents typically with TTH-like features (subject to revision)
Medication overuse headache (MOH)	> 15 d/mo	Chronic migraine, CTTH or mixed migraine and TTH-like features Overuse (≥ 10 d/mo for ≥ 3 mo) of ergots, triptans, opioids, other pain medications and combinations (≥ 15 d/mo)
Hemicrania continua	Daily and continuous	Unilateral, moderate intensity, with exacerbations of severe pain Conjunctival injection / lacrimation, nasal congestion / rhinorrhoea / ptosis / miosis Responds to indomethacin
New daily-persistent headache	Daily and unremitting from < 3 d from onset	Presents typically with TTH-like symptoms

1.3 Epidemiology of headache

Studies of epidemiology need to be population-based to avoid the risk of biases. This is frequently achieved by administering questionnaires in the community by interview or via the telephone.[6] The important outcomes of epidemiology studies are incidence and prevalence (see Box 1). In practice, prevalence is assessed far more often than is incidence. To obtain further information, prevalence data is usually analysed for gender, age, race and other social and epidemiological factors.[6]

Box 1
Incidence: the number of new cases of a disease to be reported in a 1-year period.
Prevalence: the total number of cases of a disease, calculated as *lifetime prevalence* (the total number who have ever experienced the disease) or *1-year prevalence* (the number who experienced the disease over the previous 1-year period). Comparing prevalence data is often hindered by the differences in time periods used in studies.

Overall, almost everyone gets headache: the lifetime prevalence is estimated as 93%, with a point prevalence of 11% in men and 22% in women.[7] Prevalence studies, with diagnoses confirmed using the IHS criteria,[1] indicate that the only headache subtypes with a prevalence > 1% in the general population are TTH, migraine and CDH. These headaches are considered separately below.

Tension-type headache
The pioneering studies of Rasmussen and colleagues showed that TTH is very common, indeed almost ubiquitous. The 1-year prevalence of TTH in Denmark was 63% in men and 86% in women, with a male: female ratio of 4:5.[7] Similar results were reported in a population-based study conducted in the USA, although with a lower 1-year prevalence of 38%.[8] The prevalence decreased with increasing age.[7] In Denmark, socio-demographic variables of marital status, cohabitation, educational level, occupational category or

employment status were not significantly associated with TTH. However, TTH was positively associated with neuroticism, fatigue in both sexes, time-pressure at work in women and exposure to fumes in men.[9] In the USA, TTH prevalence was associated with increasing educational levels and prevalence was higher in Caucasians than in African Americans.[8]

Migraine

There are relatively few population-based data on the incidence of migraine. Studies show that incidence peaks in childhood and adolescence, then declines over time.[10,11] The overall incidence per year is about 0.2% for boys and 0.6% for girls. The mean age of incidence is lower for boys than for girls (13.7 versus 17.6 years).[12]

In contrast, there are large amounts of information on migraine prevalence. 1-year prevalence rates from population-based studies conducted around the world are summarised in Table 3.

Table 3. 1-year prevalence of migraine from population-based studies.

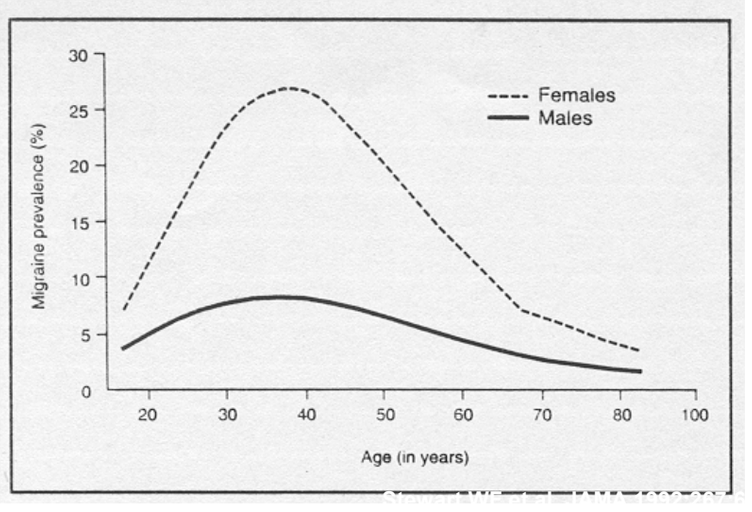
			Prevalence (%)		
Country, year	***n***	**Age range (y)**	**Men**	**Women**	**Total**
USA, 1992[13]	20,648	12–85	5.7	17.6	10.5
Canada, 1994[14]	2,992	18+	7.4	21.9	15.3
Denmark, 1991[7]	1,000	25–64	5.9	15.3	10.4
Netherlands, 1995[15]	1,008	12+	5.0	12.0	9.0
UK, 2003[16]	4,007	16–65	7.6	18.3	ND
France, 2002[17]	1,486	15+	4.0	11.2	7.9
Japan, 1997[18]	1,597	15+	3.6	12.9	8.4
Malaysia, 1996[19]	595	6+	6.7	11.3	9.0
Latin America, 2005[20]	2,637	15+	2.9–7.8	6.1–17.4	ND

ND = No data

The overall prevalence of migraine worldwide seems to be about 10% overall, 6% in men and 15% in women. One large, international prevalence study showed that migraine without aura was much more common than migraine with aura; less than one-third of the migraine sufferers experienced aura symptoms.[21] The prevalence of migraine with aura has been estimated at 3% for men and 5% for women.[11]

Migraine is highly gender- and age-dependent (Figure 1).[13]

Figure 1. Gender- and age-specific prevalence of migraine.[13]



Overall, approximately 2–3 times as many women as men report migraine, most likely due to the influence of female sex hormones. Migraine is about twice as likely to occur at the time of the menstrual period as at other times in the menstrual cycle.[22] Up to the age of 12, more boys than girls have migraine, but the female preponderance starts at age 13, when menarche has usually occurred.[23] Prevalence in women increases up to about 40 years, then declines. A similar pattern is seen in men, with peak prevalence occurring at about 35 years. Prevalence declines thereafter for both genders, and < 5% of the population is affected after age 70 years.[13]

Some studies show a low prevalence of migraine in certain Asian and African countries, which have been ascribed to cultural and environmental differences between races.[6] A study in Americans showed that migraine prevalence was higher in Caucasians (20.4%) than in African Americans (16.2%) and Asian Americans (9.2%).[24] There therefore do appear to be real racial differences in migraine epidemiology, although the condition is common in all races. There is some evidence for variations in migraine prevalence in terms of social forces. The prevalence seems to increase as the levels of education[6,13] and income[13] decrease.

Chronic daily headache

Very few population-based studies have been conducted on CDH. The available evidence suggests that CDH is a relatively common condition, affecting about 4–5% of the general adult population.[25] CDH can occur at all ages, from 5 to > 80 years, and without treatment, the condition can persist for years or decades.[26] Population-based studies have provided 1-year prevalence rates of 2.2% for chronic TTH[8,25] and 2.4% for chronic migraine.[25] Hemicrania continua and NDPH were reported rarely.[25,27] There are difficulties in assessing the prevalence of chronic migraine (often known as 'transformed migraine'), as studies published to date did not use the criteria recently published by the IHS.[2] Further studies are therefore necessary to investigate the epidemiology of chronic migraine.

As with migraine, CDH was much more common in women than in men.[25] A population-based study showed that CDH was also associated with being Caucasian, lower education

status, and in those with a history of marriage.[28] Population- and clinic-based studies identified co-morbid conditions of obesity, diabetes, arthritis, allergy, asthma, hypothyroidism and hypertension, and associated with daily caffeine consumption and habitual snoring.[28–30] New-onset CDH was associated with the baseline headache frequency and obesity.[28] In the clinic, the presentation of CDH is typically of daily TTH-like headaches, with exacerbations of migraine-like headaches.[31]

Medication overuse headache (MOH) is present in a substantial proportion of people with CDH. The overall population prevalence of MOH in a Spanish study was 1.4%, much higher in women (2.6%) than in men (0.19%).[32] Prevalence increased with age, and the mean age of sufferers was 56 years. Most patients with MOH have a longstanding history of primary headaches, with a decade or more of overuse of symptomatic medications.[33] A clinic-based study indicted that MOH was associated with asthma, hypertension and daily caffeine consumption.[30]

Other chronic headaches are much less prevalent than CDH. The best known, cluster headache, has an overall prevalence of about 0.4%; 0.3% in men and 0.1% in women.[34]

Conclusions

In conclusion, the primary, benign headaches are common conditions that affect both men and women (but particularly women) during their adult lives.

1.4 Burden of headache

The burden exerted by headache on sufferers is typically reported in terms of symptomatology, quality of life, disability (effect on sufferers' daily activities) and resultant social and economic consequences. This section reviews the first three of these items below, for TTH, migraine and CDH because these reflect the patient's perspective.

Methodology

As with epidemiological studies, population-based studies can be conducted that compare discrete headache populations with each other and the general population. Clinic-based studies are also important, as they contain specific populations of more severely-affected patients that are of clinical interest. However, the data do not coincide with the population distribution of patients. Headache symptomatology has been studied in many of the epidemiological studies described above.

Quality of life (QOL) is a measure of illness severity that combines subjective perceptions of the sufferer's life situation and objective assessments of health factors. QOL is assessed using questionnaires that patients complete at typically 1-month intervals. Questionnaires can be generic (to be used for any condition) or migraine-specific. Generic questionnaires are suitable for comparisons between study populations and different diseases. Disease-specific questionnaires focus on specific problems associated with a disease and are generally more sensitive. They may be better suited to assess changes in QOL following clinical interventions.

The best known of the generic questionnaires is the Medical Outcomes Study Short-Form 36 (SF-36) questionnaire. This contains items on physical, social and emotional functioning, pain, general medical and mental health.[35] Scores of patients are related to those of the general healthy population. The SF-36 has proven its methodological robustness and clinical utility in numerous studies in different disease areas over many years. Other generic QOL questionnaires include the EQ-5D and the WHO-QOL/WHO-QOL bref.

Several migraine-specific QOL questionnaires (e.g. MSQOL, MSQ, 24-hour QOLQ and MIGSEV) are now available, which have also been shown to have good reliability and validity (for definitions see Box 2).[36–38] However, their complexity of assessments and scoring limit general use in clinical practice.

In contrast to QOL measures, disability is a considerably less complex and more accessible concept. Disability is a consequence of illness and an important indicator of unmet treatment need. In part, disability is the product of poor QOL that is attributable to illness. The *World Health Organization* (WHO) defines disability as the inability to work and function in other roles.[39] Questionnaires assessing headache-related disability quantify the effect on sufferers' daily activities. They are more specific than the more general health-focused QOL and impact questionnaires. Impact questionnaires include disability measures, in concert with other factors influencing the life of patients (e.g. symptoms, QOL and patient suffering). Two disability-based questionnaires have been developed, the disability-specific Migraine Disability Assessment (MIDAS) questionnaire and the more wide-ranging Headache Impact Test (HIT). Both questionnaires cover all headache subtypes, not just migraine.

MIDAS is a paper questionnaire aimed to be accessible at physicians' surgeries and pharmacies. Headache sufferers answer five questions in three activity domains covering the previous 3-month period.[40] They score the number of lost days due to headache in employment, household work and family and social activities. Sufferers also report the number of additional days with significant limitations to activity (defined as at least 50% reduced productivity) in the employment and household work domains. The total MIDAS score is obtained by summing the answers to the five questions as lost days due to headache. This can be higher than the actual number of lost headache days due to any one day being counted in more than one domain. The score is categorised into four severity grades:

- Grade I = 0–5 (minimal or infrequent disability)
- Grade II = 6–10 (mild or infrequent disability)
- Grade III = 11–20 (moderate disability)
- Grade IV = 21 and over (severe disability)

Two other questions (A and B) are not scored, but were designed to provide the physician with clinically relevant information on headache frequency and pain intensity. On testing, MIDAS exhibited face validity, reliability, validity, ease of use and scoring and intuitive meaning to physicians.[40–43] Some studies have also shown it is sensitive to change following clinical intervention (see Box 2).[44,45] However, MIDAS also has some weaknesses. It only assesses about 35% of the range of headache severity between moderate and severe intensity, and does not cover milder or the most severe headaches.[46] Therefore, the MIDAS grade score may not always indicate the true medical need of patients due to floor effects (patients scoring zero on the questionnaire),[47] and the score may be weighted towards the measurement of headache frequency over disability. Nevertheless, MIDAS has proved to be a useful tool in specialist headache clinics.[48]

HIT was first developed as a web-based test, designed to be accessible via the Internet. It is a dynamic questionnaire, with items derived from validated headache questionnaires sampling all areas of headache impact.[49] It is described as dynamic because the answer to one question drives the choice of the next question, and so on. Patients are questioned until clinical standards of score precision are met, although five questions are sufficient to grade the majority of headache sufferers.[49] It takes only 1–2 minutes to complete. On testing, Internet-HIT was shown to be reliable and valid, and covered the whole spectrum of headache,[46,50,51] much more than did MIDAS.[46] Internet-HIT differentiated sufferers on the basis of diagnosis and characteristics such as headache severity and frequency.[50]

HIT-6 is a paper-based, short-form questionnaire based on the Internet-HIT question pool. Six questions cover pain severity, loss of work and recreational activities, tiredness, mood alterations and cognition. Each question is scored on a five-point scale, with the scores being added to produce the final score.[52] HIT-6 scores are categorised into four grades, representing minimal, mild, moderate and severe impact due to headache. Studies have shown that HIT-6 is reliable and valid,[52] and in the clinic can be used to help diagnose headaches (particularly) and also to select management strategies according to headache severity.[53,54] Also, HIT-6 scores were related to workplace productivity loss due to headache.[55] Internet-HIT and HIT-6 scores compared well to each other when the two forms of the questionnaire were tested on a group of headache sufferers.[56] The main disadvantage of HIT is that the grade scores are not intuitively meaningful, comprised as they are from a constellation of items.[49,52]

Assessments of disability and impact are clearly useful clinically, and have the advantage of greater simplicity of use and understanding over QOL questionnaires. They can also be used to assess all headaches, and not just migraine, as with some of the QOL questionnaires. In fact, MIDAS items[57] and HIT-6 scores[53] both correlated with QOL and other clinical assessments of headache severity. The question of which questionnaire is the best to use is probably best left to the individual investigator. Compared to each other, MIDAS has the advantage of clinically-meaningful units, while HIT covers a larger area of the headache spectrum from mild to very severe intensity.

Box 2. *Research and clinical practice criteria for evaluating clinical measures for headache severity*[58]

Overview: To be useful for clinical practice, an illness severity instrument should at minimum meet a number of key criteria. Briefly, the instrument needs to be reliable, valid and internally consistent and, if it is to be used to follow patients, it must be sensitive to change. For use in general clinical practice, the tool also needs to be easy to use and score and the score should be intuitively meaningful (i.e. face validity) to patients and physicians.

Criteria	**Analysis**
Research criteria	
Internal consistency	The extent to which the items comprising the measure are related to each other
Test-retest reliability	Stability and reproducibility of results when the instrument is administered twice to the same person (test–retest)
Content validity	Correlation between the instrument-based measure and a 'gold standard' measure Correlation between expert (researcher, physician) and patient input
Construct validity	The extent to which an instrument measures what it purports to measure and fits into a theoretical scheme about the variable of interest
Discriminant validity	The extent to which an instrument distinguishes two conditions or states known to be different
External validity	The extent to which the instrument-based measure is related to other measures considered to be relevant
Sensitivity to change	Instrument detects real change over time, such as improvement in outcome in response to effective therapy
Clinical practice criteria	
Face validity	Judgement that the measure corresponds to an individuals' perception, e.g. by selecting items deemed to be important to the disease sufferer or physician.
Ease of use	The instrument should be simple to use, score and interpret.
Intuitively meaningful	The instrument should correlate with physicians' judgements of illness severity and treatment need

Burden of episodic tension-type headache

TTH is typified by mild-to-moderate headache[2,8] that is bilateral, pressing or tightening in quality. It may be accompanied by photophobia or phonophobia, but nausea is absent.[1,2] There seems to be little effect on the patient's quality of life, or impact on daily activities, but interestingly, sufferers are frequently fatigued,[9] and suffer from neurotic and psychotic conditions.[59] One population-based study has shown that TTH can lead to lost work days and reduced efficiency at work.[8] However, HIT-6 scores for TTH are significantly lower than those for migraine and CDH.[53] TTH appears to have a complex aetiology that is affected by several psychosocial factors.[11] However, relatively little research has been conducted on TTH, and the condition is not fully understood.

Burden of migraine

Migraine symptoms reported in population-based studies include moderate to severe headaches, which are usually throbbing, one-sided and aggravated by physical activity. The headache is usually accompanied by photophobia and/or phonophobia and nausea, and less frequently by vomiting and aura symptoms. Attacks occur on average about once or twice a month (range < 6 to > 50 attacks per year), last for about 24 hours (range < 4 to 72 hours), and are separated by symptom-free intervals.[21,60] However, migraine is an unpredictable, heterogeneous disorder and attacks vary widely in frequency, duration, severity and reported symptoms.[61]

A study using the SF-36 generic questionnaire showed that migraine sufferers taking part in a clinical study had significantly lower QOL than the US general population.[62] Increasing severity of migraine was associated with worsening QOL. The main aspects of QOL affected by the migraine were pain, and interference with daily activities and social lives. When compared with other serious illnesses, migraine sufferers had lower QOL, in at least some items, than patients with hypertension, depression, osteoarthritis and type II diabetes.[62] A further study indicated that migraine sufferers have impaired QOL even when they are supposedly free from symptoms between attacks. Migraine sufferers had more physical and emotional problems compared with healthy controls.[63] Similar results are seen with the migraine-specific QOL questionnaires.[36–38] Migraine is closely linked to psychiatric disorders, particularly depression and anxiety.[6] For depression, the link is bi-directional, indicating that each disorder increases the risk of onset of the other.[64]

Migraine is associated with high levels of disability. Population-based studies in the USA,[61] Canada[65] and Japan[18] indicated that about three-quarters of sufferers have a limited ability to function during their attacks. Population-based studies with the MIDAS and HIT questionnaires show that migraine is associated with severe impact to sufferers' daily activities. Two studies, one in Europe and one in the USA, indicated that the mean MIDAS score was in the Grade III range (moderate disability) with about 50% of sufferers scoring Grade III or IV (moderate or severe disability).[40,41] The MIDAS score for migraine was significantly higher than that for non-migraine headaches.[40] Numerous studies indicate that migraine leads to lost time at work[16,66,67] and in family and social activities.[66,68,69] Studies with the HIT-6 questionnaire in clinical practice also indicate that migraine is associated with severe impact.[53,54]

Burden of chronic daily headache

There are relatively few population-based studies of CDH, and most studies are clinic based. CDH presents in a variety of forms. Sufferers typically start with one of the episodic primary headaches, usually migraine or TTH, which changes over time to a chronic headache presentation. In its chronic form, the balance between the TTH and migraine vary from patient to patient:

- At one extreme, some patients experience mild-to-moderate severity TTH only (chronic TTH).

- At the other extreme, patients may have daily, or near-daily, moderate-to-severe severity migraine attacks without significant TTH (chronic migraine). A study of patients with chronic migraine showed that over 80% suffered from fatigue, with two-thirds meeting the criteria for chronic fatigue syndrome.[70]
- Patients with a previous history of episodic migraine may develop daily headaches which may symptomatically resemble TTH. Periodic, more severe exacerbations that meet criteria for migraine usually occur up to or more than 15 days per month. Such patients should probably be classified as having chronic migraine in the new IHS criteria,[31] although this is not currently the case.[2] Using the McGill Pain Questionnaire, chronic migraine was shown to be more severe than chronic TTH, and the two conditions had differing patterns of descriptive characteristics.[71]

All forms of CDH are associated with personality disorders, particularly neuroticism and psychoticism, but these symptoms are most common in MOH sufferers.[59]

The key feature of the CDH patient with MOH is the daily or near daily overuse of headache medications, such as simple analgesics (e.g. aspirin or paracetamol),[72] combination analgesics containing caffeine, codeine or barbiturates, opioids, ergotamine[73] or triptans.[74] Many patients are taking multiple medications.[75] There tends to be a clinical syndrome of the patient obtaining transient relief from their headache medication. This is then followed by a return of the headache (withdrawal phenomenon) that necessitates further medication, and so on until a vicious cycle is established. If the headache medication is stopped, withdrawal symptoms are commonly reported. Patients with migraine as their primary headache develop migraine-like daily headaches or an increase in their migraine frequency and TTH-like daily headaches. Patients with initial TTH or combined headaches nearly always developed TTH-like daily headaches.[76]

Three population-based studies have investigated the QOL of CDH sufferers. Two studies showed that CDH without MOH[77] and MOH[32] patients had lower QOL than healthy controls on all domains of the SF-36 questionnaire. In addition, CDH patients had poorer QOL than those with episodic migraine (especially in general and mental health and vitality), and MOH patients had poorer QOL than those with CDH without MOH (especially in physical functioning and pain).[77] Similar results were reported when using a migraine-specific QOL questionnaire.[78]

Clinic-based studies show that headache-related disability is high in patients with CDH, with and without MOH. The mean MIDAS score in these patients was in the high Grade IV range (i.e. severe disability).[45,79–81] The mean MIDAS score was significantly higher in patients with chronic migraine compared to those with episodic migraine (34.9 versus 19.3, $p < 0.001$).[81]

Conclusions

In conclusion, the common primary headache subtypes of migraine and CDH are both associated with severe symptoms, reduced QOL and significant impact on the sufferers' daily activities. The available data indicates that episodic TTH may be a more severe condition than is generally thought, even though the symptoms are relatively mild.

1.5 Current status of managing headache in the clinic

Numerous population-based studies have investigated the proportion of IHS-defined migraine sufferers who actually consult a physician for care (Table 4).[18,21,65,82–88] These studies consistently show that only about 50% or fewer migraine sufferers are currently consulting a physician. Although the majority of sufferers consult at some time, many subsequently drop out from care. Interestingly, these data have not changed in studies conducted over the past decade, despite the number of educational initiatives conducted in this time. Factors that are related to consultation include being female and married, being older than 50 years, and the overall attack frequency, duration, severity and associated

disability.[82] Factors that are related to non-consultation and dropping out from consultation include a lack of perception of the severity of headache, good efficacy of OTC medications and feeling that the physician could not help them, or had failed to do so in the past.[21,65,88]

*Table 4. Consultation patterns for migraine. Proportion of migraineurs consulting physicians in population-based epidemiological studies. * Study conducted in Belgium, Canada, Italy, Sweden and the UK; **Study conducted in France, Germany, Italy, UK and USA*

Study	**Ever consulted (%)**	**Current consulter (%)**	**Drop out consulters (%)**	**Never consulted (%)**
Canada, 1993[65]	81	36	45	19
International*, 1993[21]	66	31	35	34
USA, 1998[82]	67	47	21	32
Denmark, 1992[83]	56	ND	ND	44
UK, 1996[84] 1999[85]	58 67	ND 47	ND 21	42 32
Japan, 1997[18]	31	15	16	69
USA, 2002[86]	69	48	21	31
UK, 2003[87]	86	65	21	14
International**, 2003[88]		41–63		37–59

ND = No data

The profile of patients in the population with headache, and those consulting with primary and secondary care physicians, differ markedly. Sections 1.5.1 and 1.5.2 below describe concisely clinic-based studies that the author has conducted on the consultation pattern in primary and secondary care.

1.5.1 The prevalence and diagnosis of migraine in a primary care setting: insights from the Landmark Study*

Andrew Dowson[1], Carl Dahlöf[2], Stewart Tepper[3], Lawrence Newman[4] and Landmark Study Group[5]

[1]University of London, Kings College Hospital, London; [2]Gothenburg Migraine Clinic, Gothenburg, Sweden; [3]New England Headache Center, Stamford, CT; [4]The Headache Institute, St. Luke's Roosevelt Hospital Center, New York, [5]GlaxoSmithKline; London, Toronto, and North Carolina.

Background

Migraine affects about 3% to 8% of males and 11% to 18% of females in developed countries.[1] It is recognised that most migraine sufferers do not seek medical consultation for their headaches,[2] and nearly half of migraine sufferers are under-diagnosed or misdiagnosed.[3–5] The prevalence of migraine is well-established in population-based studies. However the prevalence of migraine in patients presenting to primary care with headache is limited.

Objective

To determine the prevalence and diagnosis of migraine in subjects presenting to primary care physicians (PCPs) with a complaint of headache.

Design and methods

The Landmark Study was a prospective, international, open-label study designed to examine the association of headache impact assessed by HIT-6 and migraine diagnosis in subjects presenting to primary care physicians with a complaint of headache. All subjects who presented with headache completed a paper-based HIT-6 questionnaire and a headache survey. The investigator categorised patients as having migraine or non-migraine headaches by using his/her customary diagnostic practice. Subjects diagnosed with a secondary headache disorder or chronic daily headache were withdrawn from the study.

Patients newly-diagnosed as migraineurs and non-migraineurs completed diary cards for their first 6 headaches or up to 3 months, whichever came first. At the end of the study, an expert panel of headache specialists reviewed the diary cards utilising IHS criteria to provide a final headache diagnosis.

- IHS 1.1 Migraine without aura
- IHS 1.2 Migraine with aura
- IHS 1.7 Migrainous headache
- IHS 2.1 Episodic tension-type headache (TTH)
- IHS 13 Headache not classifiable

**The full Landmark paper has now been published (Tepper SJ, Dahlöf CGH, Dowson A et al. Prevalence and diagnosis of migraine in patients consulting their physician with a complaint of headache: data from the Landmark Study. Headache 2004;44:856–64). This summary of the full article is edited from another published article (Dowson A, Dahlöf C, Tepper S et al. The prevalence and diagnosis of migraine in a primary care setting: insights from the Landmark Study. Headache Care 2004;1:137–9).*

Results

Full details of the study results are published in the full Landmark paper.[6] A total of 1217 subjects were enrolled and 1204 completed the screening phase. 377 subjects were classified by the Expert Panel according to their completed headache diaries.

Initial PCP Diagnoses

A total of 1017 subjects (85%) presenting to primary care with a complaint of headache received a migraine diagnosis: 306 subjects were newly diagnosed migraineurs (Figure 1) and 711 subjects had been previously diagnosed with migraine. A total of 142 subjects (12%) were diagnosed with non-migraine primary headache (Figure 2). Forty five subjects (4%) were initially diagnosed with secondary and/or other headaches.

Figure 1: Expert panel diary review of newly diagnosed migraine.

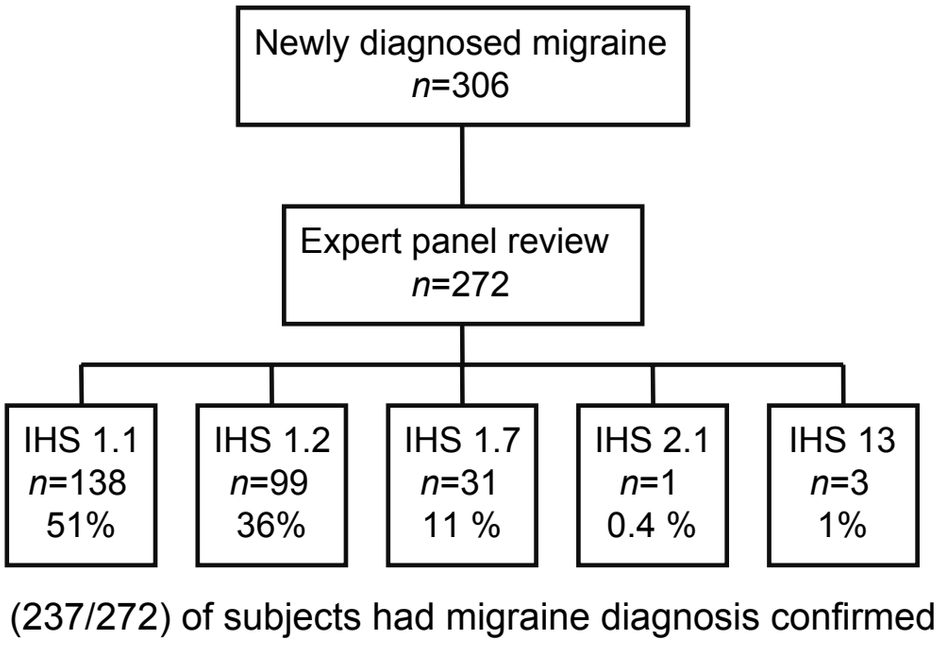


Figure 2: Expert panel diary review of non-migraine primary headache.

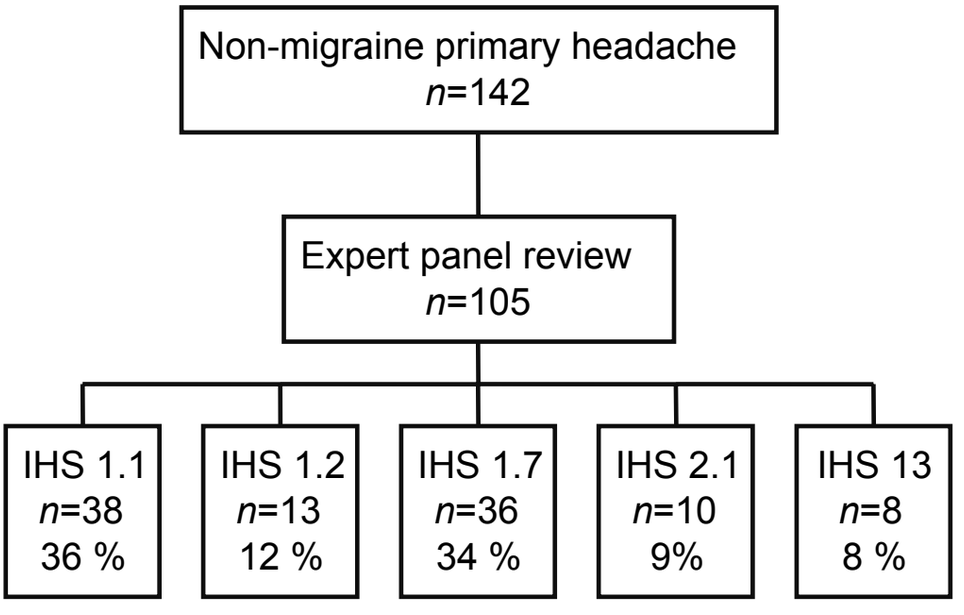
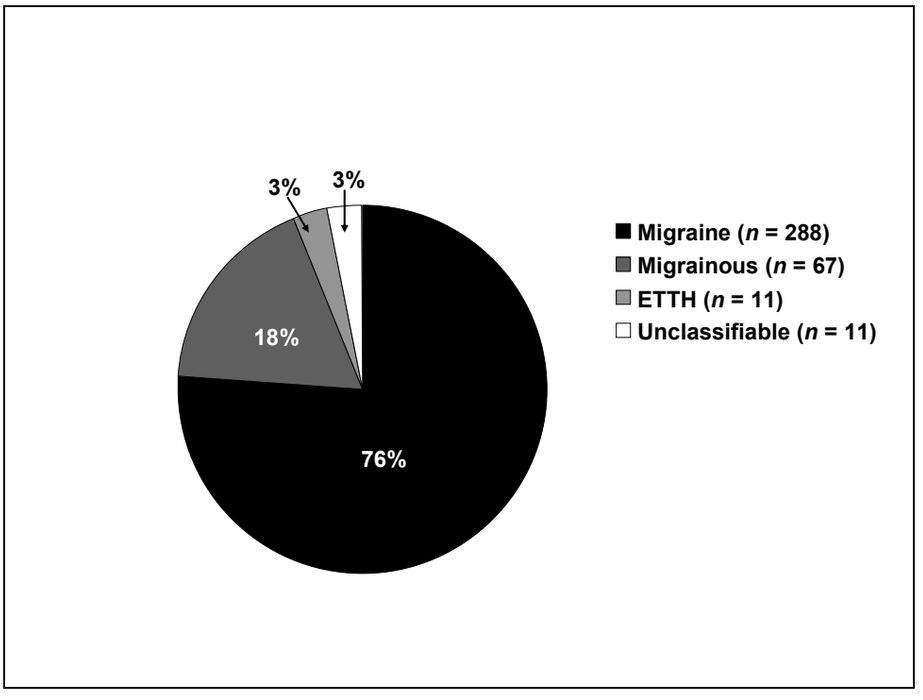


Figure 3: Prevalence of headache based upon expert panel diary review (combined newly diagnosed migraine and non-migraine)



Limitations of the study

Study limitations include the use of a diary study which may be subject to recall bias. Diaries were to be completed at the time of the events. However, people do not always complete diaries when they should. Biases by reviewers were limited by the establishment of guidelines for review *a priori*. The inter-reviewer reliability coefficient showed substantial agreement among panellists (ICC=0.71).

Conclusions

85% of the patients presenting to primary care with a complaint of headache suffered from migraine. Few patients consulted for TTH.

An initial PCP diagnosis of migraine (IHS 1.1/1.2) was found to be correct 87% of the time. However, almost 49% of PCP non-migraine diagnoses were reclassified as a migraine (IHS 1.1/1.2) disorder by the expert panel. In the absence of contradictory evidence, migraine should be the default diagnosis for patients presenting to primary care with episodic headache.

Landmark Study Group

Members of the Landmark Study Group are Carl Dahlöf (Gothenburg Migraine Clinic, Gothenburg Sweden), Andrew Dowson (University of London, Kings College Hospital, London, UK), Susan Jarvis (GlaxoSmithKline, Harlow, UK), Martin Jones (GlaxoSmithKline, Greenford, UK), Frances Kinrade (GlaxoSmithKline, Greenford, UK), Jackie Kwong (GlaxoSmithKline, Research Triangle Park, USA), Laura Lisk (GlaxoSmithKline, Greenford, UK), Jane Loftus (GlaxoSmithKline, Greenford, UK), Hank Mansbach (GlaxoSmithKline, Research Triangle Park, USA), Lawrence Newman (St. Luke's Roosevelt Hospital Center, New York, USA), Ba Pham (GlaxoSmithKline, Mississauga, Ontario, Canada), Mary S. Richardson (GlaxoSmithKline, Research Triangle Park, USA), Andrew Scott (GlaxoSmithKline, Research Triangle Park, USA), Stewart Tepper (New England Headache Center, Stamford, CT) and Christopher J. Webster (GlaxoSmithKline, Research Triangle Park, USA).

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1.5.2 Analysis of the patients attending a specialist UK headache clinic over a 3-year period*

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Abstract

Objective: This study analysed the profile of patients who attended a specialist UK headache clinic over a 3-year period.

Methods: An audit was conducted of the clinical records of patients attending the specialist headache clinic at King's College, London, between January 1997 and January 2000. Data were collected for diagnoses given, current medications taken, medications prescribed and recommended and investigations conducted. Results were calculated as numbers and proportions of patients for the 3-year period and for the three separate 12-month periods.

Results: A total of 458 patients were included in the audit. Most patients were diagnosed as having chronic daily headache (CDH, 60%) or migraine (33%). Prior to the clinic visit, most CDH and migraine patients treated their headaches with analgesics, and there was little use of prophylactic medications. In the clinic, 74% of CDH patients and 85% of migraine patients were prescribed or recommended prophylactic medications and 81% of migraine patients were given triptans for acute treatment. Investigations (imaging procedures) were conducted for 12% of patients, all proving negative.

Conclusions: CDH and migraine were the most common headache types encountered in this UK secondary-care clinic. Withdrawal of analgesics and use of prophylactic medications were used to manage CDH, while prophylaxis and triptans were used to manage migraine. The results indicate that management of CDH and migraine in UK primary care is sub-optimal, and educational initiatives are needed there to improve headache management.

**Summarised from the published version of this article (Dowson AJ. Analysis of the patients attending a specialist UK headache clinic over a 3-year period. Headache 2003;43:14–18).*

Background
Headaches are often not managed effectively in primary care, where migraine in particular is under-estimated, under-diagnosed and under-treated.[1] The field of headache research has expanded dramatically over the past decade, with new therapies (especially the triptans) introduced for migraine[2] and increased understanding of the aetiology and treatment goals for CDH.[3] Clinical practice has changed to reflect these developments, especially in specialist clinics, although primary care has been slower to respond.

Objectives
This study analyzed the diagnoses and management of patients attending one specialist headache clinic in the UK over a 3-year period. The study aims were to examine the profile of headache patients attending specialist clinics, to monitor changes in clinical practice and to gauge referral practices from primary care.

Patients and methods
This was a retrospective audit of the clinical records of patients attending the specialist headache clinic at King's College Hospital, London, UK. Records from January 1997 to January 2000 were analysed separately for three time periods: 1997–8 (January 1997 to January 1998); 1998–9 (January 1998 to January 1999); and 1999–2000 (January 1999 to January 2000). For 1997–8 and 1998–9, all patients who attended the clinic were analyzed. For 1999–2000, only the first 77 consecutive patients who attended the hospital clinic were analysed.

Data were analysed for the diagnosis given, current (pre-clinic visit) medications taken, medications prescribed and recommended at the clinic visit and investigations conducted. Results were recorded as numbers and percentages of patients.

Results
Patients: 458 patients attended the clinic and were analysed over the 3-year audit period, 215 in 1997–8, 166 in 1998–9 and the first 77 attending in 1999–2000. Patients came from the large, urban, London area. Most patients were women. Demographic data were collected for 1999–2000, where 51 patients (66.2%) were women and 26 (33.8%) were men.

Diagnoses (Table 1): The total number of diagnoses was greater than the number of patients because some patients were diagnosed with more than one headache type. Overall, the most frequent diagnosis given was for CDH (60%). The proportion of patients with this diagnosis remained relatively constant over the 3-year period. About twice as many women as men consulted with CDH in 1999–2000 (30 women and 16 men, 65.2% versus 34.8%). The second most common diagnosis was for migraine (33%). The proportion of patients with migraine fell slightly over the 3-year period, from 37% to 29%. The vast majority of patients who consulted for migraine in 1999–2000 were women (18 women and four men, 81.8% versus 18.2%). Short, sharp headaches (4%) and cluster headache (5%) were diagnosed infrequently, cluster headache being only reported by men in 1999–2000. Headaches were rarely diagnosed due to partial seizures (one patient), intermittent tension-type headache (one patient), epilepsy (one patient), possible demyelination (one patient), possible movement disorder (one patient), orgasm headache (three patients), sneeze-related headache (one patient), cranial arteritis (one patient), inner ear infection (one patient) and mobile phone-related headache (one patient).

Table 1. Diagnoses given at the headache clinic

Number of patients (%)*

Diagnosis	1997–8 n=215	1998–9 n=166	1999–2000 n=77	3-year total n=458
Chronic daily headache (CDH)	118 (55)	112 (64)	46 (60)	276 (60)
Migraine	80 (37)	51 (31)	22 (29)	153 (33)
Short, sharp headaches	11 (5)	5 (3)	3 (4)	19 (4)
Cluster headache	7 (3)	13 (8)	4 (5)	24 (5)

*Some patients were diagnosed with more than one headache

Treatments

CDH (Tables 2 and 3): Baseline: Overall, most patients were using regular (≥1 dose/day) analgesia (66%) and this proportion did not change markedly during the 3-year period. Additionally, 14% of patients were using triptans as acute medications. Relatively few patients (15%) were taking prophylactic medications.

Prescribed: Patients were advised to avoid analgesics and none were prescribed. Overall, 74% of patients were prescribed prophylaxis, the proportion nearly doubling from 1997–8 to 1998–9. The most commonly prescribed prophylactic drugs were dothiepin, sodium valproate and paroxetine (Table 3). Triptans were prescribed rarely (4%), to treat 'peak' symptoms only.

Table 2. Medications used to treat chronic daily headache (CDH): medications used prior to the clinic visit

Number of patients (%)

Medication	1997–8 n=118	1998–9 n=112	1999–2000 n=46	3-year total n=276
Regular analgesia	76 (64)	76 (68)	31 (67)	183 (66)
Prophylaxis	20 (17)	14 (13)	8 (17)	42 (15)
Triptans	17 (14)	12 (1)	9 (20)	38 (14)
Diazepam	3 (3)	0	0	3 (1)
Ergots	0	1 (1)	0	1 (<1)

Table 3. Medications used to treat chronic daily headache (CDH): medications prescribed at the clinic visit

Number of patients (%)

Medication	1997–8 n=118	1998–9 n=112	1999–2000 n=46	3-year total n=276
Analgesia	0	0	0	0
Prophylaxis	60 (51)	104 (93)	40 (86)	204 (74)*
Triptans	3 (3)	7 (6%)	0	10 (4)
Diazepam	0	0	0	0

*Prophylactic drugs includes dothiepin (176 patients), sodium valproate (154 patients), paroxetine (115 patients), gabapentin (seven patients) and carbamazepine (two patients)

Migraine (Tables 4 and 5): Baseline: Overall, most patients were using regular (≥1 dose/day) analgesia (58%) and this proportion did not change markedly during the 3-year period.

Twenty nine percent of patients had been prescribed triptans as acute medication by their primary care physician. This proportion increased only slightly, from 26% to 32%, over the 3-year period. Use of ergotamine was low and declined from 9% of patients in 1997 to none in 1999. Relatively few patients (12%) had been prescribed prophylactic medications.

Prescribed: For acute medications overall, analgesics were prescribed or recommended for 9% of patients and triptans for 81%. Ergotamine was not used for any patient. Eighty five percent of patients were prescribed or recommended prophylaxis for their migraine, with 8% provided with hormonal manipulation for menstrual migraine. By far the most commonly prescribed or recommended prophylactic drug was propranolol, with only a few patients given pizotifen, cyproheptadine, dothiepin and verapamil. These figures remained relatively constant over the 3-year study period.

Table 4. Medications used to treat migraine: medications used prior to the clinic visit

Number of patients (%)

Medication	**1997–8 n=80**	**1998–9 n=51**	**1999–2000 n=22**	**3-year total n=153**
Analgesia	47 (59)	30 (59)	12 (55)	89 (58)
Triptan	21 (26)	16 (31)	7 (32)	44 (29)
Prophylaxis	15 (19)	1 (2)	3 (14)	19 (12)
Ergotamine	7 (9)	4 (8)	0	11 (7)

Table 5. *Medications used to treat migraine: medications prescribed and recommended at the clinic visit*

Number of patients (%)

Medication	**1997–8 n=80**	**1998–9 n=51**	**1999–2000 n=22**	**3-year total n=153**
Analgesia				
Prescribed	1 (1)	1 (2)	0	2 (1)
Recommended	8 (10)	1 (2)	3 (14)	12 (8)
Triptan				
Prescribed	23 (29)	25 (49)	2 (9)	50 (33)
Recommended	39 (49)	18 (35)	17 (77)	74 (48)
Prophylaxis				
Prescribed	2 (3)	1 (2)	0	3 (2)
Recommended	64 (80)	43 (84)	20 (91)	127 (83)
Ergotamine				
Prescribed	0	0	0	0
Recommended	0	0	0	0
Hormonal manipulation				
Prescribed	0	0	0	0
Recommended	10 (13)	2 (4)	0	12 (8)

Investigations
Investigations were conducted for 19 patients (9%) in 1997–8, 17 (10%) in 1998–9 and 17 (22%) in 1999–2000. Most investigations were for patients with CDH (58%) and migraine (11%). CT and MRI scans were mainly used, with ESR, FBC and INR, EEG and demyelination investigations being used occasionally. All investigations proved to be negative.

Discussion
Over half the patients attending the two headache clinics were suffering from CDH, with a third having migraine. These proportions of patients remained stable over the period 1997 to 2000. It appears, therefore, that the main headache currently managed in secondary care is CDH, rather than migraine. Epidemiological studies show that CDH has a prevalence of about 5%,[3] whilst migraine affects 10% or more of the general population.[4] This indicates that migraine may be managed better than CDH in primary care. Cluster headache was diagnosed infrequently and primary care physicians are likely to encounter cases only rarely. To optimise resources, primary care educational initiatives for headache are probably best concentrated on CDH and migraine.

CDH disorders include chronic TTH, chronic migraine (sometimes, but not synonymously, known as transformed migraine), new daily-persistent headache and hemicrania continua.[3] The natural history of CDH usually starts with a primary intermittent headache disorder such as tension-type headache or migraine. Over a period of years, these conditions transform into daily or near-daily headaches. The cause of this transformation is often due to patients' overuse of acute headache medications (especially analgesics, ergots and triptans), leading eventually to medication overuse headache (MOH) linked to CDH.[3] Results from the present study showed that patients attending the clinic had this pattern of CDH, relying on regular analgesia (which could be prescribed or obtained over the counter without a prescription) for therapy, with a substantial minority also using prescribed triptans for relief. Disappointingly few were using headache prophylaxis before attending the clinic. The general principle of management at the clinic was to treat the chronic headache by withdrawing analgesia and prescribing prophylaxis for most patients, with triptans restricted for the acute treatment of 'peak symptoms'. The most frequently prescribed prophylactic drugs were antidepressants (dothiepin and paroxetine) and/or the anticonvulsant sodium valproate. When the chronic headache was controlled, prophylaxis could be withdrawn and acute medications prescribed for the underlying primary headache disorder. Currently recommended treatment strategies for CDH incorporate withdrawal of analgesics, use of prophylactic medications and limitations in the weekly use of acute agents.[5] This strategy is similar to that used in the present study.

Migraine patients referred to the specialist clinic in this study relied on analgesia and, to a lesser extent, triptans for acute therapy. Relatively few patients had been prescribed prophylaxis. Management at the clinic increased the use of triptans and reduced the reliance on analgesia for acute therapy, while providing most patients with prophylaxis (in the vast majority of cases the beta-blocker propranolol). This management pattern is close to those of the evidence-based guidelines of the US Headache Consortium[6] and the Migraine in Primary Care Advisors' (MIPCA)[7] in the UK, although the present study was completed before publication of these two documents.

Investigational procedures were conducted on a small minority of patients (12%) in this study. All procedures proved to be negative, and were conducted primarily for the reassurance of the patients at their request.

In conclusion, CDH and migraine were the most common headache types encountered in this UK secondary-care clinic. Withdrawal of analgesics and use of prophylactic medications were used to manage CDH, while prophylaxis and triptans were used to manage migraine.

The results indicate that management of CDH and migraine in UK primary care is suboptimal, and educational initiatives are needed there to improve headache management.

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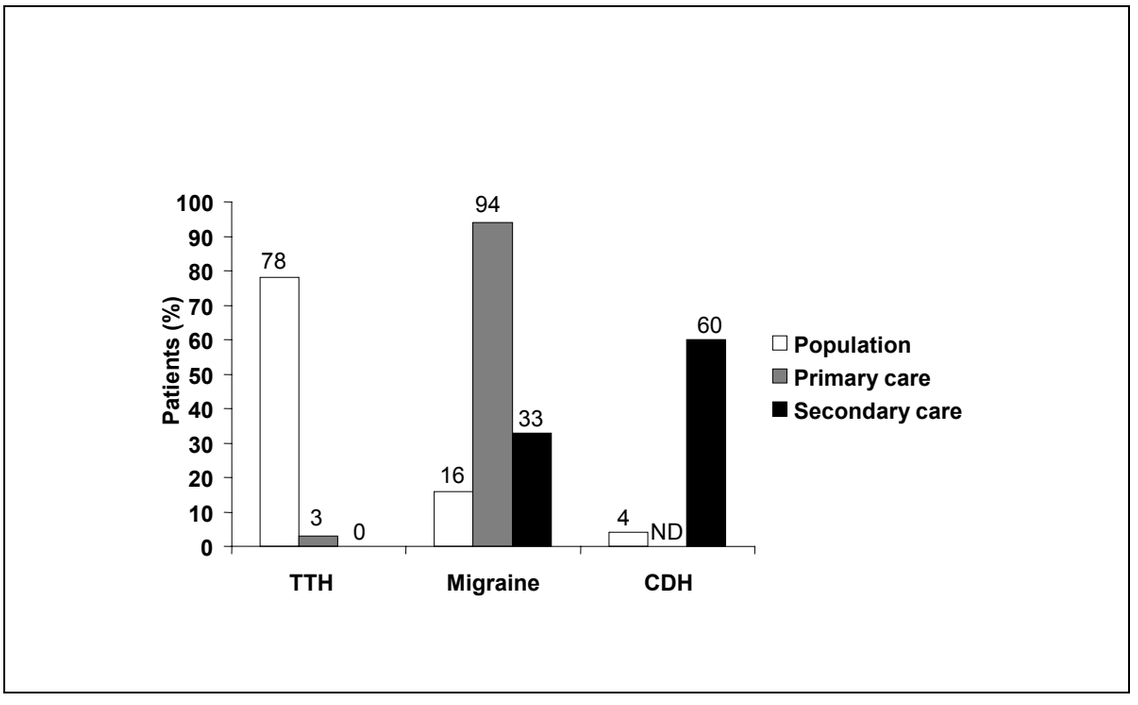
Commentary on the differences between primary care patients (1.5.1) and secondary care patients (1.5.2)

Taken together with Rasmussen et al's paper on the epidemiology of headache in the general population,[7] these two papers illustrate the different profile of headaches seen in the population and in primary and secondary care clinics (Figure 2).

Figure 2. Proportion of patients presenting with episodic TTH, migraine and CDH in the general population,[7] and in primary[89,90] and secondary care headache clinics.[91]



- In the general population, TTH was reported by the majority of people, while migraine affected about one in six people and CDH about one in 20.[7]
- In patients presenting to primary care with *episodic* headaches, virtually all had migraine, irrespective of the physician and patient diagnoses.[89,90] Very few people consulted for TTH. Patients with chronic headaches were excluded from this study.
- In secondary care, the majority of patients had CDH, while about one third had migraine. No patients were referred for TTH.[91] One study of patients with CDH in a secondary care clinic showed that 78% had transformed migraine, 15% chronic TTH and 7% other headache disorders.[92]

These studies also have important implications for headache diagnosis, which are discussed below.

Diagnosis

Population-based studies demonstrate that a high proportion of migraine sufferers who consult physicians do not receive a correct diagnosis.[82,86,87,93,94] Over the past decade, the diagnostic rate has only increased from about 45% to 60%, again despite the many initiatives designed to improve this. Features associated with an accurate diagnosis of migraine included female gender, the presence of an aura, the absence of co-morbid depression, and the presence of headache-related disability.[65,82,95]

Table 5. Proportion of patients with migraine correctly diagnosed by their physicians in population-based studies.

Study	Proportion of patients correctly diagnosed with migraine (%)
USA, 1994[82]	45
USA, 1998[93]	44
France, 1999[94]	42
USA, 2002[86]	56
UK, 2003[87]	67

The IHS classification criteria have provided guidelines for the diagnosis of migraine and TTH for well over a decade now,[1,2] although CDH (chronic migraine, chronic TTH, hemicrania continua and NDPH) was only defined in the 2004 document.[2] While these criteria are comprehensive, they are also lengthy, the physician being asked to potentially read through 160 pages to make a correct diagnosis. However, the diagnosis of CDH is not so simple, even using the IHS criteria. Several studies have demonstrated that many patients cannot be classified using the IHS criteria,[31,92,96] with many patients being classified with migraine. Multiple and cumbersome diagnostic procedures were necessary to diagnose patients with chronic headaches.[31,96]

Clearly, such complex criteria are not applicable to primary care. What are needed are simple inclusive questionnaires and/or checklists to screen for multiple headache subtypes in conjunction with exclusive questionnaires to specify the individual headache. From the Landmark study described above,[89,90] it was deduced that migraine should be the default diagnosis for patients presenting to primary care with episodic disabling headache, in the absence of contradictory evidence. Recently, several new questionnaires have been developed to aid in headache diagnosis, with most being exclusive questionnaires to diagnose migraine:

- Maizels and Burchette developed the *Brief Headache Screen* to diagnose different headache subtypes.[97] Migraine, daily headache syndromes and medication overuse were distinguished using three questions: How often do you get severe headaches?; How often do you get mild or less severe headaches?; and How often do you take pain relievers, or any medication to relieve headache symptoms?
- Lipton et al developed a 3-item screener that sensitively and specifically diagnosed migraine: Has a headache limited your activities for a day or more in the last three months?; Are you nauseated or sick to your stomach when you have a headache?; Does light bother you when you have a headache?[98] Two or three 'yes' answers coincided with a diagnosis of migraine.
- Cady et al developed a 3-item screener that sensitively diagnosed migraine: Do you have recurrent headaches that interfere with work, family, or social functions?; Do your headaches last at least 4 hours?; and Have you had new or different headaches in the past 6 months?[99] Migraine was indicted by a 'yes' answer to the first two questions and a 'no' answer to the third.
- Pryse-Phillips et al developed a 3-item screener: Do you have a headache every day?; Is your headache on one side of your head only?; Does your headache stop you from doing things? The questionnaire distinguished between pure migraine and other headache diagnoses with high reliability, validity and sensitivity.[100]

The clinical utility of these questionnaires remains to be elucidated.

Treatment

Population-based studies indicate that the majority of migraine sufferers rely on over-the-counter (OTC) medications for treatment (Table 6).[65,86,101,102] This is the case even for those who also have medications prescribed by their physician.[65,86.88] Again, this situation seems to have changed little over the past decade.

Table 6. Proportion of migraine sufferers using prescription and over-the-counter medications.

	% Sufferers		
Country	**Prescription medications**	**OTC medications**	**No medications**
USA, 1992[101]	37	59	4
Canada, 1993[65]	44*	91*	ND
Canada, 1998[102]	12	88	0
USA, 2002[86]	46*	72*	5

ND = No data
*Some sufferers took both prescription and OTC medications

Two studies in migraine patients showed that little more than a quarter of them (27%[88] and 29%[103] respectively) were satisfied with their acute medications. The main reasons for dissatisfaction related to efficacy rather than to the incidence of side effects (Table 7).[103]

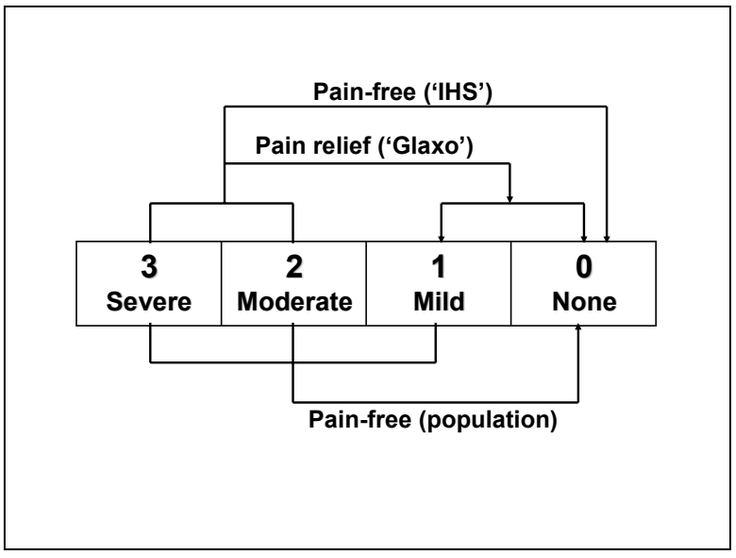
Table 7. Unmet treatment needs of migraine sufferers. Proportion of sufferers reporting the reason for dissatisfaction with their usual acute migraine treatment to be subjectively 'important' or 'very important'.[103]

Reason for dissatisfaction	**Sufferers (%)**
Pain relief takes too long	87
Does not relieve all the pain	87
Does not always work	5
Headache comes back	71
Too many side effects	35

When asked, patients stated that they primarily wanted acute medications to provide rapid and complete relief, with no recurrence. They were also interested in medications that were convenient to take at any time and place.[88,103]

The methods used in assessing efficacy of acute migraine medications follows those developed for double-blind, placebo-controlled studies with the triptans. A four-point scale is used: severe, moderate, mild and no headache, respectively Grades 3, 2, 1 and 0. Headache relief, defined as an improvement from severe or moderate to mild or none at 2 hours after treatment, was developed by Glaxo in the late 1980s to use in their clinical studies with sumatriptan.[3] Improvement to pain-free (Grade 3/2 to 0) has since been advocated by the IHS as a more clinically-relevant endpoint.[4] More recently still, these endpoints have been further refined. An improvement of any headache to pain-free is now advocated by many researchers, especially as recent recommendations state that triptans should be given as soon as possible after the headache starts, so long as the patient is sure that it is a migraine.[104] All these endpoints are illustrated in Figure 3.

Figure 3. Assessments of the efficacy of acute migraine treatments in clinical studies[3,4,104].



Other researchers propose the concept of 'sustained pain-free', in which the patient must be without pain for 24 or 48 hours after treatment, with no headache recurrence or use of rescue medications.[105] Such strict endpoints result in quite low efficacy rates, that can be criticised in terms of their clinical relevance.

Endpoints used for preventive treatments (used for frequent migraine and CDH to reduce the frequency of attacks) relate to reductions in the frequency, duration and severity of attacks. Perhaps the most stringent endpoint (and the gold standard) is a reduction of over 50% in the number of attacks in a defined time period. The latest studies with the neuromodulator topiramate in migraine illustrate the optimal treatment endpoints (change from baseline in mean monthly frequency, ≥ 50% reduction in monthly migraine frequency, number of monthly migraine days, severity, duration, days per month requiring rescue medication and adverse events).[106–108] However, preventive treatment of migraine and CDH is notoriously difficult, and high drop-out rates from treatment are reported due to wrong diagnoses, incorrect use of the available drugs (using inappropriate doses for inadequate time periods), patient expectations of a 'cure' rather than the usual reduction in frequency and the incidence of bothersome side effects.[109,110]

A survey discovered the following reasons for treatment failure that led to patients being referred to secondary care headache clinics:

- The diagnosis was incorrect or incomplete
- Important exacerbating factors were missed
- Prescribed and non-prescribed treatments were inadequate
- Patients had unrealistic expectations or co-morbidities.[111]

Improvements in the diagnosis and treatment of headache are therefore required to improve the management of refractory patients.

1.6 Shortcomings in available knowledge (rationale for thesis)

Population-based studies provide information on the pattern of illness in the general population, while clinic-based studies show the profile of patients who actually see a physician for their condition. Comparing data from these two types of studies allows the

tentative analysis of factors that drive consultation and aids in the identification of sufferers whose needs are not being met.

An enormous amount of material is available from population- and clinic-based studies on the epidemiology, burden of illness and management of migraine, much of it published in the last decade or so. Despite this, migraine is generally under-recognised, under-diagnosed and under-treated in the clinic.[58] The situation is even worse for TTH and CDH. The Landmark Study showed that very few TTH sufferers consult with a physician,[89,90] and while most sufferers are likely to be only moderately affected by the disorder, the pattern of co-morbidities suggest that there is a subgroup of sufferers who may be quite severely affected, but who are invisible to medical services at present. We have no information as yet from population-based studies on the proportion of CDH sufferers who consult, but we can deduce likely trends from other data. Chronic migraine sufferers are seen in clinics much more often than chronic TTH sufferers,[92] although they are equally prevalent in the population.[8] This suggests that chronic TTH is particularly unrecognised and managed poorly at the moment. The fact that consultation rates for migraine persist at about 50%[18,21,65,82–88] also suggests that chronic migraine sufferers are also probably under-recognised, under-diagnosed and under-treated. There is therefore an enormous unmet clinical need for the common benign, primary headaches, which has not been addressed significantly in recent years. Research needs include the following:

- Population-based epidemiological studies in TTH and CDH, particularly with respect to the definition of what constitutes chronic migraine
- Identifying factors that predict medical need in TTH sufferers (episodic and chronic)
- Population-based studies on recognition, diagnosis and management of CDH
- Clinic-based studies on the management of TTH, migraine and CDH
- In addition, educational initiatives are required to encourage sufferers with unmet medical needs to consult a physician or other healthcare professional.

The need to improve knowledge of headache severity and headache management practices has driven researchers and physicians to devise new ways of assessing the burden of illness. Methods to assess QOL are well known and generic and headache-specific QOL questionnaires have been developed that are methodologically robust and have proved valuable in research.[35–38] They are perhaps not so valuable in the clinic, where the lack of intuitively-understandable questions and units make them difficult to use with patients. Researchers have instead turned to assessments of impact (synonymous with disability) to overcome these barriers.

Assessments of disability and impact describe the consequences of illness; the effects on the everyday lives of sufferers. They are therefore potentially understandable to both the physician and the patient. MIDAS and HIT are the most investigated of these questionnaires. Both are generally robust methodologically, but are not as well categorised in terms of clinical utility. The strengths of MIDAS are that it is reliable and valid, is easy to use and has units that are easily understandable to the patient and physician.[40–43,48] Its weaknesses are that patients find it difficult to complete without supervision and that it may only show utility in more disabled patients. In secondary care clinics, many patients have high MIDAS scores, in the Grade IV range.[45] In this setting, MIDAS has proved useful as a tool to demonstrate the efficacy of treatments. In primary care and below (e.g. in the pharmacy), however, many headache sufferers score 0 on MIDAS, making it impossible to use as an outcome tool. Some of these patients may have unmet medical needs that are not detectable with MIDAS. The strengths of HIT are that it is reliable and valid, and covers the full range of headache severity, thus overcoming the floor effects seen with MIDAS.[46,49,50,53] However, it has not demonstrated the clinical utility that MIDAS has, and may be more suitable as a diagnostic tool than as an impact tool.[53,54] Research needs with impact questionnaires therefore include the following:

- Further investigation of the clinical utility of MIDAS and HIT
- Investigating other ways and tools to investigate impact
- Investigating impact as a tool to help with diagnosis.

Migraine is generally poorly diagnosed in primary care,[82,86,87,93,94] and an inaccurate diagnosis drives inadequate management to a large extent.[111] By extrapolation, diagnosis of TTH and CDH are also likely to be poor. While several new questionnaires have been developed in recent years that diagnose migraine specifically,[98–100] questionnaires to screen for different headaches are thin on the ground and not fully categorised in terms of methodology and clinical utility.[97] Research needs include the following:

- Developing new questionnaires to screen for headache subtype for research and the clinic (for patients presenting to GPs and other healthcare professionals)
- Deducing the factors that predict diagnosis, to develop a unified headache diagnostic questionnaire.

Treatments for migraine remain clearly inadequate, with most sufferers still relying on OTC medications,[65,86,101,102] even though effective acute and preventive medications are available for prescription by the physician. The situation for disabled TTH and CDH sufferers is likely to be even worse, due to the lack of knowledge about these conditions. One possible way of potentially improving treatments is to have a clear and simple way for the physician to assess the efficacy of therapies. They can then change (or not) the patient's treatment based on objective criteria. Currently-used endpoints are those developed for clinical trials conducted for regulatory purposes.[3,4] These may not be applicable to everyday clinical practice. Research needs include the following:

- Evaluation of the currently-used endpoints for their accuracy and clinical utility
- Development of new valid but simple endpoints for use in everyday clinical practice.

1.7 Objectives of the thesis

This thesis is based on research conducted over the past decade in primary care clinical practice. The major aim was to conduct clinic-based naturalistic studies designed to generate data that are applicable to everyday clinical practice. All of the studies were instigated and designed by the author, in conjunction with colleagues. Some of the studies were conducted in the author's own clinical practice and others in the area of Surrey, UK. Others were conducted nationally in the UK under the auspices of the Migraine in Primary Care Advisors, a UK-based charity dedicated to the improvement of headache management in primary care (www.mipca.org.uk), of which the author is the chairman.

The main objective of the thesis was to investigate headache-related disability, how to recognise and assess disabled patients and the clinical utility of assessing disability in primary care clinical practice. Individual objectives within this area were as follows:

1. To critically evaluate the evidence base for the quality of clinical evidence in acute migraine studies.
2. To investigate whether alternative clinical study endpoints may be useful in evaluating patients' response to acute migraine therapies.
3. To critically evaluate the evidence base for the use of disability and impact tools in migraine.
4. To investigate the disability experienced by different groups of headache patients in the clinical setting.
5. To investigate the efficacy of the MIDAS questionnaire when used by nurses in headache screening.
6. To investigate factors associated with headache diagnosis and develop a new screening questionnaire for different headache subtypes.

7. To investigate factors associated with headache management and develop a new questionnaire to help physicians decide on the need to change acute migraine medications.

1.8 Research questions

1. What is the quality of the evidence that underpins the use of acute migraine medications and how can it be used to provide guidance to physicians on how to evaluate clinical evidence rationally and in an evidence-based way?
2. Is patient preference a useful endpoint in clinical studies of acute migraine medications?
3. Does the disability associated with the headaches experienced by female migraine sufferers differ inside and outside the menstrual period?
4. What are the emotional factors implicated in how patients with TTH, migraine and CDH cope with their headaches on a chronic basis?
5. What is the methodological robustness and the clinical utility of the impact questionnaires MIDAS and HIT used to assess the severity of headaches?
6. What is the clinical utility of the MIDAS questionnaire when used by nurses in the initial management of headache patients, before they see a physician?
7. What is the clinical utility of the HIT questionnaire in terms of its use as a diagnostic or impact tool?
8. Can we develop a new diagnostic screening questionnaire for headache for use in primary care? Does such a questionnaire exhibit methodological robustness and potential clinical utility for patients and healthcare professionals?
9. Can we develop a new questionnaire to be used as screener for the need to change patients' acute migraine medications? Does such a questionnaire exhibit methodological robustness and potential clinical utility for primary care physicians?

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2

Methods

Introduction: Outline of thesis

This thesis poses several questions relating to the clinical importance of headache-related disability, how to recognise it and how to assess it.

Clinical importance of assessing disability

1. Chapter 2.1. What is the quality of the evidence that underpins the use of acute migraine medications and how can it be used to provide guidance to physicians on how to evaluate clinical evidence rationally and in an evidence-based way?
2. Chapter 2.2. Is patient preference a useful endpoint in clinical studies of acute migraine medications?

These items are analysed by searches and reviews of the relevant clinical literature on the subjects.

Recognising headache-related disability

3. Chapter 2.3. Does the disability associated with the headaches experienced by female migraine sufferers differ inside and outside the menstrual period?
4. Chapter 2.4. What are the emotional factors implicated in how patients with TTH, migraine and CDH cope with their headaches on a chronic basis?

These items are analysed by separate naturalistic studies conducted in primary care clinical practice.

Assessing headache-related disability

5. Chapter 3.1. What is the methodological robustness and the clinical utility of the disability-based questionnaires MIDAS and HIT used to assess the severity of headaches?

This item is analysed by searches and reviews of the relevant clinical literature on the subject.

6. Chapter 3.2. What is the clinical utility of the MIDAS questionnaire when used by nurses in the initial management of headache patients, before they see a physician?
7. Chapter 3.3. What is the clinical utility of the HIT questionnaire in terms of its use as a diagnostic or impact tool?
8. Chapter 3.4. Can we develop a new diagnostic screening questionnaire for headache for use in primary care? Does such a questionnaire exhibit methodological robustness and potential clinical utility for patients and healthcare professionals?
9. Chapters 3.5 and 3.6. Can we develop a new questionnaire to be used as screener for the need to change patients' acute migraine medications? Does such a questionnaire exhibit methodological robustness and potential clinical utility for primary care physicians?

These four items are analysed by separate naturalistic studies conducted in primary care clinical practice.

Literature searches and reviews

Literature searches were conducted by a combination of three different ways:

1. Through searches of MedLine and journal websites.
2. By attending and monitoring presentations at international congresses on headache and neurology: International Headache Congress, European Headache Society,

American Headache Society, Migraine Trust International Symposium, Headache Care for Practising Clinicians, American Academy of Neurology, European Federation of Neurological Societies.

3. By collating discussions at meetings of the UK Migraine in Primary Care Advisors (MIPCA) and the UK Migraine Action Association (MAA).

Studies

Design

The studies included in this thesis were all open, naturalistic studies conducted in primary care clinical practice. They were designed to mimic the situation in everyday clinical practice in terms of patients selected, drugs and doses administered and outcomes assessed.

Participants

The patients taking part in the studies were people being treated for TTH, migraine or CDH at primary care clinics in the UK. Many of the patients came from the author's own General Practice-based clinics. Other patients were referred to the author from the MAA, the UK patient support group. Finally, multicentre studies also included patients from the practices of MIPCA members, all of whom are primary care physicians. Patients were diagnosed according to the criteria of the *International Headache Society* (IHS) pertaining at the time,[1] in conjunction with the author's own clinical experience. Patients had to be between 18 and 65 years of age, not be abusing recreational drugs and not suffering from conditions that could interfere with the study results or put the patient at risk. Few restrictions were placed on the patients taking part in the studies deliberately to ensure, as far as possible, that the patients were representative of those in clinical practice.

All patients gave their written informed consent to take part in the studies and, where appropriate, institutional review body approval was obtained for the studies from local ethics committees.

Procedures

Demographic and baseline characteristics were recorded for all patients at baseline. In addition, patients were assessed with other questionnaires to assess their level of headache-related disability. Patients were then typically followed up using these questionnaires over a period of time when they were allowed to treat their headaches with their usual medications. Details of these assessment procedures are shown in Table 1.

Table 1. Details of the studies: investigations, assessments and timelines.

Chapter	Study investigation	Baseline assessments	Time of follow up	Follow-up assessments
2.3[2]	Disability of headaches inside and outside the menstrual period	Headache, depression and bodily pain questionnaire	2 months	Disability questionnaire
2.4[3]	Emotional factors associated with TTH, migraine and CDH	Short Pain Inventory (SPI©)	7 days	Short Pain Inventory (SPI©)
3.2[4]	Utility of the MIDAS questionnaire when used by nurses	Questionnaire on headache features and consultations; MIDAS questionnaire	6 months	Questionnaire on headache features and consultations; MIDAS questionnaire
3.3[5]	Validity and clinical utility of Internet HIT and SPI	Internet HIT; SPI	7 days	Internet HIT; SPI
3.4[6]	Development of a new diagnostic screening questionnaire for headache	Diagnostic Screening Questionnaire (DSQ)	ND	ND
3.5[7] and 3.6[8]	Development of a new questionnaire to screen for the need to change patients' acute medications	SF-36 QOL questionnaire; MIDAS questionnaire; Migraine Therapy Assessment Questionnaire (MTAQ)	1 week	SF-36 QOL questionnaire; MIDAS questionnaire; MTAQ

ND = no data

Instruments

Headache, depression and bodily pain questionnaire

A questionnaire was developed by the study investigators to assess the headaches, depression and bodily pain severity of patients attending a UK primary care practice (see Chapter 2.3).[2] Three questions assessed headache, five assessed depression and four assessed bodily pain severity. The answers to the questions were used to define the diagnosis and illness severity. The questionnaire was devised to be simple to use and potentially applicable to primary care clinical practice.

Disability questionnaire

A disability questionnaire was developed by the study investigators to assess headaches that took place inside and outside the menstrual period over a 2-month period (see Chapter 2.3).[2] Criteria used to develop the questionnaire included the IHS diagnostic criteria pertaining at the time.[1] Questions assessing the time lost from normal activities and the further time spent at less than 50% of normal capabilities are similar to those used in the MIDAS questionnaire,[9] and therefore have potential validity.

Short Pain Inventory (SPI©)

The SPI was used to assess the emotional factors associated with TTH, migraine and CDH[3] and to assess the validity and clinical utility of the Internet HIT and SPI questionnaires.[5]

The SPI is a 17-item self-rating questionnaire dedicated to measuring any pain, not only headache. The questions assess pain intensity, social interaction skills and components of emotional function. Patients rate each item on a five-point Likert scale: *not at all, a little, moderately, very much so and extremely.* Five subscales measure sedation, social interaction, anxiety, sadness and anger, and have been fine-tuned by maximising items that

are specific to pain. The SPI takes about one minute to complete,[10] and can be accessed via the internet with automatic scoring.[11] A scale of Total Mood Disturbance (TMD, 14 items) can be summated from the SPI, which measures the subtle mood changes that specifically covary with mild to severe pain (including sadness, anger, anxiety and sedation scores [social interaction scores are removed because this is a cognitive-behavioural parameter]). All 17 items can be summated to form the Total Pain Disturbance (TPD) score.

As the physical severity of pain worsens, so generally does each of the emotional components.[12–14] If a patient's emotional score is exaggerated or flattened relative to the normal values, then a coping score can also be given as to how well a patient is coping with their pain, relative to others at the same physical level of pain. In this way an emotional 'footprint' of the headache can be created. This can be very useful in the individual management of patients. It has been found that around 60% of the variance of physical pain is common to the overall mood of the patient.[12,13] The SPI has been shown to be far more powerful at discriminating between varying levels of physical pain severity than the McGill Pain Questionnaire (used as the gold standard measure), with the majority of the pain variance being captured by the SPI.[12]

Other studies have demonstrated that the SPI subscales could differentiate the footprint of pain resulting from headache and other pain states such as dental pain, osteoarthritis and chronic pain states.[5,13,14] In general, headache patients had the greatest level of sedation, while dental patients had the greatest levels of anger, sadness and anxiety. Patients with osteoarthritis had the lowest level of mood disturbance of all the patient groups. Overall, headache patients had a level of mood disturbance at least as severe as patients who were attending a secondary care chronic pain clinic.

MIDAS questionnaire
The sensitivity of the MIDAS questionnaire to change was investigated in a study where a nurse provided headache advice to patients attending a primary care practice.[4] It was also used to validate the Migraine-ACT questionnaire, a new questionnaire to screen for the need to change patients' acute medications.[7,8]

The development, testing and features of MIDAS are discussed in detail in Chapter 1. In brief, it assesses headache-related disability as the time lost from daily activities (employment, household work and family and leisure activities) and is scored as the number of days lost in a 3-month period.[9]

HIT questionnaire
The validity and clinical utility of the Internet HIT questionnaire were assessed in studies comparing it to the SPI questionnaire,[5] and it was also used in conjunction with the SPI to assess the emotional factors associated with TTH, migraine and CDH.[3] It was also used to validate the Migraine-ACT questionnaire, a new questionnaire to screen for the need to change patients' acute medications.[7,8]

The development, testing and features of Internet HIT and HIT-6 are discussed in detail in Chapter 1. In brief, it assesses headache impact as a constellation of pain, disability (activity limitations), tiredness and mood changes, and is scored numerically using arbitrary units.[15]

SF-36 QOL questionnaire
The SF-36 questionnaire was used to validate the Migraine-ACT questionnaire, a new questionnaire to screen for the need to change patients' acute medications.[7,8]

The SF-36 is a relatively brief generic QOL questionnaire, used in many chronic diseases, which contains 36 items, analysed as eight scales (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health) and a one-

item measure of change in health. It is scored between 0 and 100, with a score of 50 coinciding with the score for the healthy US general population.[16] Investigations in migraine sufferers have shown that the SF-36 score correlates with migraine severity and discriminates between migraine and other serious medical conditions.[17]

Migraine Therapy Assessment Questionnaire (MTAQ)
The MTAQ was used to validate the Migraine-ACT questionnaire, a new questionnaire to screen for the need to change patients' acute medications.[7,8]

MTAQ is a migraine-specific disease management questionnaire, which contains nine questions on migraine frequency and triggers, use of medications and their effectiveness, healthcare utilisation and time lost from everyday activities.[18] Each question is scored as 'yes' or 'no', and the score ranges from 0–6 (three questions are not scored). A score of ≥ 2 is used as an indicator that the patient requires follow up. It is proposed to be used in primary care to identify patients who require additional care.[18]

Psychometric properties of the questionnaires
The instruments used in the studies were either developed for use or testing by the author or were established questionnaires with well categorised psychometric properties. Table 2 shows the psychometric properties of the established questionnaires.

Table 2. Psychometric properties of the established questionnaires used in the studies.

Questionnaire	Internal consistency (Cronbach Alpha)	Test-retest reliability	Validity	Validation measure
Short Pain Inventory (SPI©)	0.93–0.94[12,13]	0.93[12]	0.77[5] 0.79[12]	Headache severity[5] McGill Pain Questionnaire[12]
MIDAS questionnaire	0.76[9]	0.80–0.83[9]	0.63[9]	Headache diary data[9]
Internet HIT	ND	0.79[19]	0.89[19]	Headache severity[19]
SF-36 QOL questionnaire	0.97[20]	0.85[20]	0.92[21]	Psychometric and clinical tests[21]
MTAQ	ND[18]	0.71[18]	0.67[18]	SF-36 QOL Questionnaire MIDAS Questionnaire Treatment satisfaction Healthcare resource use[18]

NA = no data

Overall, the SPI, MIDAS, HIT, SF-36 and MTAQ questionnaires are all highly reliable and valid, and therefore suitable for use in clinical research. In addition, the MIDAS[22] and SF-36[23] questionnaires have also been shown to be sensitive to change and are therefore suitable for use in clinical practice.

Statistical analyses
Statistical analyses were performed using the Statistica V4 (Tulsa USA) statistical package for MacIntosh. All data were double- or triple-checked for accuracy, and all analyses checked for normality. Parametric analyses were used for normally-distributed data and non-parametric analyses for non-normally distributed data. Analyses were two-sided and the level of significance was set at *p*-values less than 0.05. Patient demography was analysed using descriptive statistics only.

Parametric analyses included discriminant function analysis, simple *t-tests* and test-retest Pearson product moment correlation coefficients,[3,5] *t*-tests for dependent samples[4] and test-retest Pearson's product moment and Spearman rank measures, discriminatory t-tests and

factor analysis.[7,8] Non-parametric analyses conducted included the Mann-Whitney U Test,[2] Wilcoxon rank tests,[4] and the Wilcoxon matched-pairs test.[6]

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3

Investigating headache-related disability

3.1

Understanding the evidence: evaluating the efficacy of migraine medications in clinical practice*

Abstract

Large, randomised, double-blind, controlled clinical trials form the gold standard of clinical evidence for evaluating new medications. Meta-analyses and *post hoc* analyses of existing trials are increasingly used to compare therapies, in part to spare the expense and time required to conduct direct comparator studies. However, these analyses have been criticised methodologically, and should not be used on their own to evaluate therapies. Controlled clinical trials evaluating triptans in the acute treatment of migraine demonstrate clear superiority of the drugs over placebo, but only small differences are reported in studies comparing individual triptans and triptans with non-triptan medications. In contrast, patients can clearly distinguish between triptans and non-triptans and between different triptans in clinical practice. This incongruity may be due to the relative insensitivity of the standard clinical trial endpoint, relief of headache. New and more sensitive clinical trial endpoints are required for use in clinical studies that reflect everyday general practice (naturalistic studies). Among the potential endpoints are assessments of patient preference, impact on the patient's daily life and quality of life. However, novel endpoints should be developed, in collaboration with patients, which can summarise the whole migraine experience.

** Edited from the published manuscript: Dowson AJ, Kilminster S, Peters M, Lipscombe S, Rees T, Carter F, Darling S. Understanding the evidence: evaluating the efficacy of migraine medications in clinical practice. Headache Care 2005;2:133–43.*

Introduction

Migraine therapies are generally divided into acute (treatment of individual attacks as they occur) and prophylactic (pharmacological and non-pharmacological treatments taken daily to prevent attacks occurring). Most migraine treatments are relatively mature and the design and methodology of investigational studies varied quite widely.

The introduction of the triptans to the armamentarium of acute treatments for migraine has revolutionised the management of the condition over the past decade or so. Seven triptans are now available to the physician in many countries: sumatriptan, naratriptan, zolmitriptan, rizatriptan, almotriptan, eletriptan and frovatriptan. Triptans can be prescribed in several different formulations: conventional tablets, melt-in-the mouth or orally disintegrating tablets (ODTs), nasal sprays, subcutaneous injections and, in some countries, suppositories are all available. In general, the primary studies with the triptans were of good quality and were conducted to similar principles of design and methodology.[1] However, the resultant competition between the different manufacturers has led to a plethora of supporting clinical studies, and meta-analyses and *post hoc* analyses of clinical studies, all trying to establish superiority of one triptan over another. The result is a confusion of different study designs, endpoints and analyses, which can make it difficult for the physician to evaluate the evidence and to select the most appropriate drug for the individual patient.

This article aims to provide an objective overview of the clinical methodology used in, and data resulting from, studies conducted with the triptans and other acute migraine treatments. We also analyse the misunderstandings and pitfalls, which have biased the results from studies, and provide guidance on what to look for when evaluating the evidence from migraine studies. This general guidance is intended to be applicable to the evaluation of other migraine treatments (acute and preventive) and to treatments for other therapy areas. This article is based on discussions held at a meeting of the Migraine in Primary Care Advisors (MIPCA), which took place on 1 May 2003.

Clinical trial methodology

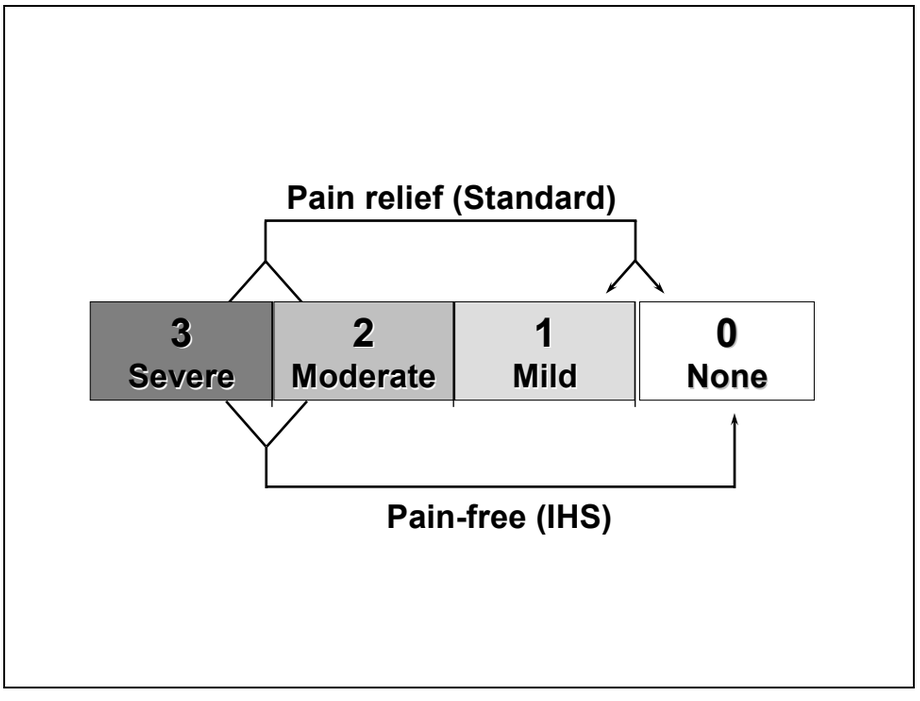
Historically, the design and methodology of clinical studies of acute migraine treatments were decided on an *ad hoc* basis, as no agreed criteria were available. Indeed, diagnostic criteria were not established by the International Headache Society (IHS) until 1988.[2] However, there was increasing pressure from regulatory authorities during the 1970s and 1980s to demonstrate a strong evidence base of efficacy and safety for new drugs. Scientists and clinicians took up this challenge in the late 1980s and early 1990s and developed new guidelines for study design, selection of patients, study methodology, endpoints and analyses of study data that are mostly still in use today in short-term controlled studies in migraine:[1]

- Studies are multicentre, randomised, double-blind, placebo- or comparator-controlled and generally parallel group in design. A crossover design is used only infrequently, due to the possibility of carryover effects.
- Eligible patients are those diagnosed with migraine according to the IHS criteria.[1] Patients usually have to be adults with established migraine who experience between one and four migraine attacks per month and without significant co-morbidities.
- Patients treat either one or three migraine attacks of moderate-to-severe intensity with study medication and evaluate the effect of treatment on record cards.
- Patients self-rate the intensity of their headache and other symptoms. The primary endpoint chosen was the relief of headache, defined as an improvement from severe or moderate to mild or no pain at 2 hours after treatment (Figure 1). Secondary endpoints included: headache relief at other time points, pain-free status at 2 hours and other time points, time to self-rated ‘meaningful relief’, time to return of normal

daily activities, presence of non-headache symptoms (nausea, vomiting, photophobia and phonophobia), and the incidence of headache recurrence and adverse events.
- Large numbers of patients are required and must be recruited to achieve sufficient power for the statistical analyses. Data are collected as the proportion of patients reporting the respective endpoints and are analysed using non-parametric statistical tests.

In contrast, long-term studies may be stand-alone, or open-label extensions to the controlled clinical studies. Patients treat all their migraine attacks with the triptan for a 6- or 12-month period. The primary endpoint is usually the incidence and nature of reported adverse events. Efficacy data are also collected in terms of the percentage of patients or attacks where headache relief is reported.

Figure 1. Primary endpoints from migraine clinical studies: Standard[1] and IHS[4] recommended outcomes.



Perspective on clinical trial methodology

When reviewing data from separate clinical studies, it is important to review the methodology used. Evidence from clinical studies can be graded in terms of quality:[3]

- Grade A encompasses consistent evidence from one or more well-designed and randomised clinical studies, as well as that from systematic meta-analyses.
- Grade B evidence is derived from well designed but non-randomised studies, and from non-systematic meta-analyses and *post hoc* analyses of controlled studies.
- Grade C evidence is derived from opinion and practices used in the absence of objective evidence.

Grade A evidence is essential in order to make clear recommendations for clinical practice. Grade B and C evidence should only be used to guide the objectives and design of future clinical studies.[3] In practice, evidence from Grade B and Grade C studies is used to guide clinical decisions in the absence of Grade A evidence.

Clinical studies need to be powered appropriately to detect expected differences between study drugs. Increasing the numbers of patients directly increases the power and clinical

relevance of the results. It is also important that study groups (e.g. active treatment and placebo) are of equivalent size. In migraine studies, about 100–200 patients per group are usually sufficient to distinguish between active treatment and placebo, but several hundred patients or more may be needed in each group to power differences between two active treatments of similar efficacy.

It is important that patient groups are similar in different treatment groups. For example, hospital-based patients may respond differently to outpatients or primary care patients. The physician should be aware that it is possible to manipulate patient populations to obtain the result desired. Patients may not always be from a homogeneous group. For example, the typical recruitment of patients with 1–4 headache attacks per month in triptan studies may include sufferers of both migraine and chronic headache. The latter may be difficult to treat and it is unlikely that a triptan would be effective on its own for patients with chronic headaches. Furthermore, large differences in placebo response may point to large differences in the case mix.

The design and endpoints should also be consistent across studies. Most randomised, controlled studies with the triptans follow the standard criteria[1] but studies comparing triptans to non-triptan medications frequently use different endpoints that may lead to atypical results. The original standard primary endpoint of headache relief[1] has come under challenge recently. The IHS now recommends that patients be pain-free at the 2-hour endpoint (Figure 1).[4] An even more stringent endpoint of 'sustained pain-free' is also advocated in recent publications.[5] This specifies that patients be pain-free at 2 hours after treatment, and that they experience no headache recurrence and use no rescue medication in the 24 or 48 hours after treatment. One problem with these newer endpoints is the low proportion of patients who respond, and that these definitions of efficacy may not correlate with a clinically relevant response. Interestingly, the results from many secondary endpoints (e.g. 'meaningful relief', return to normal functioning and relief of non-headache symptoms) usually parallel headache relief rates in clinical studies. Headache relief may, therefore, be the most clinically-meaningful endpoint that we have for migraine studies. However, the 4-point 'Glaxo' scale may not be optimal, as 5- or 7-point Likert scales are favoured in most therapy areas.[6] In addition, tolerability forms an important endpoint in all studies, assessed as the incidence, nature and intensity of reported adverse events. It should be noted that tolerability may not be related to safety, and that it is the side effects that are clinically significant. Drug-related adverse events, rather than the total incidence of all events, may be the clinically important endpoint.

Clinical study data on the triptans from well-designed, randomised studies

Due to the similarities in study design, methodology and endpoints used in most clinical studies with the triptans, the data are directly comparable. We review data from placebo-controlled and active comparator-controlled studies below.

Placebo-controlled studies

A summary of the efficacy of the different triptan drugs from placebo-controlled studies is shown in Table 1.[7–11]

Table 1. Summary of the efficacy of the different triptan drugs from randomised, placebo-controlled clinical trials: proportion of patients reporting headache relief (improvement from severe or moderate to mild or no pain).[7–11] This table is adapted and updated from Reference 7.

		Proportion of patients (%)	
Triptan	**Dose and route of administration**	**Headache relief from triptan (%)**	**Headache relief from placebo (%)**
Sumatriptan	6 mg subcutaneous	81–82	31–39
Sumatriptan	100 mg film-coated tablet	56–62	17–26
Sumatriptan	100 mg fast-disintegrating tablets[86]	72	42
Sumatriptan	50 mg film-coated tablet	50–62	17–32
Sumatriptan	50 mg fast-disintegrating tablets[86]	67	42
Sumatriptan	25 mg tablet	52	17–27
Sumatriptan	20 mg nasal spray	55–64	25–36
Sumatriptan	12.5 mg suppository	43–69	21–48
Sumatriptan	25 mg suppository	64–74	21–48
Naratriptan	2.5 mg tablet	43–50	18–27
Zolmitriptan	2.5 mg tablet	62–65	34–36
Zolmitriptan	2.5 mg ODT	63	22
Zolmitriptan	5 mg nasal spray	70	30
Rizatriptan	10 mg tablet	67–77	35–40
Rizatriptan	10 mg ODT	74	28
Almotriptan	12.5 mg tablet	57–70	38–42
Eletriptan	40 mg tablet	62–67	19–26
Frovatriptan	2.5 mg tablet	38–40	22–35

ODT = orally disintegrating tablet

Reviewing the primary endpoint (headache relief at 2 hours) data shows that:

1. The placebo response rate is highly variable, ranging from <20–48%.
2. All triptan modalities and formulations are significantly superior to placebo in terms of headache relief.
3. Most of the oral triptan formulations (including the conventional and orally disintegrating tablets [ODTs]) provide broadly similar levels of headache relief, although efficacy may vary somewhat in different studies with the same drug. However, naratriptan and frovatriptan have lower reported 2-hour efficacy rates compared to the other oral triptans.
4. Subcutaneous sumatriptan is more effective than any other triptan formulation. Nasal spay formulations may be superior to oral forms, and certainly have a faster onset of action (within 15 minutes as compared to 30 minutes or more for tablets).

Active comparator studies

Relatively few well-designed, head-to-head, Grade A comparator studies between the oral triptans have been published and we have only found 12 to date conducted with marketed formulations (Table 2).[12–23]

Table 2. Summary of the efficacy of the marketed oral triptans from randomised, controlled, direct comparator clinical studies: proportion of patients reporting headache relief (improvement from severe or moderate to mild or no headache pain) at 2 hours after treatment.[12–23]

Sumatriptan comparator studies

		Proportion of patients (%)		
Study	**Comparator drug**	**Sumatriptan**	**Placebo**	***p*-value (active comparators)**
Zolmitriptan 5 mg vs. Sumatriptan 100 mg[12] (*n*=1,058)	59	61	44	NS
Zolmitriptan 2.5 mg vs. Sumatriptan 50 mg[13] (*n*=1,522)	63	67	None	NS
Rizatriptan 10 mg vs. Sumatriptan 100 mg[14] (*n*=1,268)	67	62	40	NS
Rizatriptan 10 mg vs. Sumatriptan 50 mg[15] (*n*=1,329)	72	68	38	NS
Eletriptan 40 mg vs. Sumatriptan 100 mg[16] (*n*=692)	65	55	24	NS
Eletriptan 40 mg vs. Sumatriptan 100 mg[17] (*n*=2,113)	67	59	26	<0.001
Naratriptan 1, 2.5, 5, 7.5, 10 mg vs. Sumatriptan 100 mg[18] (*n*=643)	52–69	60	31	NS
Almotriptan 12.5 mg vs. Sumatriptan 50 mg[19] (*n*=1,173)	58	57	None	NS
Almotriptan 12.5 mg vs. Sumatriptan 100 mg[20] (*n*=668)	57	64	42	NS

Eletriptan comparator studies

		Proportion of patients (%)		
Study	**Comparator drug**	**Naratriptan**	**Placebo**	***p*-value (active comparators)**
Eletriptan 40 mg vs. Zolmitriptan 2.5 mg[21] (*n*=1,312)	60	64	22	NS

Naratriptan comparator studies

		Proportion of patients (%)		
Study	**Comparator drug**	**Naratriptan**	**Placebo**	***p*-value (active comparators)**
Rizatriptan 10 mg vs. Naratriptan 2.5 mg[22] (*n*=522)	45*	21*	None	<0.001
Eletriptan 40 mg vs. Naratriptan 2.5 mg[23] (*n*=548)	56	42	31	<0.01

NS = not significant
* Pain-free at 2 hours
In this context, 'comparator' refers to the triptan being compared with sumatriptan, eletriptan and naratriptan in the three sub-tables.

Overall, headache relief rates at 2 hours did not differ significantly in studies comparing sumatriptan (50 mg and 100 mg) with zolmitriptan 2.5 mg and 5 mg,[12,13] rizatriptan 10 mg,[14,15] eletriptan 40 mg,[16] naratriptan[18] and almotriptan 12.5 mg.[19,20] One study showed that eletriptan 40 mg was significantly superior to sumatriptan 100 mg,[17] but the numerical advantage was small and it required a study population of over 2,000 patients to achieve statistical significance. A further large study showed similar headache relief rates with eletriptan 40 mg and zolmitriptan 2.5 mg.[21] One other factor confounds these results. Sumatriptan (but not eletriptan) was encapsulated in all comparator studies with eletriptan, and studies have shown that the absorption of sumatriptan is reduced by this procedure.[24] These results should, therefore, be approached with caution. Eletriptan 80 mg was shown to be significantly superior to sumatriptan 100 mg[17] and zolmitriptan 2.5 mg,[21] but this high dose is not recommended for use in clinical practice. However, two studies have shown that rizatriptan and eletriptan are significantly superior to naratriptan in terms of headache relief rates 2 hours after treatment.[22,23]

Rizatriptan and almotriptan do have some evidence of superiority over sumatriptan in these studies. Rizatriptan appears to be more rapidly acting than sumatriptan,[14,15] with a significantly higher headache relief rate reported at 1 hour in one study.[14] Almotriptan was reported to be as effective as sumatriptan, but was associated with a significantly lower incidence of adverse events,[19,20] with significantly fewer chest symptoms reported in one study.[19] In these studies, both almotriptan and sumatriptan were encapsulated.

Comparison of triptans with non-triptan acute treatments for migraine
Well-designed Grade A clinical studies comparing triptans and non-triptan medications using the endpoint of headache relief are also relatively scarce, and we have located nine studies comparing oral triptans with ergotamine and analgesic-based preparations (Table 3).[25–33]

Table 3. Summary of the efficacy of the marketed oral triptans and non-triptan medications from randomised, controlled, direct comparator clinical studies: proportion of patients reporting headache relief (improvement from severe or moderate to mild or no headache pain) at 2 hours after treatment.[25–33]

	Proportion of patients (%)			
Study	**Triptan**	**Non-triptan drug**	**Placebo**	***p*-value (active comparators)**
Sumatriptan 100 mg vs. ergotamine 2 mg + caffeine 200 mg[25] (*n*=580)	66	48	None	<0.001
Eletriptan 40 mg vs. ergotamine 2 mg + caffeine 200 mg[26] (*n*=733)	54	33	None	<0.001
Sumatriptan 100 mg vs. aspirin 900 mg + metoclopramide 10 mg[27] (*n*=358)	56	45	None	NS
Sumatriptan 100 mg vs. aspirin 900 mg + metoclopramide 10 mg[28] (*n*=421)	53	57	24	NS
Zolmitriptan 2.5 mg vs. aspirin 900 mg + metoclopramide 10 mg[29] (*n*=666)	33	33	None	NS
Sumatriptan 50 mg vs. aspirin 1,000 mg vs. ibuprofen 400 mg[30] (*n*=312)	56	53* 60**	31	NS
Sumatriptan 100 mg vs. tolfenamic acid 200 mg[31] (*n*=141)	79	77	29	NS
Sumatriptan 50 mg vs. naproxen 500 mg + metoclopramide 16 mg[32] (*n*=546)	53	53	29	NS
Sumatriptan 50 mg vs. paracetamol 500 mg +domperidone 10 mg[33] (*n*=120)	33	36	None	NS

* Aspirin 1,000 mg; ** Ibuprofen 400 mg; NS = not significant

Two studies compared triptans with Cafergot, an oral preparation of ergotamine 2 mg plus caffeine 200 mg. Both sumatriptan 100 mg and eletriptan 40 mg resulted in significantly superior headache relief, compared with Cafergot.[25,26] However, the drug preparations may not have been equivalent in these studies. Oral ergotamine formulations have poor bioavailability and suboptimal efficacy. Parenteral ergotamine formulations, delivered rectally or by injection, are superior to oral formulations and a better study design would have been to use a double-dummy procedure to compare the different formulations.[3]

Several studies have compared oral triptans to analgesic-based drugs: aspirin plus metoclopramide,[27–29] aspirin alone or non-steroidal anti-inflammatory drugs (NSAIDs),[30–32] and paracetamol plus domperidone.[33] In all of these studies, headache relief rates were

similar in the triptan and analgesic groups, although the triptans had superior pain-free data in some.

One multicentre, randomised study has compared sumatriptan suppositories with a fixed combination of indomethacin, prochlorperazine and caffeine in 112 patients.[34] Again, headache relief at 2 hours was similar in the two groups (sumatriptan = 65% *versus* 71% for the combination), although 2-hour pain-free data were significantly superior for the indomethacin combination (34% *versus* 49%, $p<0.01$).

Perspective on clinical study data

Evidence from randomised and well-designed Grade A clinical studies shows that, compared with placebo, all triptans are effective and well-tolerated in the acute treatment of migraine. Of the oral triptans, sumatriptan, zolmitriptan, rizatriptan, almotriptan and eletriptan have similar efficacy profiles. Direct comparator studies indicate that rizatriptan and eletriptan may be slightly superior to sumatriptan, although the differences are numerically small and, therefore, of uncertain clinical significance. The data for eletriptan are also confounded by problems with the formulation of sumatriptan used in the comparisons. Almotriptan may be better tolerated than sumatriptan, especially in terms of chest-related symptoms, but again the clinical significance of these results is questionable. Overall, naratriptan and frovatriptan appear to be less effective than the other oral triptans. Subcutaneous and nasal spray triptan formulations are more effective and faster-acting than the oral formulations.

Oral sumatriptan and eletriptan are both significantly more effective than oral Cafergot. However, since oral formulations of ergotamine do not provide optimal efficacy, the clinical significance of these data is questionable. Several controlled studies using the conventional design and endpoints showed that oral triptans were not superior to oral analgesic-based therapies. However, the triptan response rate in these studies tended to be less than that reported in placebo-controlled studies, in some cases markedly so.[29,33] This may (but not necessarily) indicate that these studies had design faults, which could limit their reliability. Numerous studies have shown that patients consider triptans to be much more effective than non-triptans when used in everyday clinical practice.[35–38]

Meta-analyses and *post hoc* analyses with the triptans

Meta-analyses and *post hoc* analyses can be used to combine and compare data from multiple clinical studies. Formal meta-analyses combine data from published and unpublished studies, and can be considered Grade A evidence if they are comprehensive and reproducible. Other analyses for combining data include the calculation of therapeutic gain (TG), number needed to treat (NNT) and number needed to harm (NNH, Table 4),[39] and form Grade B evidence. These approaches have been used frequently with the triptans, in part probably to compensate for the relative lack of controlled comparator studies between them.

Table 4. Definitions of post hoc clinical endpoints: therapeutic gain, number needed to treat and number needed to harm[39]

Therapeutic gain (TG): the proportion of patients benefiting from treatment, adjusted to the placebo rate

= Proportion of patients benefiting on treatment _ Proportion of patients benefiting on placebo

Number needed to treat (NNT): the number of patients that have to be treated in order for one patient to be treated successfully, adjusted for placebo

= 100 / Therapeutic gain (% of patients)

Number needed to harm (NNH): the number of patients that have to be treated in order for one patient to report an adverse event, adjusted for placebo

= 100 / Proportion of patients reporting adverse events on treatment – Proportion of patients with adverse events on placebo

Meta-analyses

Two meta-analyses have been published comparing the oral triptans, using sumatriptan 100 mg as the baseline comparator. Ferrari and co-workers analysed 53 published and unpublished clinical studies involving 24,089 patients.[40] Their analyses indicated that, compared with sumatriptan, rizatriptan 10 mg exhibited better efficacy and consistency of response, and similar tolerability. Almotriptan 12.5 mg exhibited better sustained pain-free, consistency of response and tolerability data, while naratriptan showed superior tolerability. All other triptans (except frovatriptan, which was not included in the analyses) had similar clinical profiles to sumatriptan, and all were effective and well tolerated. The authors concluded that, of the marketed doses, rizatriptan 10 mg and almotriptan 12.5 mg offered the best chance of overall success. Belsey has published a further meta-analysis of 28 studies involving 13,204 patients. He analysed TG, NNT and NNH data and concluded that, of the oral triptans, only rizatriptan 10 mg was markedly superior to sumatriptan 100 mg in terms of overall efficacy and tolerability.[41]

Post hoc analyses

Several *post hoc* analyses of clinical data have been conducted with the oral triptans, investigating a variety of endpoints. One study analysed TG data, which showed clearly that subcutaneous sumatriptan 6 mg provided superior efficacy to any of the oral triptans.[42] All the oral triptans were effective, although naratriptan and frovatriptan were the least effective, and almotriptan also seemed to be relatively less effective than oral sumatriptan, zolmitriptan, rizatriptan and eletriptan.[42,43] An analysis combining data from three head-to-head comparator studies between eletriptan 40 mg and sumatriptan 100 mg indicated that eletriptan was the more effective drug.[44] Significantly more patients on eletriptan (67% *versus* 57%, $p < 0.0001$) reported headache relief at 2 hours after treatment, the primary endpoint, and secondary endpoints gave similar results. In a different type of *post hoc* analysis, almotriptan 12.5 mg proved to be more effective than rizatriptan 10 mg and sumatriptan 50 mg and 100 mg, in terms of a composite endpoint of cost-effectiveness ratio for sustained pain relief and no adverse events.[45,46]

The manufacturers of rizatriptan have conducted several *post hoc* analyses comparing their drug to the other oral triptans. Combining data from several clinical studies, more patients taking rizatriptan were satisfied with their therapy,[47] were pain-free at 2 hours and 24 hours after treatment,[5] and were free of nausea after 2 hours than with other triptans.[48]

Perspective on meta-analyses and post hoc analyses

Overall, the data from the meta-analyses and *post hoc* analyses with the triptans are consistent with those from controlled clinical studies. All the oral triptans were effective and well tolerated, and there were more similarities than differences between the drugs. Rizatriptan 10 mg and eletriptan 40 mg exhibited the best efficacy profiles, while naratriptan 2.5 mg and almotriptan 12.5 mg exhibited the best tolerability. However, these analyses have come under criticism from several sources.

Rigorous meta-analyses do provide Grade A clinical evidence.[3] However, there is evidence that the meta-analyses conducted with the triptans may not fulfil the necessary criteria for this. The two meta-analyses did not provide consistent data, and the selection of studies, patient populations and endpoints differed. The meta-analysis by Ferrari *et al*[40] is the most robust of the two, involving a substantially larger number of studies and patients than that of Belsey.[41] However, even this large analysis has been criticised in terms of its methodology, statistical analyses and the clinical significance of its results.[49–53] Using analyses of TG and NNT to compare triptans has also been criticised. Placebo response rates are crucial to the calculation of these values, and are highly variable in migraine studies[54] while the response to active treatments tends to be less variable (Table 1). Several pieces of research have shown that NNT values are correlated more strongly to the placebo response than to the active treatment response.[55] A systematic analysis of placebo-controlled studies with the triptans showed that the triptan response rate followed a normal distribution, while that of placebo did not.[56] Both TG and NNT analyses failed the test of normality. The authors concluded that these transformations of data are a potential source of bias in meta-analyses of acute migraine treatments. Another group of authors has concluded that analysing TG and NNT adds no new information to the evaluation of placebo-controlled trials.[55] There is also some argument as to whether the placebo response should be so disregarded, as placebo may activate the same pain modulating brain structures as pain-relieving drugs.[57,58] Estimations of TG and NNT may, therefore, significantly underestimate the efficacy of active treatments. It has been concluded that migraine therapies can only be effectively compared using well-designed head-to-head studies, and not by meta-analyses.[55]

Triptans in clinical practice

One of the characteristic features of the triptans is that their reported efficacy is greater when used in clinical practice than when used in controlled clinical trials. In studies which reflected everyday clinical practice (naturalistic studies), reported headache relief rates following treatment with sumatriptan and zolmitriptan were typically close to 80%.[59,60] There are several possible reasons that may explain these findings:

- The populations of patients may differ. Young and middle-aged adults predominate in clinical trials, while the general population of migraine sufferers contains all age groups, from children and adolescents, to older people.[61]
- The severity of the headache may differ. Migraine sufferers in the general population experience, on average, about one migraine attack per month.[61] In clinical studies, patients may have up to four attacks per month.[1] It is likely that some of these patients have chronic daily headache, a condition that is more severe and more difficult to treat than migraine.[62]
- Clinical studies are mostly conducted in Western Europe and North America, in Caucasian patients. Other countries and races may respond differently to the triptans.
- Patients in clinical practice may not use the strict doses that are given in clinical studies. Dose-titration studies have shown that, given the choice, the majority of patients end up using higher doses of the triptans, e.g. sumatriptan 100 mg and zolmitriptan 5 mg.[59,60] For some triptans, e.g. naratriptan and frovatriptan, the recommended dose may not be at the top of the dose-response curve. The use of

relatively high doses may, therefore, result in a markedly greater efficacy than that reported in clinical studies.

- In clinical practice, patients may not wait until the headache is moderate or severe before treating with a triptan. In fact, recent evidence from randomised and controlled studies indicates that triptans are most effective when taken early in the migraine attack when the headache is mild. With sumatriptan 100 mg, pain-free rates of 71% were achieved 2 hours after the treatment of mild headache, compared to 54% when the initial headache was moderate or severe (p<0.05).[63] Similar results have been reported with zolmitriptan[64] and almotriptan,[65] and it seems likely that future treatment guidelines will recommend that triptans be taken early in the attack when the headache is mild. Suggestions have recently been published on how to conduct randomised, controlled 'early treatment' studies with the triptans.[66]

The search for new study endpoints

The primary endpoints used in clinical trials with the triptans were designed to demonstrate significant differences between active treatments and placebo.[1] This was done to comply with the need to produce documents suitable for submission to regulatory authorities worldwide, rather than to devise endpoints suitable for use in everyday clinical practice. In fact, the main endpoint of headache relief proved unable to distinguish between triptans and other active treatments. More sensitive endpoints may be required for use in clinical practice. In a survey, migraine patients reported the following attributes of acute treatments to be most important to them: complete pain relief, no headache recurrence, rapid onset of action, no side effects and relief of non-headache associated symptoms.[67] A global measure of efficacy and tolerability is probably the best option to cover all these areas. Such global measures that have been used in migraine studies include assessments of patient preference and satisfaction, the impact on patients' daily lives and quality of life.

Patient preference and satisfaction

Patient preference is a subjective global measure of efficacy and tolerability that can be simply assessed by the patient. Numerous migraine studies have used these assessments as secondary endpoints. In these studies, patients consistently preferred oral triptans over non-triptan acute medications.[68] Additionally, patients were able to distinguish between different oral triptans, and expressed clear preferences between them. However, their responses were idiosyncratic. The main reasons patients gave for preferring one triptan over the other was a faster onset of action, a longer duration of effect and fewer adverse events. However, these reasons were all given for sumatriptan, zolmitriptan and rizatriptan in different studies, and the response could not be predicted in advance.[69–71] One caveat of assessing patient preference is that it can only relate the performance of one drug to a second one. This endpoint does not provide absolute information about a drug, and precludes meta-analysis.

Impact assessments

Assessing the impact of migraine on patients' daily lives has become an increasingly used measure of migraine severity over the past few years. Impact questionnaires have been developed, validated, and tested as outcome measures. The Migraine Disability Assessment (MIDAS) Questionnaire has shown sensitivity to change in studies of migraine and chronic daily headache,[72,73] and further research may prove it to be a useful clinical study endpoint. Two other impact questionnaires, the Headache Impact Test (HIT)[74] and the Short Pain Inventory (SPI),[75] require development as outcome measures.

Quality of life measures

Migraine sufferers are known to have significantly poorer quality of life than the general population during their attacks, and also between attacks when they are regarded as symptom-free.[76,77] Generic and migraine-specific QOL questionnaires have been developed

for migraine, and consistently show that effective migraine treatment results in improved patient QOL.[78] Using one of the migraine-specific questionnaires as an outcome measure (the 24-hour Migraine-Specific QOL Questionnaire), it was demonstrated that rizatriptan 10 mg was significantly superior to non-triptan acute medications in terms of work and social functioning, energy, and patients' feelings and symptoms.[79]

New initiatives

All the above questionnaires have the potential to summarise the whole migraine experience and act as effective outcome measures. However, more work is required to define patients' responses and validate these assessment tools against the existing gold standard measure of headache relief. A new questionnaire, the Migraine Assessment of Current Therapy (Migraine-ACT) assesses the need for reviewing acute medications in terms of four questions in clinically-relevant domains: impact, global assessment of relief, consistency of response and emotional response.[80] Patients answer the questions as 'yes' or 'no' and an increasing number of 'no' answers indicates increasing medical needs. It therefore combines elements of patient satisfaction, impact and QOL. A large prospective study showed that Migraine-ACT exhibited high reliability and validity, and had considerable potential clinical utility.[80] What is now needed is to investigate the sensitivity to change of Migraine-ACT and to develop a similar questionnaire for preventive medications.

Another approach is to examine the principles underlying patient response to therapy, using qualitative research. Qualitative research aims to increase the understanding of patients and physicians and could help to provide a more realistic assessment of headache treatments and to develop relevant patient-centred endpoints.[81] Open ended-questions allow patients and physicians to speak freely about their perspectives, including beliefs about interventions, and the benefits and preferences of therapies. Asking a different type of questions, qualitative research can provide information not available from conventional quantitative methods. Qualitative research can be combined with quantitative methods, by conducting a qualitative study to generate hypotheses, which can be tested using quantitative methods.[82] Qualitative research is now recommended by the UK Medical Research Council for use in the development of clinical trials programmes, to gain better understanding of patients' needs and to develop new clinical endpoints.[83] Qualitative methods can also follow quantitative methods, to help explain quantitative findings, e.g. explaining anomalous results such as the unexpected similarity in efficacy of triptan and non-triptan medications and differences in placebo response in separate patient populations.[84] Combining qualitative and quantitative methods in randomised controlled trials is believed by some researchers to be the best means of assessing whether (and why) interventions work (efficacy) and whether (and how) they work in clinical practice (effectiveness). Such initiatives can increase the generalisability of results and generate information to help successfully implement and refine effective interventions in natural settings.[85]

Conclusions – understanding the evidence

In evaluating clinical evidence, the randomised, double-blind, controlled clinical trial remains the gold standard for evaluating the clinical profile of migraine drugs. However, even these studies may have deficiencies, and there are several items to look out for when evaluating good quality headache studies:

- The number of patients in the study needs to be appropriate for the analyses planned. In general, there should be at least 50 patients per treatment group, with equal numbers of patients in the active and placebo (or active competitor) groups. It is interesting that large numbers of patients are required to show significance in evaluating migraine therapies, up to 200 per group in placebo-controlled studies[2,7] and up to 1,000 or more in triptan comparator studies.[17]

- Patient withdrawals from the study should be low, and not exceed 10% of the total. The proportion of patients withdrawing should be similar in the separate treatment groups.
- Outcome measures should be quantifiable, discriminate well and have intuitively meaningful units. Categorical scales (e.g. five- or seven-point Likert scales) are preferable to visual analogue scales, although 10-point numerical scales work well in the Netherlands.
- The data should be clinically relevant. For treating migraine, speed of onset, duration of response, and assessments of functional status or well-being are important in addition to headache relief at defined time points.[3,8]

On the whole, the results from meta-analyses and *post hoc* analyses were congruent with those from controlled clinical studies. However, they have also generated controversy, and their chief utility may be to suggest avenues for future clinical studies, rather than being used on their own as a means of selecting acute treatments for migraine.

However, results from clinical trials may not reflect the situation in clinical practice for migraine. For example, clinical studies show only small clinical differences between the oral triptans,[12–21] whereas patients exhibit clear, if individual, preferences between them.[69–71] The challenge is to develop studies that can effectively distinguish between the triptans, or to distinguish between patient-dependent sensitivity to individual triptans. This may be achieved by conducting naturalistic studies in everyday clinical practice with the full range of patients who suffer from migraine, allowing them to use the drugs according to normal prescription recommendations. The development of new, more sensitive and valid endpoints to assess migraine relief in collaboration with patients would facilitate this process.

Acknowledgements

The authors are pleased to acknowledge the input of the other delegates at the MIPCA meeting held on 1 May 2003, and additional MIPCA members who reviewed this manuscript: Dr Jerry Sender, Dr Ahmet Fuat, Dr David Watson, Dr Gregory Parkin-Smith (physicians), Ms Heather MacBean (nurse practitioner) and Ms Ann Turner (Director of the Migraine Action Association, the UK patient support group). We are also grateful to AstraZeneca, who sponsored the meeting with an unrestricted educational grant.

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3.2

Patients' preference for triptans and other medications as a tool for assessing the efficacy of acute treatments for migraine*

Abstract

Oral triptans are effective and well tolerated acute treatments for migraine, but clinical differences between them are small and difficult to measure in conventional clinical trials. Patient preference assesses a global measure of efficacy and tolerability, and may be a more sensitive means of distinguishing between these drugs. In a series of studies, patients consistently expressed a clear preference for triptans over their usual non-triptan acute medications, e.g. analgesics and ergotamine. Direct comparator studies of patient preference with oral triptans showed that patients could distinguish between different triptans, and between different formulations of the same triptan. Patients could even distinguish between the three oral doses of sumatriptan. The most frequently provided reasons for preference were speed of response and overall effectiveness. Patient preference is a sensitive and valid clinical trial endpoint and physicians should consider using it when reviewing the efficacy of acute migraine medications.

** Edited from the full published article: Dowson AJ, Tepper SJ, Dahlöf C. Patients' preference for triptans and other medications as a tool for assessing the efficacy of acute treatments for migraine. J Headache Pain 2005;6:112–20.*

Introduction

Oral triptans (5-hydroxytryptamine-1B/1D receptor agonists) are effective and well tolerated acute treatments for migraine. [1, 2] However, direct comparator trials and systematic reviews indicate that differences between oral triptans are relatively small. [3–5] The standard clinical trial endpoint of headache relief [6] may be relatively insensitive and not relevant to everyday clinical practice. [7] There are also issues of study design and encapsulation of certain formulations that may reduce the clinical applicability of some study results. [8] Meta-analyses may be rather blunt measures of efficacy, better reflecting placebo response rather than active response [9]. Therefore, other measures of efficacy need much greater study. [10]

Since patients are treated on an individual basis, the more important question is not which triptan is best relative to another, but whether the chosen triptan provides the outcome desired by the patient and healthcare provider. A measure that evaluates the patient's subjective judgement of the efficacy and tolerability of therapy may be a more sensitive and valid measure of efficacy than the standard endpoints. Patient preference evaluates a global measure of the clinical profile, encompassing efficacy, speed of onset of action, tolerability, consistency of response, ease of use and feelings of well being on an individual basis. [5] Using patient preference and satisfaction data may be one approach to comparing the triptans that provides a more real-life perspective. [11, 12] The International Headache Society (IHS) guidelines for controlled trials of migraine treatments state that the global evaluation of migraine medications by patients is a clinically relevant measure. [13]

Many triptan studies have reported patients' overall evaluation of their migraine treatments. This article reviews these data, from three types of patient preference study: comparisons of triptans *versus* patients' usual non-triptan treatments, direct comparisons of different triptans and comparisons of different formulations or doses of the same triptan. We also review the methodological robustness of the studies for study design and symmetry in the groups compared, and in blinding techniques.

Comparing triptans with non-triptan medications

These comparisons were conducted in two ways. Firstly, a large meta-analysis was conducted to capture data on patients' satisfaction with their usual acute medications before they entered clinical studies. Secondly, a series of patient preference studies compared triptans with patients' usual non-triptan medications.

Meta-analysis of sumatriptan clinical studies

A meta-analysis was conducted to investigate patients' satisfaction with their usual acute migraine medications before entering 10 UK clinical studies with sumatriptan. [14] In all studies there were assessments of acute medications taken for the migraine attacks and their efficacy. The proportions of patients rating each of the drug categories as ineffective/poor/reasonable and good/excellent were calculated, and 95% confidence intervals constructed for the proportions using the normal approximation (Table 1).

Table 1. Patients' (n = 3,378) assessment of acute migraine treatments in the meta-analysis of sumatriptan versus usual acute treatments [14]

Medication	**Patient rating % [a] (95% confidence interval)**		
	Ineffective/poor /reasonable	**Good/excellent**	**Number of patients**
Sumatriptan	**12%** (6% to 17%)	**88%** (83% to 94%)	688
Ergotamine	**62%** (53% to 71%)	**38%** (29% to 47%)	249
Paracetamol/codeine/ buclizine	**75%** (71% to 79%)	**25%** (21% to 29%)	530
Aspirin/metoclopramide	**77%** (69% to 85%)	**23%** (15% to 31%)	110
Paracetamol/metoclopramide	**81%** (77% to 85%)	**19%** (15% to 23%)	307
Ibuprofen	**83%** (78% to 88%)	**17%** (12% to 22%)	233
Paracetamol/codeine	**88%** (85% to 92%)	**12%** (8% to 15%)	355
Aspirin	**90%** (86% to 94%)	**10%** (6% to 14%)	210
Co-proxamol	**91%** (87% to 95%)	**9%** (5% to 13%)	166
Paracetamol	**97%** (96% to 98%)	**3%** (2% to 4%)	530

[a] *Approximate 95% confidence intervals are given, the exact confidence coefficients may be lower.*

Overall, the majority of patients (88%) who used sumatriptan as their usual migraine medication rated it as good or excellent. In contrast, only 38% of patients who usually used ergotamine, 25% of those who normally used paracetamol/codeine/buclizine, 23% of those who used aspirin/metoclopramide and 19% of those who used paracetamol/metoclopramide rated these medications as good or excellent.

Patient preference studies (Table 2)

Table 2. Summary of studies comparing patients' preference for triptans versus their usual non-triptan acute treatments for migraine.

		% patients	
Triptan and dose	**Preference for triptan**	**Preference for usual non-triptan therapy**	**No preference**
Sumatriptan subcutaneous 6 mg [15] (*n* = 217)	85	10	5
Sumatriptan oral 50 mg [16] (*n* = 402)	73	18	9
Sumatriptan oral 50 mg [18] (*n* = 29)	69	16	14
Naratriptan oral 2.5 mg [19] (*n* = 115)	63	27	10
Triptans [22] (*n* = 663)	52*	21*	9

* 18% of patients preferred to use both a triptan and an analgesic to treat individual migraine attacks

Sumatriptan
A prospective, multicentre, open-label, 2-month crossover study compared patients' preference for subcutaneous sumatriptan 6 mg with their usual acute migraine treatments. [15] Single and combination analgesics were used by 49% of patients, ergotamine by 24%, non-steroidal anti-inflammatory drugs (NSAIDs) by 19% and dihydroergotamine (DHE) by 7%. At the end of the study, 85% of patients expressed a preference for subcutaneous sumatriptan, 10% preferred their usual treatments and 5% had no preference ($p<0.001$). Some of the comparisons in this study necessitated asymmetric comparison of formulations, i.e., injection *versus* tablet.

A large, open-label, 4-attack observational study compared patients' preference for and satisfaction with oral sumatriptan 50 mg with those for their usual non-triptan prescription or over-the-counter therapy (mostly non-narcotic analgesics and NSAIDs). [16, 17] At the end of the study, 73% of patients expressed a preference for sumatriptan, and only 18% preferred their usual therapy. The most common reasons given for preferring sumatriptan were effective pain relief (98% of patients), restored ability to function (93%), requirement for fewer doses (93%), relief of migraine-associated symptoms (89%), rapid onset of efficacy (86%), no tired feelings (85%) and fewer side effects (81%). Significantly more patients were satisfied with sumatriptan as compared with their usual therapies ($p<0.001$) and with the overall quality of their medical care when it included sumatriptan ($p<0.001$).

An open-label, observational, multi-attack preference study in US primary care clinical practice allowed patients not using triptans to switch to oral sumatriptan 50 mg to treat their migraine attacks. [18] At baseline, patients were mostly using NSAIDs and other simple analgesics (69%), OTC or prescription combination therapies (28%) and narcotics (10%), with the majority (76%) being dissatisfied with their nontriptan therapies. At the end of the study 69% of patients expressed a preference for sumatriptan, 16% for their previous therapy and 14% had no preference. The main reasons given for preferring sumatriptan were speed of relief and overall effectiveness (69% and 30% of patients, respectively). Use of sumatriptan correlated with a reduction in unscheduled physician visits, emergency room visits and hospitalisations for migraine.

Naratriptan
An open-label study conducted in US primary care assessed migraine patients' satisfaction with and preference for oral naratriptan 2.5 mg compared with their previous non-triptan therapies (simple analgesics [59%], combination products [46%] and narcotics [13%]). [19] After three treated attacks, more patients were satisfied with naratriptan than with their previous therapies (75% *versus* 47%), and 63% preferred naratriptan, 27% their non-triptan therapy and 10% expressed no preference. The main reasons for preferring naratriptan were effective pain relief (86% of patients) and restoration of ability to function (81%).

Zolmitriptan
An open-label, multicentre study of 112 patients treating 281 migraine attacks assessed efficacy, safety and patient acceptance of oral zolmitriptan 2.5 mg. [20] At the end of the study, 78% of patients stated that zolmitriptan was superior to their previously used abortive treatments (analgesics and NSAIDs).

Rizatriptan
An open-label, single-attack crossover study compared migraine patients' (*n* = 216) satisfaction with two formulations of oral rizatriptan 10 mg (conventional tablet and orally disintegrating tablet [ODT]) over their previous non-triptan medications. [21] The study reflected normal clinical practice, with all patients being triptan naïve. At the end of the study, more than twice as many patients taking rizatriptan reported that they were 'very' or 'somewhat satisfied' with the medication compared with their previous non-triptan medications ($p<0.05$). In all studies in which the ODT preparations are compared with conventional tablets, there is an asymmetry in comparison groups with respect to the formulations assessed.

Overall preference for triptans versus analgesics
A study conducted in US secondary care assessed the choice of acute migraine medications in patients who had been prescribed triptans in the past. [22] Patients were asked whether they currently preferred to use triptans or analgesics (OTC, prescription simple and combination analgesics, and prescription narcotics). Fifty two percent of the patients preferred using a triptan alone, 21% analgesics alone, 18% triptans plus analgesics for the same attack and 9% had no preference. The main reasons for preferring triptans over analgesics were efficacy (62% of patients), reduced side effects (8%) and a combination of the two (30%).

Studies comparing the different triptans (Table 3)

Table 3. Summary of studies comparing patient preference for different triptans.

		% patients	
Comparison	**Preference for sumatriptan**	**Preference for comparator triptan**	**No preference**
Sumatriptan oral 50 mg versus zolmitriptan oral 2.5 mg [23] (*n* = 94)	29	44	27
Sumatriptan oral versus zolmitriptan oral 2.5 mg [20] (*n* = 112)	36	45	19
Sumatriptan oral 50 mg versus rizatriptan ODT 10 mg [12] (*n* = 374)	43	57**	0
Sumatriptan oral 50 mg versus rizatriptan ODT 10 mg [27] (*n* = 481)	36	64***	0

** $p<0.01$; *** $p\leq0.001$; ND = no data

Almost all preference studies that compare the triptans use sumatriptan as the comparator drug. There is a relative lack of comparative clinical data between the newer triptans, both for conventional efficacy measures and for patient preference and satisfaction measures.

Sumatriptan versus zolmitriptan
An open-label, non-randomised, crossover study investigated patients' preferences for oral sumatriptan 50 mg *versus* oral zolmitriptan 2.5 mg tablets. [23] Patients treated three attacks with each triptan (in any order) then completed a preference questionnaire. At the end of the study, 42 patients (44%, CI 34–58%) preferred zolmitriptan, 27 patients (29%, CI 20–38) preferred sumatriptan and 25 patients (27%, CI 18-36%) reported no preference. The reasons given in the 69 patients who expressed a preference between the triptans were: faster onset of action (73%), longer duration of effect (39%), fewer adverse events (35%) and lower price (13%). Only one-quarter of the patients reported that sumatriptan and zolmitriptan were equivalent. These results are similar to those from the open-label, multicentre study conducted described earlier, [20] in which 45% of patients assessed zolmitriptan as superior to sumatriptan and 36% assessed sumatriptan as superior to zolmitriptan.

Sumatriptan versus rizatriptan
A randomised, double-blind, triple-dummy, parallel group study compared rizatriptan tablets 5 mg and 10 mg, sumatriptan 100 mg and placebo in 1,268 patients treating a single migraine attack. [24] Headache relief rates after rizatriptan 10 mg were reported to be somewhat higher than those after sumatriptan. However, patient satisfaction data were also collected, and showed no significant differences between the rizatriptan and sumatriptan groups. [25]

Two studies have compared patient preference for sumatriptan conventional tablets with the ODT formulation of rizatriptan. A multicentre, randomised, open-label, two-period crossover study compared the proportion of patients who preferred rizatriptan ODT 10 mg to

sumatriptan 50 mg tablet. [12] Patients treated two migraine attacks, one each with rizatriptan and sumatriptan. Significantly more patients preferred rizatriptan to sumatriptan at the end of the study (57% *versus* 43%, $p<0.01$). A *post hoc* analysis of the data indicated that patients tended to prefer the triptan that supplied the most rapid pain relief. [26] A second randomised, open-label, crossover study assessed patient preference for rizatriptan ODT 10 mg versus sumatriptan 50 mg conventional tablet to treat a single migraine attack. [27] At the end of the study, significantly more patients preferred rizatriptan to sumatriptan (64.3% *versus* 35.7%, $p\leq0.001$). Faster headache relief was the most important reason given for preference of both drugs (46.9% and 43.4% of patients preferring rizatriptan and sumatriptan, respectively). Two hours after treatment of the attacks, significantly more patients receiving rizatriptan than sumatriptan (73.3% *versus* 59.0%, $p\leq0.001$) reported satisfaction (completely, very or somewhat satisfied) with therapy and found the drug convenient (very convenient, convenient or somewhat convenient) to take (87.2% *versus* 76.3%, $p\leq0.001$). The crossover design of these two studies helps mitigate the asymmetry of the comparison groups.

Sumatriptan versus eletriptan
A randomised, double-blind, parallel-group study compared the efficacy, safety and tolerability of oral eletriptan 20 mg, 40 mg and 80 mg *versus* oral sumatriptan 100 mg and placebo for a single migraine attack (n = 692). [28] Patients were asked at a follow-up visit to rate the acceptability of their study medication compared to medications used previously. Patients rated sumatriptan (64%) and all doses of eletriptan (64%, 74% and 84% for the 20 mg, 40 mg and 80 mg doses, respectively) more acceptable than placebo (32%), with the highest acceptability rate reported for eletriptan 80 mg. Sumatriptan, but not eletriptan was encapsulated for blinding purposes in the study, making the comparative groups asymmetric, a potential bias that was maximized by the parallel group design. Encapsulation of sumatriptan has been shown to negatively affect its pharmacokinetics and absorption. [8]

Sumatriptan versus almotriptan
A double-blind, multicentre, randomised, parallel-group study (n = 1,173) compared treatment satisfaction, functional status and health-related quality of life (HRQOL) of patients treated with oral almotriptan 12.5 mg or oral sumatriptan 50 mg for one migraine attack. [29] The patients reported similar satisfaction with pain relief associated with the two drugs, but were significantly less bothered with side effects from almotriptan than sumatriptan (p=0.016). Improvements in functional status and HRQOL were similar in the two treatment groups. Both almotriptan and sumatriptan were encapsulated for blinding purposes in the study, thus no bias based on blinding was present.

Multiple comparisons between the triptans
A *post hoc* comparison was made of patients' overall satisfaction with treatment from five double-blind, placebo-controlled studies in which rizatriptan 10 mg conventional tablets were compared with other oral triptans. [30] Three studies compared rizatriptan with sumatriptan (rizatriptan 10 mg *versus* sumatriptan 100 mg in a parallel-group study, n = 916; rizatriptan 10 mg *versus* sumatriptan 50 mg in two crossover studies, n = 1,599). One study compared rizatriptan 10 mg with naratriptan 2.5 mg (n = 502) and another compared rizatriptan 10 mg with zolmitriptan 2.5 mg (n = 701), both being parallel-group studies. Patients reported their satisfaction with treatment on a seven-point scale at 2 hours after treatment. Significantly more patients receiving rizatriptan 10 mg than all the other triptans reported that they were 'completely' or 'very' satisfied: rizatriptan *versus* sumatriptan 100 mg (33% *versus* 26%, $p<0.05$); rizatriptan *versus* sumatriptan 50 mg (40% *versus* 35%, $p<0.05$); rizatriptan *versus* naratriptan 2.5 mg (33% *versus* 19%, $p<0.01$); and rizatriptan *versus* zolmitriptan 2.5 mg (38% *versus* 30%, $p<0.05$).

A randomised, multicentre, open-label, five-way crossover study assessed patient preference for sumatriptan 50 mg and 100 mg, naratriptan 2.5 mg, zolmitriptan 2.5 mg and rizatriptan 10

mg (*n* = 372). [11, 31] Patients were randomised to treat one migraine attack with each of the five triptans in sequence, in a total of 119 possible treatment sequences. Patients assessed which triptan they preferred at the end of the study. The results showed that sumatriptan 100 mg was preferred by 33% of patients, significantly higher than the random preference rate of 20% ($p<0.001$). Preference rates for sumatriptan 50 mg, naratriptan, rizatriptan, and zolmitriptan were not significantly higher than the random preference rate. The patients' primary reason for preferring a medication was 'best relief of migraine pain', and the treatment that patients preferred corresponded to the medication that was most likely to confer for them a pain-free response 2 hours postdose.

A second small study (*n* = 28) conducted in clinical practice compared patient preference to sumatriptan 50 mg or 100 mg, naratriptan 2.5 mg or 5 mg and zolmitriptan 2.5 mg or 5 mg. [32] Patients were randomised to treat two attacks with each of the triptans. At the end of the study, 50% of patients preferred sumatriptan, 32% naratriptan and 18% zolmitriptan.

A retrospective audit of patient data from a secondary care headache clinic (*n* = 176) investigated the pattern of preference for and switching between sumatriptan, naratriptan and zolmitriptan in clinical practice. [33] Most patients (68%) had switched between triptans at least once in the previous 2 years. No triptan showed a significantly higher level of preference, although there were some gender differences. Women tended to prefer zolmitriptan over the other two triptans and switched between triptans more often than men. Most patients reporting migraine with aura used sumatriptan to treat their attacks.

In a retrospective review of 386 patients who used subcutaneous sumatriptan and were switched to a different triptan or formulation, 19.5% returned to subcutaneous sumatriptan. [34] For the other triptans/formulations, the percentages for returning were: sumatriptan 25 mg, 7.8%; sumatriptan 50 or 100 mg, 42.3%; sumatriptan nasal spray, 17.7%; zolmitriptan, 17.6%; rizatriptan, 16.5%; naratriptan: 9.4%. Of those who used more than three triptans or formulations, the last triptan used was: sumatriptan, 29.5%; zolmitriptan, 31.8%; rizatriptan, 25.0%; naratriptan, 12.5%. Different formulations of sumatriptan were used by 129 subjects (33.4%). Of the patients who used sumatriptan as the first triptan and switched to other triptans, sumatriptan was also the last triptan used by 53.8% of them. This study involved asymmetries of formulations in assessing patient preferences and reasons for switching behaviours.

A Swedish study has investigated migraine patients' preference for zolmitriptan 5 mg nasal spray compared with that to oral triptans in a realistic clinical practice setting (*n* = 83). [35] Patients, 96% of whom were currently using a triptan (usually oral), were invited to try zolmitriptan nasal spray 5 mg for up to six migraine attacks, to see if efficacy could be improved. Initial data indicated that 76% of patients wanted to continue to use zolmitriptan nasal spray. The main reasons for this preference were a fast onset of action, a lack of adverse events and only needing to take a single dose. The first reason may be intrinsic to a nasal spray compared to a tablet; the other two reasons should not have been impacted by asymmetry of compared formulations.

Studies comparing different formulations of the same triptan

Sumatriptan, zolmitriptan and rizatriptan are available in different formulations, and a small number of studies have compared patient preference for different formulations or doses of these drugs.

Sumatriptan

An open, multicentre, randomised, crossover study with an optional open, parallel-group extension (*n* = 385) investigated the efficacy, safety and patient preference for oral sumatriptan 100 mg and subcutaneous sumatriptan 6 mg formulations. [36] Patient

preference for the subcutaneous formulation more than doubled from the pre-treatment phase to the end of the crossover period in those patients previously naïve to sumatriptan. During the optional parallel-group phase of the study, 38% of patients chose to use both sumatriptan formulations, treating some attacks with subcutaneous sumatriptan and some with oral sumatriptan. The main reason for choosing subcutaneous sumatriptan was speed of relief, while convenience was the major reason for choosing the tablet.

An open, randomised, three-attack crossover study compared patient opinions of oral sumatriptan 100 mg with subcutaneous sumatriptan 6 mg (*n* = 124). [37] At the end of the study, patient opinion was more often positive after subcutaneous sumatriptan than after oral sumatriptan. Subcutaneous sumatriptan was significantly more effective than oral sumatriptan, but more adverse events were reported following the subcutaneous formulation.

A telephone survey was conducted in 707 patients who had used sumatriptan tablets and/or injection long-term for migraine in clinical practice. [38] Results showed that more patients preferred the tablets over the injection, but that more patients reported that the injection was the most effective formulation. The most frequently given reasons for the injection being superior were efficacy and speed of action. The most frequently given reasons for the tablet being superior were fewer side effects and lack of experience with other formulations. Most patients (94%) reported that sumatriptan was superior to their previous non-triptan therapies.

An open, randomised, crossover study compared patient preference for sumatriptan 50 mg tablets and sumatriptan 20 mg nasal spray. [39] Patients, who were naïve to both formulations, preferred both formulations approximately equally (47% for tablets and 53% for nasal spray). Patients preferred the nasal spray for its fast onset of action and the tablets for their convenience.

Rizatriptan

Patients (*n* = 367) taking part in a clinical study of rizatriptan were allowed to continue open-label treatment with both the film-coated tablet and ODT formulations for a 6-month period. [40] At the end of the study, 51.2% preferred the ODT and 48.8% the film-coated tablet. Although individual patients had strong reasons for preferring one formulation over the other, no group preferences were detected for the individual formulations.

Comparing the different doses of oral sumatriptan

A multinational, randomised, double-blind, crossover, 8-week study was conducted to assess patient dose preference, efficacy and tolerability for oral sumatriptan 25 mg, 50 mg and 100 mg in the acute treatment of migraine. [41] Patients (*n* = 257) were randomised to treat three migraine attacks, using a different dose for each. At the end of the study, 34.6% of patients preferred the 100 mg dose, 30.4% the 50 mg, 20.6% the 25 mg dose and 12.8% expressed no preference. Efficacy and speed of action were the two main reasons given for preferring the higher doses. However, adverse events were rarely given as a reason for preferring the lower doses of sumatriptan. Although the 50 mg dose has been shown to have the optimal benefit: risk ratio of the formulations, [42] some patients clearly preferred a higher dose.

Discussion

Patients' assessments of their preference for, and satisfaction with, their migraine treatments may be measures of clinical efficacy relevant to real-life clinical practice, taking into account both efficacy and tolerability. We now have considerable clinical data on patient preference, allowing the evaluation of the triptans and other acute migraine treatments.

All studies of preference [14–19, 22] and satisfaction [17, 19, 20, 21] for triptans compared with patients' usual non-triptan medications have demonstrated the superiority of the triptans. Patients' most commonly given reasons for preferring triptans were effective relief, speed of

relief, restored ability to function and fewer side effects. [16, 18, 19, 22] These are significant results, as some controlled clinical trials have shown that sumatriptan was not superior to rapid-release tolfenamic acid, [43] paracetamol/domperidone, [44] aspirin/metoclopramide, [45, 46] isometheptene/paracetamol/dichlorphenazone, [47] and paracetamol/aspirin/caffeine. [48] In contrast, a controlled clinical trial showed that oral sumatriptan 100 mg was significantly superior to oral ergotamine plus caffeine. [49] These results indicate that patient preference may be a more sensitive and valid measure of efficacy and clinical utility than conventional clinical trial endpoints.

Relatively few clinical trials have directly compared patients' preference for individual triptans, and all included sumatriptan. [12, 20, 23, 27] Data from these four studies were broadly similar, (Table 3) some patients preferring one triptan and some the other, even though fewer patients preferred sumatriptan to the comparator triptan in all cases. The main reason for preference was a faster onset of action. Other reasons given included a longer duration of effect and fewer adverse events. Each of these reasons was given for all the triptans. The data in these preference studies were broadly similar to those from randomised, double-blind comparator studies between these triptans. [50, 51]

Five further studies compared patient preference between multiple triptans. Two studies showed that more patients preferred oral sumatriptan 50 mg or 100 mg than other oral triptans. [11, 31, 32] Two studies showed few differences between several oral triptans, [33, 34] and a further study showed that patients preferred zolmitriptan nasal spray over oral triptans. [35] Different study designs and the patients' initial triptan may have biased the results from these studies.

Patient satisfaction data from double-blind, controlled clinical trials showed similar trends to those reported above for patient preference. Patients were equally satisfied with the efficacy of sumatriptan 100 mg and rizatriptan 10 mg, [24, 25] sumatriptan 100 mg and eletriptan 20 mg and 40 mg [28] and sumatriptan 50 mg and almotriptan 12.5 mg. [29] In a review of five clinical trials, the proportions of patients preferring sumatriptan, zolmitriptan and rizatriptan were not markedly different from each other. [30] Patients were also able to express preferences between different formulations of the triptans, [36–38, 40] although these data are biased due to the asymmetry of the treatment groups. Patients could even distinguish between different doses of oral sumatriptan. [41]

There are several limitations to the available analyses of patient preference and satisfaction. Many of the studies are published only as abstracts, and much of the desired data is not recorded. As secondary endpoints, assessments of patient preference were not subjected to rigorous statistical testing, as were the study primary endpoints. The preference and satisfaction studies were open-label and bias could therefore occur. Patients may have had previous access to one or more of the drugs being investigated. It is interesting that in all cases, the triptan preferred most was that of the company sponsoring the study. In the double-blind, controlled studies analysed, the patient preference/satisfaction endpoint was a secondary or *post hoc* endpoint, and may therefore not have been powered appropriately. Studies involving different formulations are biased by the asymmetries previously discussed in this article. The solution is to conduct double-blind, controlled studies with patient preference as the primary endpoint, and to investigate which set of triptans in which order, scheme, dosage and formulation leads to the fastest effectiveness in a particular patient. In such a design, non-responders are switched to another triptan, dosage or formulation to reach (in theory) 100% effectiveness. Such a naturalistic design would best serve the needs of the clinician who is interested in the best fit of a patient with a triptan.

Clinical implications

When given the opportunity, most migraine patients are able to distinguish between triptans and non-triptan acute therapies for migraine, and between the individual oral triptans. This

sophisticated individual preference is not usually seen in controlled parallel design clinical trials, where differences between the oral triptans, when statistically present, are small. [4] Unfortunately for the physician, patients have very individual preferences for triptans that are not predictable in advance. The problem therefore, is to investigate the fastest route to detect the right match between patient and triptan (in terms of dose, order of switching and formulation). Patients clearly prefer triptans to simple and combination analgesics and ergotamine, and thus triptans should be a first-line alternative in most migraine patients. [52] In assessing individual triptans in clinical practice, patients are looking for a therapy that provides rapid and effective relief of the migraine. [18, 19, 22, 38] and are willing to switch between triptans to achieve this goal. [33]

Patient preference is clearly a sensitive and valid overall measure of the clinical profile of triptans, encompassing both efficacy and tolerability. In reviewing migraine patients, the physician should elicit their preference for, and satisfaction with, their current medication before making further treatment decisions. There is no need to change the patients' medication if they are satisfied with their current medications and prefer them to those used previously. When the patient's medication is changed, at review the physician should ask about the patient's preference for the new medication. In addition, physicians should also take into consideration patients' preference for a specific delivery system. For patients with attacks of varying severity and/or lifestyle needs, more than one formulation may be appropriate.

In conclusion, patient preference is a sensitive and valid clinical trial endpoint and physicians should consider using it when reviewing the efficacy of acute migraine medications.

Acknowledgements
The statistical analysis for the meta-analysis of sumatriptan *versus* normal acute medications [14] was carried out by Leanne Rice of Statistics and Data Management Department, Glaxo Laboratories UK Ltd, Stockley Park West, Uxbridge, UB11 1BT, UK.

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3.3

A general practice study on the prevalence of headache, depression and bodily pain, and the disability associated with headaches occurring inside and outside the menstrual period in migraine sufferers*

Abstract

Objectives: This study investigated the prevalence of headache, depression and bodily pain in women attending a UK general practice. The disability associated with migraine and other headache attacks occurring during and outside the menstrual period was assessed in those women with migraine.
Methods: 1,434 of 3,470 female patients (41.3%) aged 14–50 years registered at a UK general practice completed two questionnaires. The first questionnaire assessed the point prevalence of headache and bodily pain, and the 5-year prevalence of depression in the total population. The second questionnaire assessed the disability of all headaches over a 2-month period (to capture a complete menstrual cycle) for patients reporting migraine who were still menstruating. Disability was assessed as the time lost and time spent at less than 50% productivity in normal activities due to headache, and analyzed as rank sums using the Mann-Whitney U Test.
Results: The first part of the study showed that the prevalence of headache (66.1%), depression (55.4%) and bodily pain (40.6%) were high in this population of women. In the second part of the study, 30 migraine patients who were still menstruating (11.1% of those eligible) reported 89 migraine and 114 non-migraine headache episodes. For migraine, the rank order of time at less than 50% productivity was significantly greater for attacks taking place inside the menstrual period than for those occurring outside the menstrual period (p=0.01). For non-migraine headaches, the time lost appeared to be numerically greater for attacks taking place outside the menstrual period than for those occurring inside the menstrual period, and the comparison approached significance (p=0.06).
Conclusions: The patients reported a high prevalence of headache, depression and bodily pain**.** For migraine sufferers, migraine attacks that took place during the menstrual period tended to be more disabling than those taking place outside the menstrual period, but the opposite was true for non-migraine headache.

** Edited from the full published paper: Dowson AJ, Kilminster SG, Salt R, Clark M, Bundy MJ. Disability associated with headaches occurring inside and outside the menstrual period in those with migraine: A general practice study. Headache 2005;45:274–82. Additional statistical analyses were conducted by Professor Jan Passchier.*

Introduction

Headache and depression are two of the commonest conditions that the primary care physician has to deal with. Most people suffer from headaches, usually tension-type headaches (TTH), migraine or chronic daily headache (CDH). TTH affects over 50% of the general population,[1] migraine about 12%[2] and CDH about 5%.[3] Major depression is reported to affect up to 12% of the general population.[4] Migraine,[5] CDH[6] and depression[4] are all disabling conditions to the patient and cause major societal burdens due to the associated high direct medical costs of care and indirect costs of lost work productivity.[7,8]

Although definitive criteria are not available, menstrually-associated migraine attacks tend to be defined today as those that begin during the time period from the day prior to the start of menstruation and Day 2 of menstruation.[9] Such attacks are common, and more than 50% of women with migraine report an association between migraine and menstruation, [10] although in most cases they also have migraine attacks outside the menstrual period. A population-based study conducted in the Netherlands provided a prevalence rate of 3% for menstrual migraine.[11] Studies indicate that menstrually-associated migraine attacks are the result of estrogen withdrawal in the late luteal phase of the normal menstrual cycle, but other factors such as prostaglandin release have also been implicated.[9] Menstrually-associated migraine attacks are treated with standard acute therapies and with specific prophylactic treatments such as estrogen supplements.[9] It used to be widely considered that menstrually-associated migraine attacks were more severe and less responsive to treatment than non-menstrually-associated attacks,[9,12] but these suppositions have now been disputed. A population-based epidemiologic study indicated that menstrually-associated migraine attacks were slightly more painful, but not more disabling, than attacks occurring at other times in the cycle.[13] Similar results have been reported for TTH attacks occurring inside and outside the menstrual period.[14] A small study with sumatriptan indicated that the drug was less effective for menstrually-associated than for non-menstrually-associated migraine attacks (56% *versus* 81% of patients reporting relief of their migraine headache 4 hours after treatment, when treated during and outside the menstrual period, respectively).[15] However, more recent studies have indicated that triptan drug[16] and nondrug treatments[17] are equally effective in treating migraine attacks occurring inside and outside the menstrual period. In contrast, some recent studies indicate that migraine attacks occurring during the menstrual period tend to be more frequent, more severe, of longer duration and more resistant to treatment than those occurring at other times of the month.[11,18] In clinical practice, menstrually-associated migraine attacks tend to be treated in the same way as non-menstrually-associated attacks.

This study was set up to investigate two questions related to women's health issues:

1. What is the prevalence and severity of headache, depression and bodily pain?
2. Are migraine and other headache attacks occurring during the menstrual period more or less disabling than those occurring outside it in patients with migraine?

The study extends previous research[13] into primary care clinical practice. We recorded headache characteristics and the disability caused by migraine and other headache attacks taking place inside and outside the menstrual period. Disability was assessed by recording the time lost from normal activities and the time spent at less than 50% of normal capabilities due to headache. Recent research has shown that these assessments form a reliable and accurate measure of headache-related disability, when incorporated into the Migraine Disability Assessment (MIDAS) Questionnaire.[19]

Patients and methods

Patients

All non-hysterectomized women aged 14–50 years at a health centre in Cranleigh, Surrey, UK, were invited to take part in a two-part study. The study was approved by the local

investigational review board, the South West Surrey Local Ethics Committee, and all patients who took part in the study provided their written informed consent to participate.

Study design

Part 1

All patients were asked to complete and return by mail a questionnaire assessing their headaches, depression and bodily pain severity (Appendix 1). The point prevalence and severity of headache and bodily pain and the 5-year prevalence and severity of depression were assessed and patients with frequent headaches, and disabling and non-disabling intermittent headaches identified using the questionnaire.

Part 2

Patients who had disabling intermittent headaches and were still having menstrual periods were asked to complete another questionnaire assessing the disability of all headaches that occurred inside and outside the menstrual window. Patients were monitored over a 2-month period, to ensure that a complete menstrual cycle was covered for all patients.

Questionnaires

Headache, depression and bodily pain questionnaire

The questionnaire was developed by the study investigators (Drs Dowson, Kilminster, Clark and Bundy). Three questions (Questions 1–3) assessed headache, five assessed depression (Questions 5–9) and four assessed bodily pain severity (Questions 10–13).

The answers to Questions 2 (‘How often do they [headaches] occur?’) and 3 (‘Do the headaches interfere with your ability to perform normal daily activities?’) were used to categorize the patients’ headache. Patients who answered ‘a’ to Question 2, with headaches on most days in the month, were categorized as having frequent headaches. Those who answered ‘b’, ‘c’ or ‘d’ to Question 2, with up to four or more headaches per month, were categorized with non-disabling intermittent headache if the headaches did not interfere with their ability to perform normal activities (Question 3a) and with disabling intermittent headache if the headaches did interfere with these activities (Question 3b).

The patients’ degree of depression was assessed arbitrarily from Questions 5, 6 and 7, covering sleep disturbance, mood disturbance and suicidal ideation. Patients who answered ‘no’ to all questions were classified as not being depressed. Those who answered ‘yes’ to one, two and three of these questions were classified as having mild, moderate and severe depression, respectively. Depression is therefore here conceived as a continuous variable. In addition, patients who answered ‘yes’ to Question 9 (defined as those who had received treatment from a doctor for sleep disturbance, mood disturbance or suicidal ideation) were classified as having at least moderate depression, depending on their answers to Questions 5, 6 and 7 (i.e. none and one ‘yes’ answer = moderate depression; two and three ‘yes’ answers = severe depression).

Pain severity in any part of the body was assessed from Questions 10, 12 and 13. Patients who responded ‘yes’ to Question 10 but ‘no’ to Questions 12 and 13 were assessed as having mild pain. Those who responded ‘yes’ to Questions 10 and 12 but ‘no’ to Question 13 were assessed as having moderate pain. Those who responded ‘yes’ to Questions 10, 12 and 13 were assessed as having severe pain. Question 11 was not counted, but provided information designed to be useful to the physician.

Menstrual headache questionnaire

Patients with disabling intermittent headache in Part 1 of the study who were still menstruating were eligible to complete Part 2. Patients reported all their headaches over a 2-month period, using the menstrual headache questionnaire that was mailed to them (Appendix 2). The study investigators developed the menstrual headache questionnaire,

based on the International Headache Society (IHS) diagnostic criteria pertaining at the time.[18] Patients prospectively recorded their menstrual status, time of onset and resolution of the headaches and other symptoms (self-selected), headache severity, presence of non-headache symptoms, time lost from normal activities and the further time spent at less than 50% of normal capabilities, use of contraceptives and other drugs and any present pre-menstrual symptoms.

Headaches were diagnosed by the study physicians as migraine or non-migraine using the information recorded by the patients in the questionnaire, using their clinical judgment in conjunction with reference to the relevant IHS diagnostic criteria.[18] Headaches were further subdivided into those that started inside and outside the menstrual period. Data were analyzed as the number of headache episodes, the time lost from normal activity (total time and mean time per attack) and the additional time at less than 50% of normal capability (total time and mean time per attack) for migraine and non-migraine headaches.

Endpoints and analyses

Part 1

The primary endpoint was the prevalence and severity of headaches, depression and bodily pain. Results were recorded as descriptive statistics only; the number and percentage of patients with total, mild, moderate or severe symptoms, and subdivided by the age of the patient. The relationship between age and headache prevalence was analyzed using Chi-square tests for independent samples. Similar analyses for depression and bodily pain were not carried out given the small differences between the data samples.

Part 2

The primary endpoint was the disability experienced by the patients, assessed as time lost from daily activities. The other components of the questionnaire were recorded, but data are not presented here. Non-parametric rank testing with the Mann-Whitney U Test for related samples was used to analyze the time lost and time at less than 50% of normal capacity due to the migraine and non-migraine headaches, comparing attacks from inside and outside the menstrual period. The level of significance was set at p=0.05.

Results

Patient disposition

Of the 3,470 female patients in the practice who were sent the initial questionnaire, 1,434 (41.3%) completed and returned it (Table 1). Of these, all but five patients were aged between 17 and 54 years. Approximately equal proportions of patients aged 17–24, 25–34, 35–44 and 45–54 years completed the questionnaire. The proportions of patients in these age groups were similar to those in the total population in the practice.

Table 1. Patient demography. Number (and percentage) of women in the general practice who took part in the study.

	Number of patients (%)					
	14–16y	17–24y	25–34y	35–44y	45–54y	Total
Patients taking part in study	5 (0.3)	234 (16.3)	305 (21.3)	498 (34.7)	392 (27.3)	1434 (100)
Patients in the practice	79 (2.3)	609 (17.6)	744 (21.7)	979 (28.2)	1059 (30.5)	3470 (100)

Prevalence of headache, depression and bodily pain

Headache

Overall, 948 patients (66.1%) completing the initial questionnaire reported current headache (Table 2). A total of 62 patients (4.3%) reported headache on most days and were

categorized as having frequent headache. Two hundred and seventy one patients (18.9%) had headache episodes up to more than four times a month that interfered with their ability to perform daily activities, and were categorized with disabling intermittent headache. A total of 615 patients (42.9%) had headache episodes up to more than four times a month that did not interfere with their ability to perform daily activities, and were categorized with non-disabling intermittent headache. Similar proportions of patients aged 17–24, 25–34, 35–44 and 45–54 years reported any headache, and disabling and non-disabling intermittent headaches. However, frequent headaches were reported significantly more often by patients aged 17–24 years than by older patients (Chi-square (3) = 22.9, $p < 0.001$).

Table 2. Headache. Number (and percentage) of women in the general practice who reported any headache, frequent headaches, disabling intermittent headaches** and non-disabling intermittent headaches***.*

	Number of patients (%)				
	17–24y	25–34y	35–44y	45–54y	Total
Patients reporting any headache	158 (67.5)	189 (62.0)	338 (67.9)	263 (67.1)	948 (66.1)
Patients reporting frequent headaches*	24 (10.3)	11 (3.6)	15 (3.0)	12 (3.1)	62 (4.3)
Patients reporting disabling intermittent headaches**	38 (16.2)	60 (19.7)	85 (17.1)	88 (22.4)	271 (18.9)
Patients reporting non-disabling intermittent headaches***	96 (41.0)	118 (38.7)	238 (47.8)	163 (41.6)	615 (42.9)
Patients taking part in the study	234	305	498	392	1434

*Putatively diagnosed as CDH.[21]
**Putatively diagnosed as migraine.[21,23]
***Putatively diagnosed as TTH.[21,23]

Depression
Overall, 794 patients (55.4%) completing the initial questionnaire reported the defined depression symptoms in the previous 5 years. Similar proportions of patients aged 17–24, 25–34, 35–44 and 45–54 years reported depression (Table 3). Approximately 20% of all patients reported mild or moderate depression, with 15.3% reporting severe symptoms. The distribution of mild, moderate and severe depression was similar among patients aged 17–24, 25–34, 35–44 and 45–54 years.

Table 3. Depression. Number (and percentage) of women in the general practice who reported mild, moderate and severe depression.

	Number of patients (%)				
	17–24y	25–34y	35–44y	45–54y	Total
Patients reporting depression (mild, moderate or severe)	140 (59.8)	178 (58.4)	265 (53.2)	210 (53.6)	794 (55.4)
Patients reporting mild depression	51 (21.8)	72 (23.6)	101 (20.3)	67 (17.1)	292 (20.4)
Patients reporting moderate depression	52 (22.2)	60 (19.7)	92 (18.5)	78 (19.9)	282 (19.7)
Patients reporting severe depression	37 (15.8)	46 (15.1)	72 (14.5)	65 (16.6)	220 (15.3)
Patients taking part in the study	234	305	498	392	1434

Bodily pain severity
Overall, 40.6% of patients completing the initial questionnaire reported current pain symptoms in any part of the body, with the incidence generally increasing with increasing age (Table 4). However, more patients aged 17–24 years reported bodily pain than those

aged 25–34 years, with the excess being accounted for by reports of mild pain. Thirteen percent of all patients reported mild pain, 5.9% moderate pain and 21.7% severe pain. While the incidence of mild and moderate bodily pain was generally similar among the age groups, the incidence of severe pain increased with increasing age, from 15.8% for those aged 17–24 years to 28.6% for those aged 45–54 years.

Table 4. Bodily pain severity. Number (and percentage) of women in the general practice who reported mild, moderate and severe pain in any part of the body.

	Number of patients (%)				
	17–24y	25–34y	35–44y	45–54y	Total
Patients reporting pain (mild, moderate or severe)	92 (39.3)	94 (30.8)	207 (41.6)	187 (47.7)	582 (40.6)
Patients reporting mild pain	42 (17.9)	31 (10.2)	62 (12.4)	49 (12.5)	186 (13.0)
Patients reporting moderate pain	13 (5.6)	17 (5.6)	29 (5.8)	26 (6.6)	85 (5.9)
Patients reporting severe pain	37 (15.8)	46 (15.1)	116 (23.3)	112 (28.6)	311 (21.7)
Patients taking part in the study	234	305	498	392	1434

Disability of headaches occurring inside and outside menstruation

Thirty of the 271 patients (11.1%) with disabling intermittent headache in the first part of the study completed the menstrual headache questionnaire. They detailed a total of 203 headaches that started inside and outside their menstrual periods during the 2-month study period. Patients reported slightly fewer migraine attacks (89) than non-migraine headaches (114). Migraine attacks were approximately equally frequent inside (47 attacks) and outside (42 attacks) the menstrual period. However, non-migraine headache was reported about three times more often outside the menstrual period (85 attacks) than inside it (29 attacks).

Meaningful mean or median values could not be calculated for the time lost and time at less than 50% productivity data, due to the data being not normally distributed. Floor effects were observed as many values were zero. For migraine, the rank order of time lost was numerically but non-significantly greater for attacks taking place inside the menstrual period than for those occurring outside the menstrual period (1,344.5 *versus* 1070.5, p=0.23, Figure 1). The rank order of time at less than 50% productivity was significantly greater for attacks taking place inside the menstrual period than for those occurring outside the menstrual period (1,453.6 *versus* 961.5, p=0.01, Figure 1). For non-migraine headaches, the rank order of time lost was marginally significantly greater for attacks taking place outside the menstrual period than for those occurring inside the menstrual period (5,009.0 *versus* 1,432.0, p=0.06, Figure 2). The rank order of time at less than 50% productivity was numerically but not significantly greater for attacks taking place outside the menstrual period than for those occurring inside the menstrual period (4,902.5 *versus* 1,538.5, p=0.37, Figure 2). The rank order of data for migraine headaches during menstruation was similar to that of non-migraine headache, for both the time lost and time at <50% productivity analyses (Figures 1 and 2).

Figure 1. Time lost and time at less than 50% productivity per attack for migraine attacks occurring inside and outside the menstrual period for patients with migraine (n = 30): analysis of rank sums.

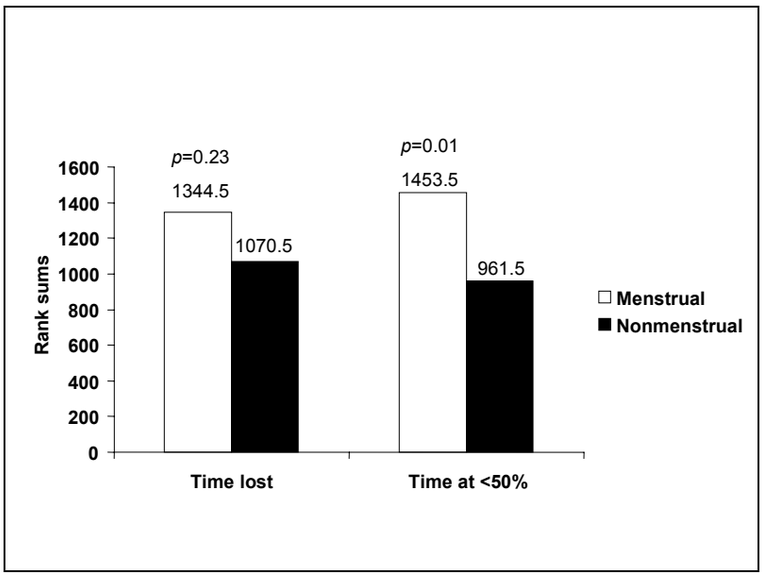
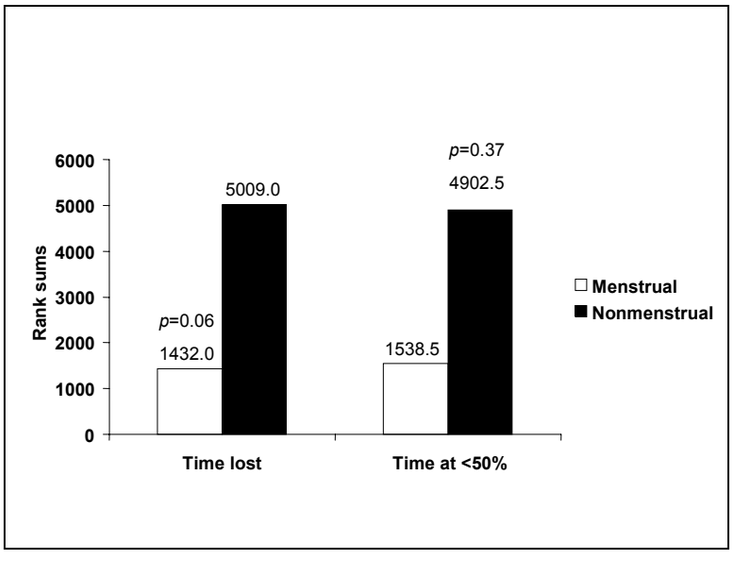


Figure 2. Time lost and time at less than 50% productivity per attack for non-migraine headache attacks occurring inside and outside the menstrual period for patients with migraine (n = 30): analysis of rank sums.



Discussion

This study provides a snapshot of headache, depression and bodily pain in women attending a primary care clinical practice. While the data are preliminary, they provide an insight into clinical issues important to primary care, and suggest future avenues of research. The patients recruited to the study came from a single UK primary care practice, with a responder rate of 41.3% completing the initial questionnaire. This is a relatively high response rate; surveys conducted with the general public more typically elicit a response rate of about 10%. Respondents were approximately equally distributed among the different age groups.

The patients who completed the initial questionnaire reported high levels of headache, depression and bodily pain. About two-thirds of patients reported any headache, with 4.3% being categorized with frequent headaches, 18.9% with disabling intermittent headache and 42.9% with non-disabling intermittent headache. While no formal diagnoses were conducted, there are good reasons for categorizing patients with frequent headaches as having CDH, those with disabling intermittent headaches as having migraine and those with non-disabling intermittent headaches as having TTH. CDH is often defined as daily, or near-daily headache.[21] Results from the Spectrum and Landmark Studies indicate that a default diagnosis of migraine can be given to patients with disabling episodic headaches, and non-disabling episodic headaches are usually TTH.[22,23] Support for this comes from the relative prevalence of putative CDH, migraine and TTH in this study, which were similar to those reported for women in previous population-based studies (1-year prevalence: TTH = 86%;[1] migraine = 18%;[2] CDH approximately 4–5%[3]), and were generally consistent across all age groups.

Over 50% of the patients reported symptoms indicative of depression, with 15.3% reporting severe depression. The prevalence of depression was remarkably similar for all age groups and severity levels, but was higher than has been previously reported for the general population (about 12%[4]). The levels of reported bodily pain were also high, with 40.6% of patients reporting pain and 21.7% reporting severe pain. Again, all age groups reported a high prevalence of bodily pain, but reporting of pain overall and severe pain increased with increasing age of the patient. Overall, these results indicate that headache, depression and bodily pain are common in the general adult female population.

A low proportion of patients (11.1%) identified with migraine (disabling intermittent headache) and still having periods responded to the menstrual headache questionnaire. The reasons for this relatively poor response are not clear, although it is well known that less than half of migraine sufferers consult with their primary care physicians for care.[19] In addition, patients find it difficult to complete a diary over a period longer than a few weeks.[24] The total number of headache episodes reported was also modest (89 migraine and 114 non-migraine headache episodes). However, there were some strong trends in the results from the questionnaire that have implications for clinical practice.

Migraine headaches were relatively more frequent inside than outside the migraine attack, as shown by the roughly equal numbers of attacks in the approximately 1 week of menstruation and the 3 weeks outside it. In contrast, non-migraine headaches were approximately equally distributed inside and outside the menstrual period.

Migraine attacks that occurred inside the menstrual period scored numerically higher than those occurring outside the menstrual period in terms of rank sums of time lost and time at less than 50% productivity. These results are in line with a recent study indicating that menstrually-associated migraine attacks were slightly more painful than non-menstrually-associated ones.[13] However, the differences between menstrually-associated and non-menstrually associated migraine attacks was not high in the present study, and significance was only reported for the analysis of time at less than 50% productivity. Results for non-migraine headache were the opposite of those for migraine, with those occurring outside the menstrual period scoring numerically, but not significantly, higher than those occurring inside the menstrual period in terms of the rank sums of time lost and time at less than 50% productivity. Recent data from the Landmark and Spectrum studies indicate that all headaches experienced by migraine sufferers with disabling headaches are sensitive to triptans and may be part of the overall migraine process.[23,25] This raises the possibility that both the migraine and non-migraine headaches analyzed in this part of the study were essentially migrainous in character, at least in this group of patients with disabling headache.

Assessments of disability are important measures, and not only in terms of the response to headache treatments. They are key measures in aiding communication between patients and physicians,[19] assessing headache patients' illness severity and treatment needs,[17] and patients' subjective perceptions of migraine and CDH management.[26]

Study limitations and suggestions for future research

Part 1

The questionnaires used in the study were not validated tools, but were devised by the investigators to be simple to use and potentially applicable to primary care clinical practice. The questionnaires were not tested for reliability or validity, and additional studies would be required for this. Headache subtypes could be diagnosed from the initial questionnaire, as described previously in this paper. While the diagnoses were not tested for accuracy, they follow criteria developed by the IHS,[20,21] and are therefore likely to be valid. However, simple diagnostic screening questionnaires for headache have recently been developed and validated,[27,28] and may therefore be more preferable to use. The initial questionnaire also did not provide a clear diagnosis for depression, but simply used clinical markers to guide the physician. Again, it would probably be preferable to use a validated depression questionnaire in future studies.

The prevalence study design was perhaps not optimal. Additional items that should have been taken into account included defining the sample in relationship to the population under study, random sampling, defining an acceptable response rate (>50%), and conducting a non-response analysis. Despite this, the prevalence of the headache subtypes was close to expected values, although depression was probably over-estimated. There was the possibility of the responders being a self-selecting population with significant problems.

Part 2

The menstrual headache questionnaire was based on the IHS diagnostic criteria[20] and items contained in the MIDAS questionnaire.[19] Thus, while this questionnaire was also not validated, it contained items with proven reliability and validity. However, the questionnaire should be tested for these properties if it is used again.

Some methodological issues were raised by the analyses that have implications for the design of future studies. The data were confounded by the fact that some of the events were repeatedly measured in individual patients, and that some patients only had one type of headache. A much larger sample of patients would be necessary to allow both within and between patient group comparisons. In the present study, data were analyzed only between the groups for 30 patients experiencing 203 headache attacks. The results should therefore be taken with caution. However, non-parametric testing with the Mann-Whitney U Test showed one significant and one marginally significant result from only four analyses, which indicates that the results were unlikely to have arisen by chance. Analysis of means or medians was not a useful measure in the present study because the data were not normally distributed (in fact they were seriously skewed). Many headache attacks scored zero on the two analyses, leading to floor effects being observed. Such floor effects have been reported with use of the MIDAS Questionnaire, on which the analyses were based.[29] Future studies may benefit from using assessments of headache impact which provide a normal distribution of results, such as the Headache Impact Test[30] or the Short Pain Inventory.[31]

Studies of headache in general practice are urgently required, as clinical experience does not always follow data from controlled clinical trials.[32] We encourage the use of validated instruments in these studies, which have become available since the inception of the present study. However, despite the methodological deficiencies in the present study, the clinical importance of headache, depression and bodily pain were emphasized, and information was gleaned on the disability associated with migraine and non-migraine headaches inside and outside the menstrual period. We look forward to further studies on this important topic.

Conclusions

This study showed that headache, depression and bodily pain were common in women aged 14–50 years registered at a UK general practice. For migraine sufferers, migraine attacks that took place during the menstrual period tended to be more disabling than those taking place outside the menstrual period, but the opposite was true for non-migraine headache. These results provide a snapshot of headache, depression and bodily pain in a subset of women attending a UK primary care practice.

Acknowledgements

The authors wish to thank the staff of Cranleigh Health Centre for their assistance during this study, and the patients who took part. The study was funded by a grant from Merck, Sharp and Dohme Research Limited.

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Appendix 1. The headache, depression and bodily pain questionnaire

Please circle the answers that you feel apply to you

1. Do you suffer from headaches?
    a. No (go to question 4)
    b. Yes

2. How often do they occur?
    a. Most days in the month
    b. More than four times a month
    c. One to four times a month
    d. Less than once a month

3. Do the headaches interfere with your ability to perform normal daily activities, i.e. Do you have to stop doing things you would normally do?
    a. No
    b. Yes

4. Do you have periods?
    a. No
    b. Yes

5. In the last five years have you ever suffered from sleep disturbance, such as waking in the early hours of the morning regularly or having difficulty getting off to sleep, that has lasted for more than two weeks at a time?
    a. No
    b. Yes

6. In the last five years have you ever had an episode of low mood, poor concentration, disinterest or tearfulness that has gone on for more than two weeks?
    a. No
    b. Yes

7. In the last five years have you ever had feelings of worthlessness, guilt or suicidal ideas that have persisted for more than two weeks?
    a. No
    b. Yes

8. If you answered Yes to any of questions 5, 6 or 7, did you discuss these feelings with your doctor?
    a. No
    b. Yes

9. If you saw your doctor, did you receive any treatment?
    a. No
    b. Yes

10. Do you suffer from any other type of pain (other than headaches) that occurs regularly?
    a. No
    b. Yes

11. Where do you feel the pain and when you get it how long does it last?
    Site of pain:-

Duration of pain:-

12. Have you seen a doctor about this pain:
    a. No
    b. Yes

13. Have you ever received treatment for this pain?
    a. No
    b. Yes

Thank you for taking the time to answer these questions for us. If you answered Yes to many of these questions, and especially questions 5, 6 and 7, it may suggest that you are suffering from one of these conditions. If you have not discussed these symptoms with your doctor we suggest that you contact him/her at the Health Centre and he/she may be able to offer you help with your symptoms.

Appendix 2. The menstrual headache questionnaire

Date	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**etc**
Menstrual bleeding										
Time of onset - first symptom (specify) - headache										
Time of resolution - headache - last symptom (specify)										
Maximum intensity of headache (mild, moderate or severe)										
Other symptoms (specify)										
Time lost from normal activity (hours)										
Time spent at less than 50% of normal activity (hours)										
Drugs taken										
Contraceptive drug (if any)										
Pre-menstrual symptoms or intercurrent illness (if any)										

3.4

Emotional function with tension-type headache, migraine and chronic daily headache*

Abstract

Background: The Short Pain Inventory (SPI©) is a prospective, validated questionnaire that assesses pain severity and mood disturbances for a variety of conditions.
Objectives: In this prospective, within-group, comparative study, the SPI was used to assess how the mood disturbances and coping abilities change over time in patients with tension-type headache (TTH), migraine and chronic daily headache (CDH) attending a primary care headache centre. The healthcare resource utilisation of these patients was also assessed retrospectively.
Methods: Patients (*n* = 75) were diagnosed with episodic TTH, migraine or CDH, and completed a healthcare utilisation questionnaire. Patients completed the SPI 10 times over a 7-day period, starting 1 hour after the onset of their next headache. The SPI data were analysed statistically as Z scores and coping Z scores for the Total Pain Disturbance, Total Mood Disturbance, and individual sub-scores for sedation, social interaction, sadness, anxiety and anger. Data from the healthcare resource utilisation questionnaire were analysed as descriptive statistics.
Results: All 75 patients completed the healthcare utilisation questionnaire and 42 (56.0%) completed the SPI for the 7-day period. All headache patients showed considerable mood disturbances during a headache. In general the disturbances were severe in intensity and of the order CDH>migraine>TTH. The pattern of mood disturbance was different for each type of headache, as was the patients' ability to cope with the mood changes. Patients with CDH experienced pain and emotional symptoms, particularly sedation, throughout the 7-day monitoring period. For TTH and migraine, the pain and emotional symptoms resolved within 1–2 days after the headache. The level of healthcare resource utilisation was also in the order CDH>migraine>TTH, similar to the data reported for the SPI.
Conclusions: Patients with headache had significant emotional symptoms associated with their headaches. These symptoms resolved within 1–2 days for patients with episodic TTH and migraine. However, patients with CDH were profoundly affected, and did not improve physically or emotionally from their headache over a 7-day period. Headache patients generally experienced higher levels of sedation than did patients with other pain conditions.

** Edited from the full article: Dowson AJ, Bundy M, Kilminster SG. Emotional function with tension-type headache, migraine and chronic daily headache. Headache Care 2005; manuscript in preparation.*

Introduction

Three subtypes of headache, tension-type headache (TTH), migraine and chronic daily headache (CDH: comprising chronic migraine, chronic TTH, hemicrania continua and new persistent daily headache in the new International Headache Society (IHS) classification criteria[1]), comprise the majority of the benign, primary headaches reported in general clinical practice. All these headache subtypes are common in the general adult population: prevalence rates are >50% for TTH; 12% for migraine; and 4% for CDH.[2–4] Physicians' management of these headache subtypes differs markedly in terms of overall strategy, selection of treatment modalities and duration of therapy. Also, they may be confused with each other on diagnosis. Migraine may present with symptoms typical of TTH,[5] and migraine may transform to CDH over periods of years or decades.[6] Patients with CDH may experience headaches characteristic of TTH and migraine in the constellation of their symptoms.[7] Diagnostic procedures may not, therefore, distinguish clearly between the headache types. A means of distinguishing the characteristic features, or 'footprints' of these headaches would be of great value in primary care, where time is limited, and the experience of the physician uncertain.

Several tools have been developed to assess headache features, as an aid to clinical management. The tools are broadly of three types: scales that specifically measure the functional ability of the patient, scales that index the migraine pain experience, including functional ability, and more generic measures.[8–13] Of the former type, impact questionnaires (e.g. the Migraine Disability Assessment [MIDAS] Questionnaire and the Headache Impact Test [HIT]) assess the effect headaches have on the patient's ability to work and function normally over 1- or 3-month periods.[8,9] Migraine-specific Quality of Life (QOL) tools assess the functional status (physical and emotional), well-being and overall health of the patient, usually over a 1-month period.[10–12] Generic QOL tools measure these values also, and also include a social dimension.[13] In addition, recently developed questionnaires have investigated ways of assessing the efficacy of interventions, using impact-type,[14] QOL-type[15] or a combination of different types of questions.[16] All of these tools assess retrospective data.

A biopsychosocial model has been proposed for chronic pain, whereby physical symptoms and emotional distress lead to the suffering that drives the patient to consult a physician.[17] The level of pain and emotional disability are directly linked, while the emotional impact can also be expressed as how well the patient is coping with the illness relative to a certain level of pain.[18] The relationship between pain level, emotional disability and how well the patient copes with them is relatively little understood and worthy of investigation.

Whilst the symptomatology of most headache subtypes is well understood, the emotional components of headaches are not. Our interest was to learn about how patients suffering from TTH, migraine and CDH differ in their pain level and emotional well-being, and the way they cope with these headache conditions over time. We also wanted to assess how the differences in emotional disturbance and coping may affect healthcare resource utilisation in these patient populations. We chose a prospective tool that has been developed specifically to measure the emotional consequences and associations of physical pain, the Short Pain Inventory (SPI©).[18]

In this study, the SPI was used to prospectively assess how the mood disturbances and coping abilities change over time in patients with TTH, migraine and CDH attending a primary care headache centre. The healthcare resource utilisation of these patients was also assessed retrospectively. The study was conducted as part of ongoing use of the SPI in the UK National Health Service (NHS), and to investigate the spectrum of primary care patients (including those with TTH).

Methods

Patients

Patients who took part in the study were attending a general practice headache clinic at Cranleigh Health Centre, Surrey, UK (Dr Bundy). The study was approved by the South West Surrey Local Research Ethics Committee.

Study design

This was a prospective, within-group, comparative study to assess the emotional 'footprint' of headaches, measured by the SPI, over 7 days following the onset of a headache. The questionnaires were administered by a psychologist (Dr Kilminster). A specialist neurologist (Dr Dowson) provided a diagnosis for each patient at the study outset, utilising clinical judgement and the IHS criteria then current.[19]

Patients completed a retrospective healthcare resource utilisation questionnaire at screening, covering the previous 6 months. Information was recorded as the number of: consultations for headache; prescriptions for headache and other conditions; GP visits; GP services used (out-of-hours telephone calls, emergency telephone calls and home visits); and referrals to a specialist physician.

Patients had a 6-week window from study onset to experience a headache and complete a series of SPI questionnaires. Patients self-completed the SPI at home at the following times over a 7-day period:

- Practise session at the clinic (baseline)
- Within 1 hour after the first headache started or on waking with a headache (Day 1). For CDH, the definition was the onset of a subjective 'bad headache'.
- Just after the pain was worst (peak) [Day 1].
- 1 hour after the headache had resolved or on waking with the headache resolved (Day 1)
- 24 hours after the headache started (Day 2)
- Evening of Day 2 about 8 pm (Day 2)
- Days 3–7 inclusive at about 8 pm.

SPI questionnaires were completed for 7 days, even if the headache lasted for longer than this time period. Explanation on how to complete the questionnaires was kept to a minimum.

Instruments: the SPI questionnaire

The SPI is a 17-item self-rating questionnaire dedicated to measuring any pain, not only headache. The questions assess pain intensity, social interaction skills and components of emotional function. Patients rate each item on a five-point numerical Likert scale: *not at all* (score 0)*, a little* (1)*, moderately* (2)*, very much so* (3) *and extremely* (4)*.* Five subscales measure sedation, social interaction, anxiety, sadness and anger, and have been fine-tuned by maximising items that are specific to pain. The SPI takes about one minute to complete,[18] and can be accessed via the internet with automatic scoring.[20] A scale of Total Mood Disturbance (TMD, 14 items) can be summated from the SPI, which measures the subtle mood changes that specifically covary with mild to severe pain (including sadness, anger, anxiety and sedation scores [social interaction scores are removed because this is a cognitive-behavioural parameter]). All 17 items can be summated to form the Total Pain Disturbance (TPD) score. As the physical severity of pain worsens, so generally does each of the emotional components.[21–23] If a patient's emotional score is exaggerated or flattened relative to the normal values, then a coping score can also be given as to how well a patient is coping with their pain, relative to others at the same physical level of pain. In this way an emotional 'footprint' of the headache can be created. Normative coping scores can be calculated for all items on the SPI Questionnaire. This can be very useful in the individual management of patients. We have found that around 60% of the variance of physical pain is explained by the overall mood of the patient.[21,22] The SPI has been shown to be far more

powerful at discriminating between varying levels of physical pain severity than the McGill Pain Questionnaire (used as the gold standard measure), with the majority of the pain variance being captured by the SPI.[21]

A recently published paper showed that the SPI was a reliable and valid measure of headache severity, and superior to the HIT. However, the HIT score was better related to headache diagnosis than was the SPI score.[24] As the pain severity increased from none to extreme, there was a highly significant increase in the SPI subscale scores for sedation, social interaction, sadness, anxiety and anger, as well as the SPI TMD score. Correlations between headache severity and the SPI subscale scores ranged from 0.60 to 0.70, and were 0.76 for the TMD score and 0.77 for the TPD score. The correlation between SPI sedation scores and headache severity was validated in a placebo-controlled, crossover trial of 10mg temazepam in 12 healthy volunteers, by analysing Critical Flicker Fusion thresholds.[24,25]

Other studies have demonstrated that the levels of SPI subscales associated with headache exhibited marked differences when compared with those of other pain states such as dental pain, osteoarthritis and chronic pain states.[22–24] In general, headache patients had the greatest level of sedation, while dental patients had the greatest levels of anger, sadness and anxiety. Patients with osteoarthritis had the lowest level of mood disturbance of all the patient groups. Overall, headache patients had a level of mood disturbance at least as severe as patients who were attending a secondary care chronic pain clinic.

Endpoints

The primary study endpoints were derived from the SPI questionnaire: the pattern of pain intensity (assessed as none [Grade 0], mild [Grade 1], moderate [Grade 2], severe [Grade 3] and extreme [Grade 4]) and emotional items (sedation, social interaction, sadness, anxiety and anger, total TMD and TPD scores) over the 7 days during and following the headache. The healthcare utilisation data formed the secondary study endpoint.

Statistical methods

SPI

All spoiled SPI forms were included for the intention-to-treat basis. This was done so as to reduce the administrator bias and evaluate the SPI as it would be used realistically in clinical settings. Statistical analysis was by discriminant function analysis, simple t-tests and test-retest Pearson product moment correlation coefficients. Statistical analysis was carried out on a Power Macintosh G4/400/200 machine with Statistica V4. All data points were double validated against source forms. The analysis was carried out by a medical statistician. Diagnostic labels derived from the IHS classification criteria[19] were dummy coded. Summary and derivative SPI measures were then used as dependent variables in simple t-tests. Data were 100% validated against source documents.

Simple box plots with mean ± 1 and 1.96 standard errors about the mean were used. Elsewhere, graphical information was plotted as Z scores. The SPI raw scores were used for the summary and components. SPI disturbance and coping Z scores were computed. With the SPI, the extent to which the patient is coping with their pain can be estimated as coping Z scores, calculated by removing the effects due to physical pain. Put simply, normative coping values of the mood change were computed relative to patients with either no pain, mild, moderate, severe and extreme pain. For disturbance score, the normative values were those of subjects without pain. The SPI Coping score shows how much emotional upset the patient is in relation to the normal ranges expected in each of the five grades of physical pain. A fully automated and much simplified electronic version of SPI has been developed and is accessible via the internet at www.headachetest.co.uk. Previous studies have shown that the analysis of only four patients was sufficient to distinguish between headache subtypes and 12 were sufficient to assess time of day effects with SPI.[20]

Healthcare resource questionnaire
Data derived from the healthcare resource questionnaire were analysed by descriptive statistics only.

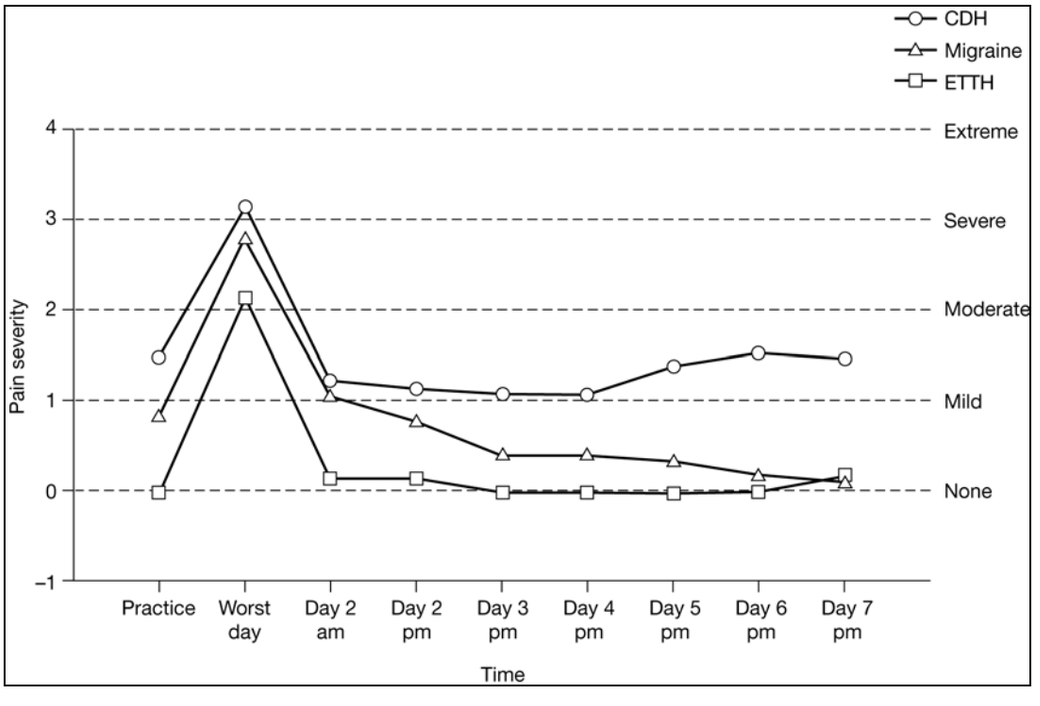
Results

Patient demography and baseline characteristics
Seventy five patients took part in the study and completed the healthcare utilisation questionnaire. Their mean age was 44.3 years (SD 9.8), and the majority (97.3%) were women. At screening, episodic TTH was diagnosed for 15 patients (20%), migraine for 41 patients (54.7%) and CDH for 19 patients (25.3%). Migraine patients were subdivided into those with low-frequency attacks (≤ 3 attacks per month, *n* = 30) and high-frequency attacks (> 3 attacks per month, *n* = 11). Extreme pain (Grade 4) was reported by 2.6% of patients, very much pain (Grade 3) by 8.2%, moderate pain (Grade 2) by 10.5%, a little pain (Grade 1) by 34.2% and no pain (Grade 0) by 44.7% of patients.

Forty two of the 75 patients (56.0%) returned the completed SPI questionnaires within 6 weeks. Six of these patients had TTH (14.3%), 23 had migraine (54.8%) and 13 had CDH (31.0%). The major dropout rate was in the TTH group. Due to the low frequency of their headaches, many TTH patients did not experience an initial headache over the 6-week window.

SPI: Changes in coping scores during, and for 7 days after, the headache
Pain severity
The physical severity of the pain varied considerably over the week following the initial headache (Figure 1). At the peak of the headache, patients with episodic TTH presented on average with mild to moderate pain (score 1–2), migraine patients with moderate to severe pain (score 2–3) and CDH patients with severe pain (score 3). TTH pain largely resolved within 24 hours and migraine pain within 2 days, but the CDH pain remained at least mild in intensity for the whole 7-day period.

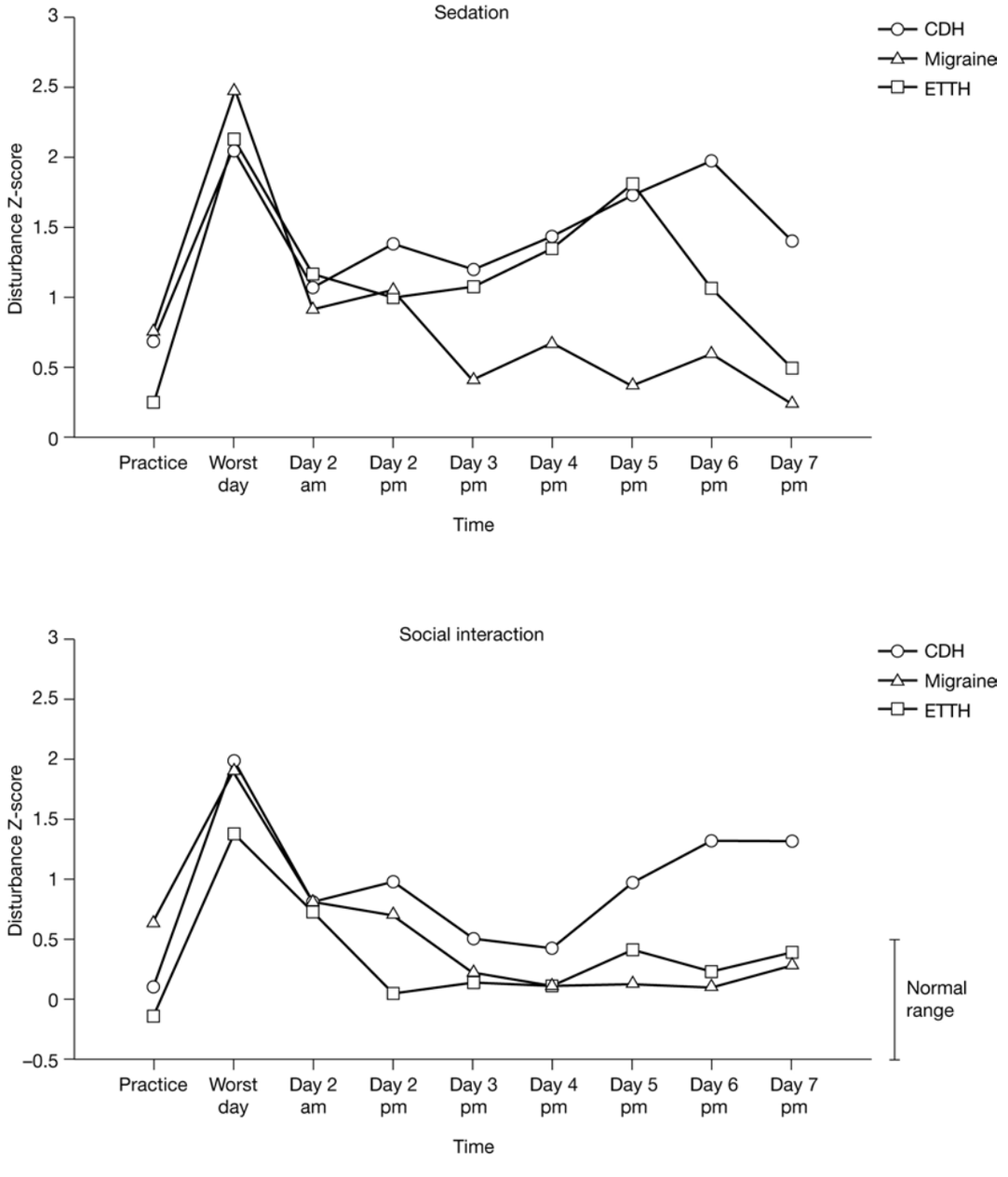
Figure 1. SPI: Physical pain severity during the headache and over the following week for patients with episodic TTH, migraine and CDH.

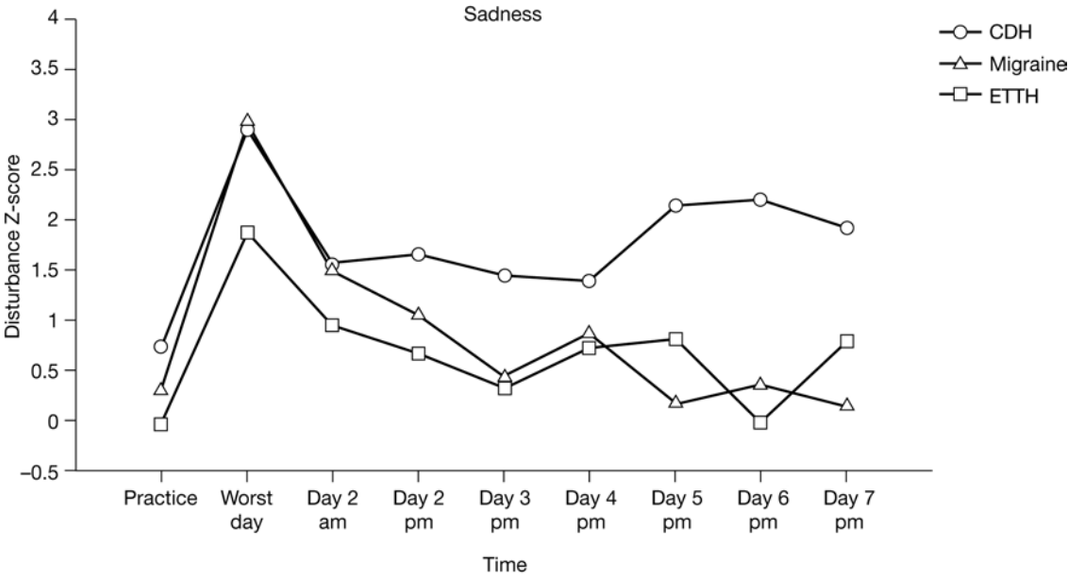


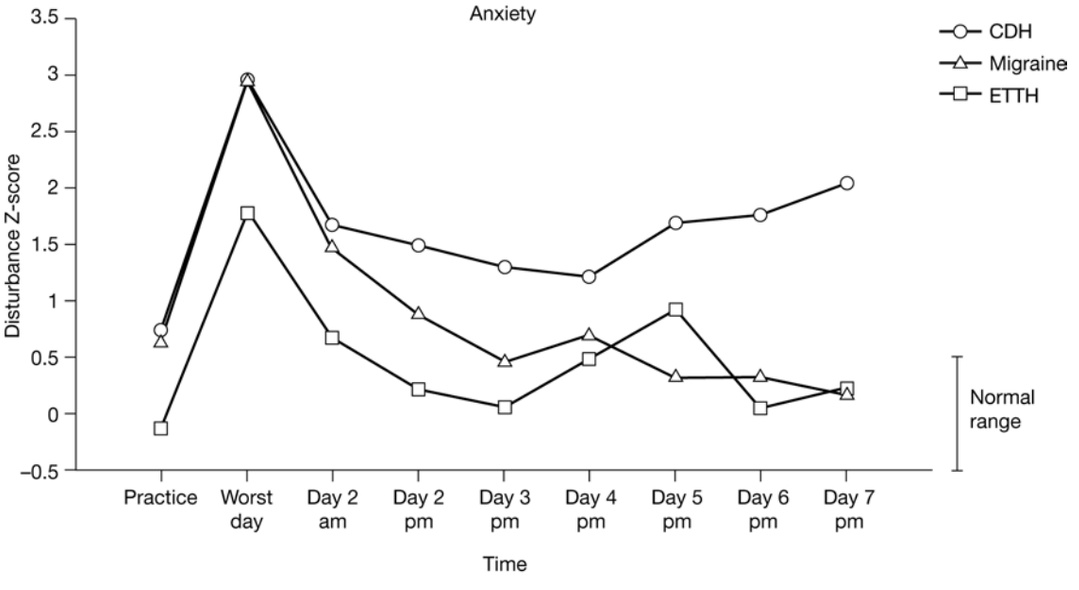
Changes in emotional items

The disturbance in the sedation, social interaction, sadness, anxiety and anger items of the SPI over 7 days during and following the headache are shown in Figure 2 as Z scores. Coping Z scores for sedation, social interaction, sadness, anxiety and anger items of the SPI over 7 days during and following the headache are shown in Figure 3.

Figure 2. SPI: Sedation, social interaction, sadness, anxiety and anger Z scores during the headache and over the following week for patients with episodic TTH, migraine and CDH.




Sadness
CDH
Migraine
ETTH
Disturbance Z-score
4
3.5
3
2.5
2
1.5
1
0.5
0
−0.5
Practice
Worst day
Day 2 am
Day 2 pm
Day 3 pm
Day 4 pm
Day 5 pm
Day 6 pm
Day 7 pm
Time


Anxiety
CDH
Migraine
ETTH
Normal range
Disturbance Z-score
3.5
3
2.5
2
1.5
1
0.5
0
−0.5
Practice
Worst day
Day 2 am
Day 2 pm
Day 3 pm
Day 4 pm
Day 5 pm
Day 6 pm
Day 7 pm
Time

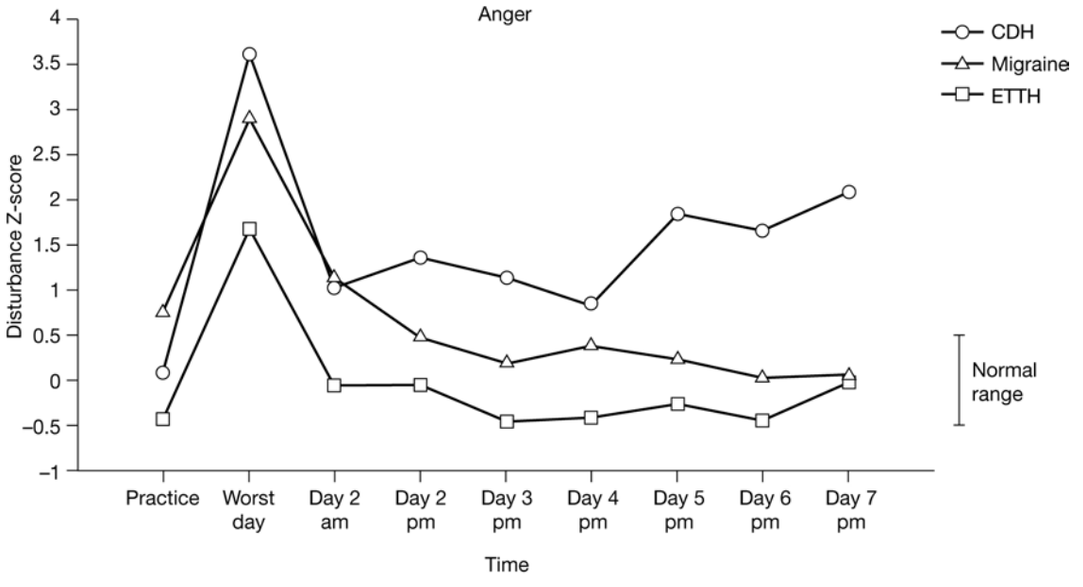
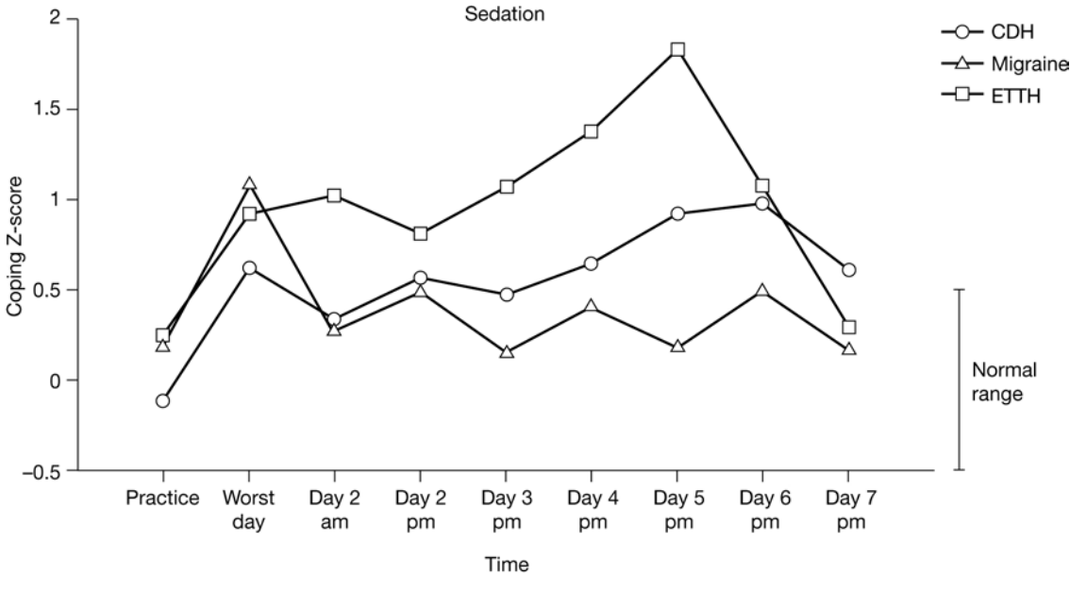
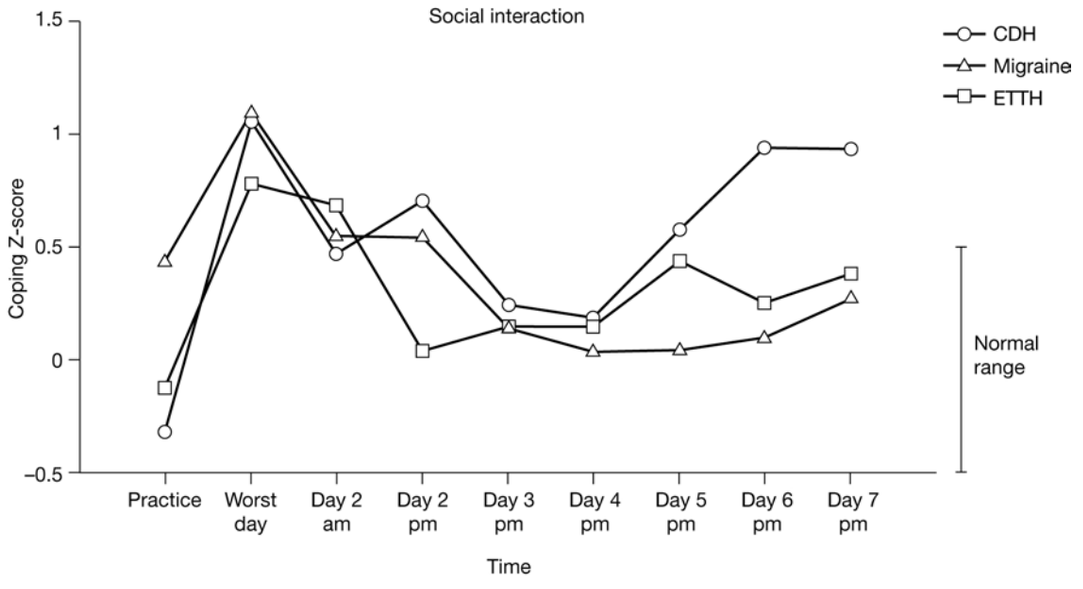
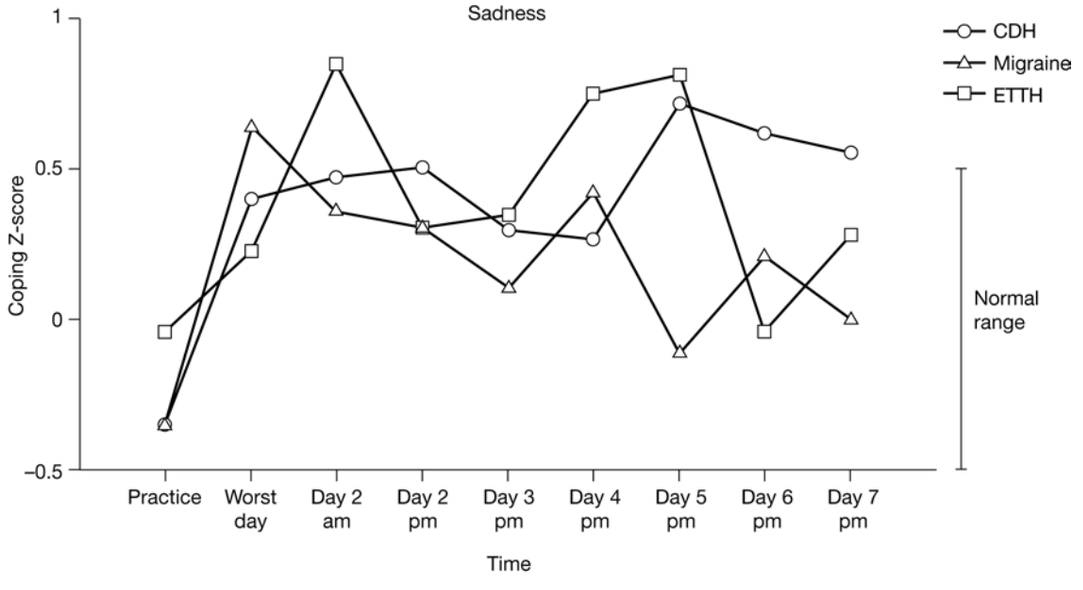
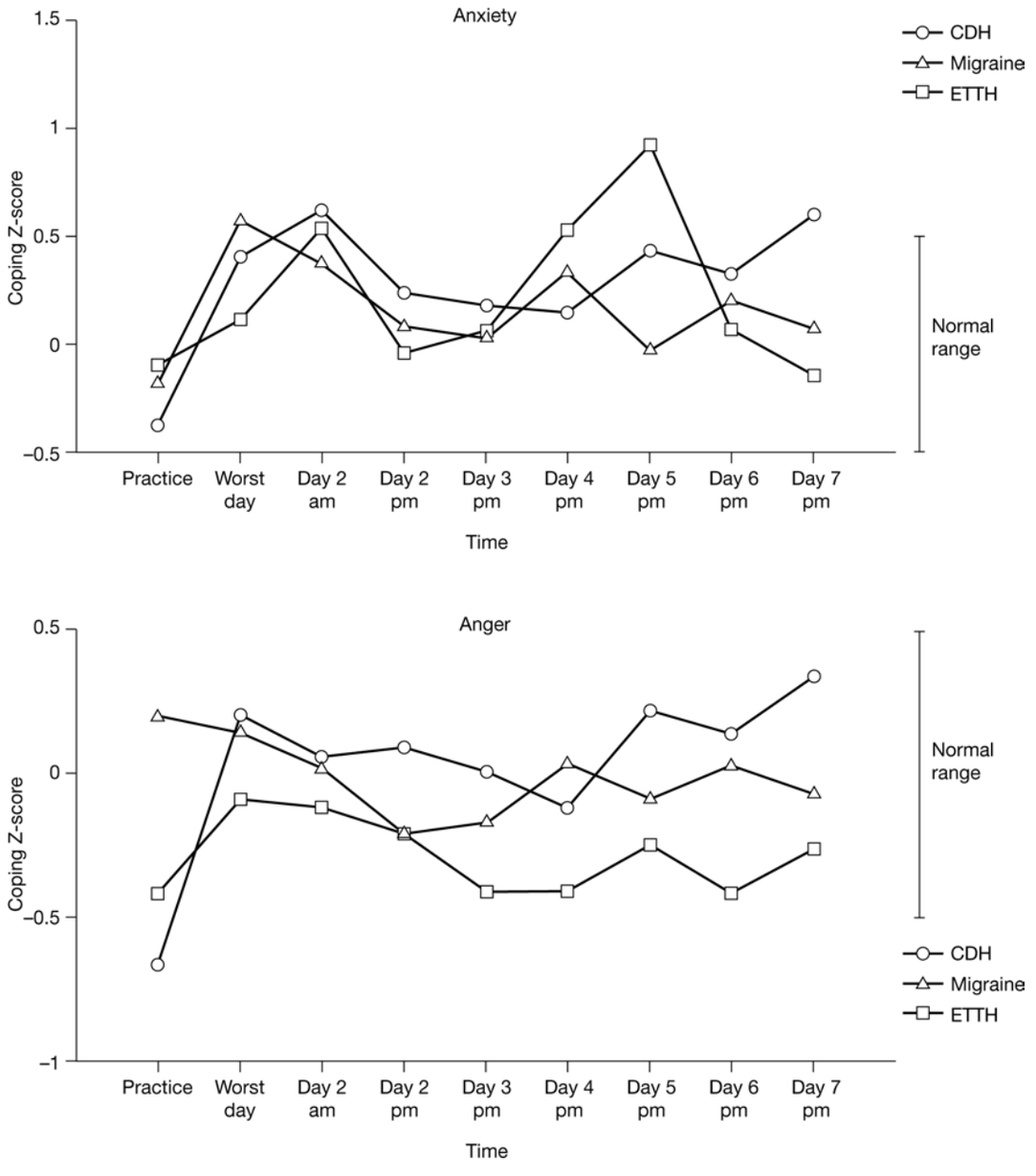


Figure 3. SPI: Sedation, social interaction, sadness, anxiety and anger coping Z scores during the headache and over the following week for patients with episodic TTH, migraine and CDH.




Social interaction
CDH
Migraine
ETTH
Coping Z-score
1.5
1
0.5
0
−0.5
Normal range
Practice
Worst day
Day 2 am
Day 2 pm
Day 3 pm
Day 4 pm
Day 5 pm
Day 6 pm
Day 7 pm
Time


Sadness
CDH
Migraine
ETTH
Coping Z-score
1
0.5
0
−0.5
Normal range
Practice
Worst day
Day 2 am
Day 2 pm
Day 3 pm
Day 4 pm
Day 5 pm
Day 6 pm
Day 7 pm
Time



Sedation disturbance Z scores revealed differences between the patient groups. Although all headache groups showed severe sedation at the point of worst pain during their headaches, the footprint of sedation over the remaining week was very different. With migraine, the sedation had resolved 2 days after the headache. However, patients with CDH and episodic TTH showed marked levels of sedation throughout the week. With TTH, this resolved by Day 7, but the CDH patients were chronically sedated. Analysing the coping Z scores, TTH patients appeared to be coping less well than the other groups, with substantial sedation in excess of the physical pain they experienced.

Despite the fact that all patients appeared sociable at screening, disturbances in social interaction remained above the normal range throughout the 7-day period for CDH patients. Two days after their headaches, patients with migraine and TTH had returned to normal levels of social interaction. Examining the social interaction coping scores showed that, for 5 days of the week, the CDH patients had difficulty coping. Patients with migraine and TTH returned to normal within 24 hours of the headache.

Disturbances in sadness remained elevated for the CDH patients throughout the 7-day assessment period. However, sadness resolved 2 days after the headache in the migraine and TTH groups. Coping scores for sadness were not sustained above +0.5Z for any of the groups. Therefore, much of the sadness induced is likely to be a direct result of the physical pain endured. There was some suggestion that patients with TTH were coping less well considering their lower level of pain and lower frequency of headaches compared to the other groups.

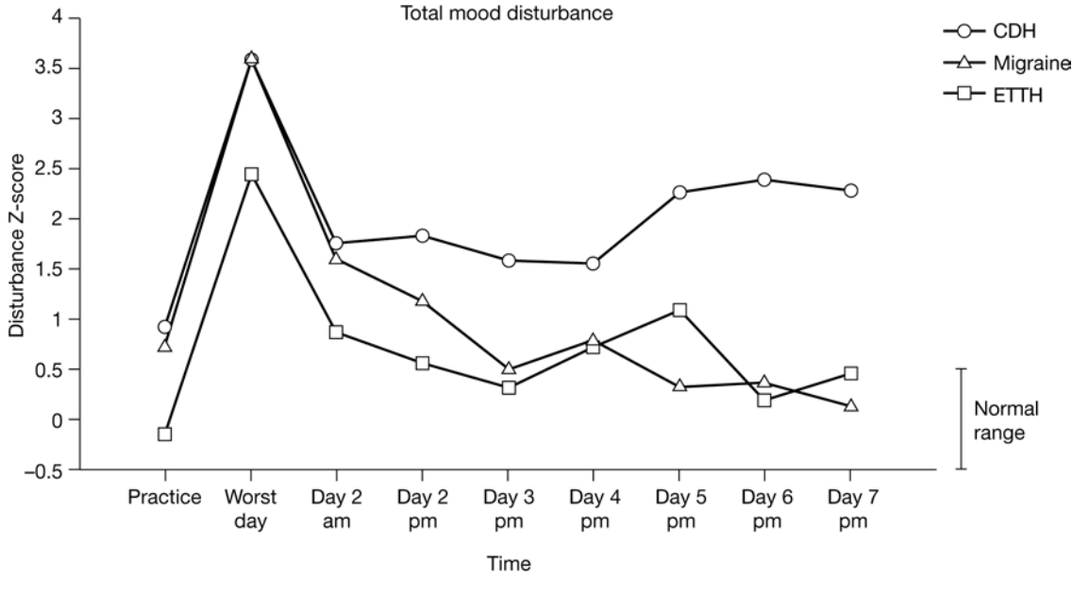
Disturbances in anxiety remained elevated for the CDH patients throughout the 7-day assessment period. However, anxiety had resolved 2 days after the headache in the migraine and TTH groups. The SPI anxiety coping Z score showed that patients' weekly anxiety remained within normal coping levels. There was a suggestion from the data that TTH patients might be coping less well with anxiety.

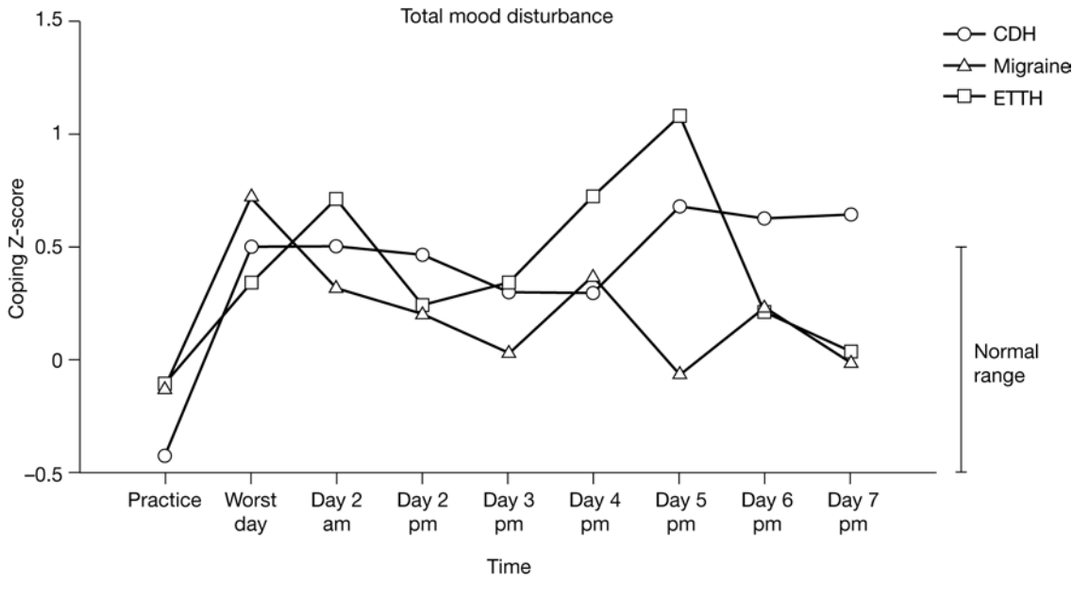
The SPI anger disturbance Z scores showed a similar pattern to the pain severity changes over the week. Patients with migraine and TTH recovered within 24 hours of the headache, but CDH patients remained above normal levels for the whole week of assessments. The SPI anger coping Z scores showed that all the headache patients were coping well with anger.

Total mood disturbance

The TMD Z scores and coping Z scores, which include the sedation, sadness, anxiety and anger components, are shown in Figure 4. In general, patients with CDH and migraine had equivalent and severe mood disturbances during the period of the headache itself. However, the mood of CDH patients never returned to normal over the 7-day assessment period, while that of TTH and migraine patients did so within 48 hours of the headache. The coping scores showed that TTH and CDH patients had mild difficulty coping with their mood disturbances. The highest levels were seen temporarily with TTH patients. Migraine patients mostly coped well with their mood disturbances.

Figure 4. Total mood disturbance Z scores and coping Z scores during the headache and over the following week for patients with episodic TTH, migraine and CDH.





The TPD Z score was computed from all 17 SPI subscales. The results closely resembled those for the TMD discussed above (Figure 4). As before, the CDH patients did not recover over the 7-day assessment period and their pain was typically +2Z above normal.

Healthcare utilisation

Patients diagnosed with episodic TTH, migraine and CDH showed marked differences in their utilisation of healthcare resources (Table 1). Patients with TTH used few resources, and did not consult or receive prescriptions for headache. Most patients with migraine had consulted for headache, with over three-quarters receiving a prescription for headache from their GP. Most patients with CDH had consulted for headache, each receiving, on average, more than one prescription for headache. Patients with CDH consulted their GPs (all causes) and received more overall prescriptions than patients with migraine or episodic TTH. Out-of-hours GP services (telephone calls, emergency calls and home visits) were hardly ever used by these groups of headache patients. Headache referrals were infrequent for episodic TTH patients, but were used for approximately one-third of migraine and CDH patients. Patients with low-frequency migraine used fewer resources than those with high-frequency migraine and CDH, who had a similar pattern of use.

Table 1. Healthcare utilisation by patients in the study, reported at baseline for the previous 6-month period.

Number of patients (ratio per patient)

Healthcare resource	**Episodic TTH (*n* = 15)**	**Migraine (*n* = 41)**	**Low-frequency migraine (*n* = 30)**	**High-frequency migraine (*n* = 11)**	**CDH (*n* = 19)**
Headache consultations	0	31 (0.76)	19 (0.63)	12 (1.09)	12 (0.63)
Prescriptions for headache	0	34 (0.83)	10 (0.33)	24 (2.18)	26 (1.37)
Total prescriptions	9 (0.6)	143 (3.49)	68 (2.27)	75 (6.82)	131 (6.89)
GP visits	20 (1.33)	108 (2.63)	67 (2.23)	41 (3.73)	76 (4.0)
Out-of-hours calls	0	1 (0.02)	1 (0.03)	0	0
Emergency calls	0	0	0	0	0
Home visits	0	1 (0.02)	1 (0.03)	0	2 (0.11)
Referrals	1 (0.07)	13 (0.32)	8 (0.27)	5 (0.45)	6 (0.32)

Discussion

This study demonstrates the link between pain, emotional disability and the associated way that patients with TTH, migraine and CDH cope with their headaches over time. We have previously demonstrated that the SPI is a very discriminating measure of headache severity.[24] Results from the current study show that it also discriminates the emotional impact of different headache subtypes. It is clear that episodic TTH, migraine and CDH leave different 'footprints' in terms of the emotional experience, associated tiredness, disruption to social interactions and the time course of each of these components.

At peak intensity the pain level as assessed by the SPI was mild to moderate for episodic TTH, moderate to severe for migraine and severe for CDH. These gradations of intensity are similar to those generally reported for the separate headache subtypes.[1] Patients with the three headache subtypes all exhibited sedation, disturbances in social interaction, sadness, anxiety and anger at the peak of the headache. In general, the severity of these emotional components was more intense for CDH and migraine than for episodic TTH. However, the pattern of these emotions differed between the three groups in the 7-day period following the headache.

Analysis of the SPI data demonstrates that CDH is an appropriate term for the condition. Physical pain was always present over the 7 days, and fluctuated between mild to moderate pain over the post-headache period. Marked levels of sedation, disturbed social interaction, sadness, anxiety and anger were also seen over the week following the headache. CDH patients are clearly chronically fatigued. For half of the week, their level of sedation was due to impaired coping with tiredness above and beyond the level caused by physical pain. This may reflect the known association of CDH and Chronic Fatigue Syndrome[26] and, certainly, tiredness is a major feature of the post-dromal period of headache in CDH. CDH patients also showed chronic disturbances in social interaction and sadness that never recovered over the 7-day period. For at least part of the week, these disturbances were caused by a failure to cope above and beyond the level of physical pain endured. On the other hand, coping scores for anxiety and anger were mostly within normal levels, the high levels of state

anxiety and anger disturbance being caused by the physical pain severity. Overall, the level of emotional disturbance experienced by CDH patients was similar to that seen in patients attending chronic pain clinics.[22] An unfortunate feature of CDH patients is that their mood disturbance never returns to normal and patients obtain no respite from the pain and its emotional consequences.

Migraine physical pain improved to mild or no pain within 48 hours of the headache. Although marked levels of sedation, disturbed social interaction, sadness, anxiety and anger were seen during the headache, these symptoms typically resolved within 2 days. Coping scores for these symptoms were at normal levels after the headache. These data indicate that the patients were coping well with the emotional symptoms, which resulted from the level of physical pain experienced. Unlike CDH patients, migraine patients are not chronically sedated.

Physical pain associated with episodic TTH resolved within 24 hours. Marked levels of sedation were seen during the headache and continued for most of the following week. Coping scores for sedation were the most disturbed of all the three types of headache, seemingly being more severe than those related to CDH. This shows that the sedation was probably not related to physical pain, but was exaggerated by it. It may be a feature of a delayed recovery from the headache insult or be a precipitating factor for the headache. This, perhaps surprising feature considering the relatively mild intensity of TTH, is probably underestimated in the management of these patients. Levels of disturbance in social interactions, sadness, anxiety and anger were all less intense during the headache than those associated with migraine and CDH, and resolved within 1–2 days following the headache. Coping scores for social interaction, anxiety and anger demonstrated that these symptoms were not above normal ranges, taking into account the level of physical pain. Coping scores for sadness were sometimes above the normal range for 3 out of the 7 days post-headache. This suggests mood lability in terms of sadness that is not related to the physical pain experienced. Coping Z scores for anger tended to be rather low. It is possible that episodic TTH is typified by a period of anger repression and extreme tiredness, although the study sample was too small to be definite about this.

In this study, the level of mood disturbance was directly related to the level of healthcare utilisation in the same group of patients. Direct comparisons cannot be made, as the two assessments were not contemporaneous. However, the link is logical. Patients with chronic, severe emotional impact are more likely to require medical services than those in which the impact is transient. Patients with episodic TTH had a low use of resources, in terms of GP consultations and prescription medications. Patients with migraine frequently consulted their GP for care and usually required prescription headache medications. Those with high-frequency migraine had markedly higher patterns of healthcare utilisation than those with low-frequency attacks. Patients with CDH consulted their GPs frequently and had high usage of prescription medications. Patients with high-frequency migraine are at risk of developing CDH,[6] and at least some of the patients in this group may actually have been in this situation. Mood disturbances may, at least in part, drive patients to consult their GPs for headache care.

This work has potential clinical implications to the management of headache. Despite its importance to illness severity, the emotional component of headache is likely to be rarely elicited by physicians, as it plays no part in the current classification criteria.[1] Specialist physicians may find that the use of SPI forms a useful additional screening and outcome tool for the evaluation of their patients, particularly those who may later develop depression and/or anxiety conditions. It may be useful not only to estimate the consequences of pain but also stress as a causative trigger to headache. However, should primary care physicians may find it too demanding for everyday use, an automated much simplified electronic version

has been developed over the internet at www.headachetest.co.uk.[20] This has the benefit of full electronic delivery of the test and automatic scoring.

The recently developed Migraine Assessment of Current Therapy (Migraine-ACT) questionnaire contains one question on emotional response (Are you comfortable enough with your medication to be able to plan your daily activities?).[16] This question is suitable for use in primary care, and 'no' answers indicate that the patient has unmet treatment needs. A single questionnaire item on mood cannot possibly accurately and comprehensively assess mood, and the questionnaire was not set up to do this. Patients with chronic emotional problems linked to headache may require referral to a specialist. But one should be mindful that mood disturbance can be as much a cause as an effect.

This study has certain limitations. Relatively small numbers of patients took part, and a high proportion of patients did not complete a SPI questionnaire in the 6 weeks allowed. A longer study duration could have led to a reduction in the drop out rate.

In conclusion, patients with episodic TTH, migraine and CDH all had considerable mood disturbances during their headaches. The more pain they experienced, the greater was the level of mood disturbance. The pattern of mood disturbance was different for each type of headache, as is the patients' ability to cope with the mood changes. Patients with episodic TTH and migraine had significant emotional symptoms associated with their headaches, which resolved within 1–2 days. However, patients with CDH were most profoundly affected, and did not recover physically or emotionally from their headache over a 7-day period. The association of mood disturbances with common headache subtypes may explain in part the reported co-morbidity of headache with psychiatric disorders.[27] Patients with chronic headaches have clear emotional needs, both for their headache and other disorders, which may not be currently appreciated or addressed by healthcare services. Future large studies with SPI in headache are warranted to further define and quantify the emotional component of headache impact.

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4

The clinical utility of assessing disability in primary care clinical practice

4.1

Assessing the impact of migraine and other headaches*

Abstract

Migraine is a remarkably disabling condition, although unpredictable and heterogeneous in frequency, duration and severity. It can be difficult to manage in primary care, where it is under-recognised, under-diagnosed and under-treated. Proposals have been made that migraine care could be improved by incorporating assessments of migraine impact into management strategies. Research has shown that measuring headache-related disability, together with assessments of pain intensity, headache frequency, tiredness, mood alterations and cognition can be used to assess the impact of migraine on sufferers' lives and society. From this research two simple and brief impact tools were developed; the Migraine Disability Assessment (MIDAS) Questionnaire and the Headache Impact Test (HIT). Both tools are scientifically valid measures of headache severity and have the potential to improve communication between patients and their physicians, assess headache severity and act as outcome measures to monitor treatment efficacy. Each of these tools offers its own advantages. For example, HIT was designed for greater accessibility (on the internet at www.headachetest.com and www.amlhealthy.com and as a paper-based form known as HIT-6) and has a wider coverage of the spectrum of headache than MIDAS. Impact tools are also being increasingly recommended as part of generalised headache management guidelines to produce an individualised treatment plan for each patient in concert with other clinical assessments. It is not possible as yet to unequivocally recommend the optimal impact tool for use in primary care, but it should be usable by GPs, pharmacists, nurses and patients, and for research purposes.

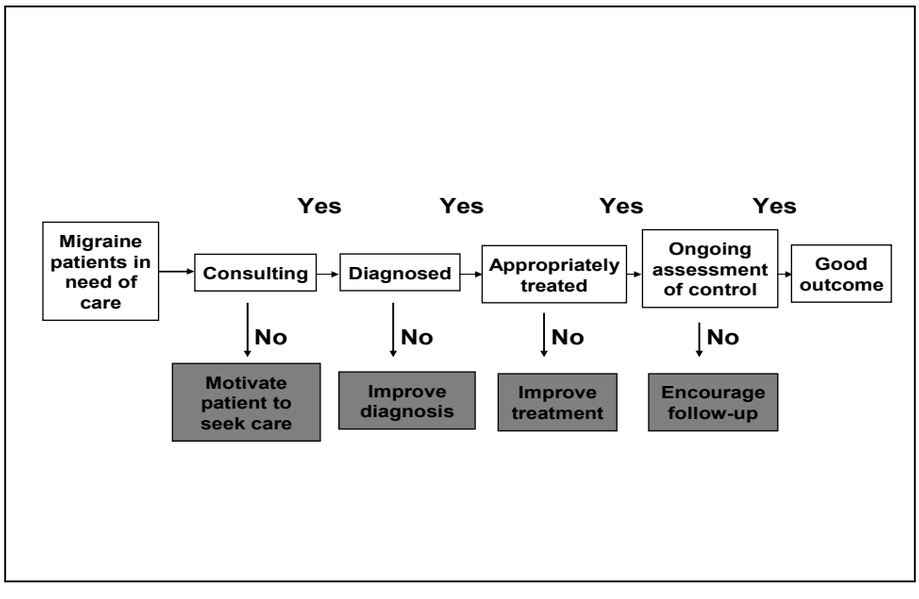
** Edited from the full published article: Dowson AJ. Assessing the impact of migraine. Curr Med Res Opin 2001;17:298–309.*

Introduction

Migraine is a common, debilitating neurological disorder that affects about 12% of the general population. It is more prevalent in women than in men and in Caucasians than in Black and Asian races.[1] Migraine attacks consist of moderate to severe headaches, which are typically throbbing, one-sided and aggravated by physical activity. The headache is usually accompanied by photophobia and/or phonophobia and nausea, and less frequently by vomiting and aura symptoms. Attacks occur on average about once or twice a month, last for about 24 hours, and are separated by symptom-free intervals.[2] Migraine attacks result in significant reductions in sufferers' health-related quality of life (HRQoL) compared with normal healthy subjects.[3] However, migraine is an unpredictable, heterogeneous disorder and attacks vary widely in frequency, duration, severity and reported symptoms.[4]

Due to this variability, migraine can be difficult to manage in primary care. In clinical practice, migraine is under-estimated, under-diagnosed and under-treated, leading to many patients dropping out from care (Figure 1). A recent study in the UK showed that 86% of migraine sufferers had consulted their physician at some time for treatment. However, 37% of sufferers had dropped out, leaving 49% as currently consulting.[5] Studies in the USA and France indicated that about half of all migraine sufferers who consulted their general practitioners did not receive a correct diagnosis.[6,7] Patients may not receive appropriate treatment even when they do consult and are diagnosed correctly. International and UK studies have shown that only a minority of migraine sufferers take prescription medications[8,9] and patient satisfaction with their usual analgesic acute medications is low.[9,10]

Figure 1. Barriers to migraine care. For effective migraine care, sufferers need to consult their physician and be diagnosed, treated and followed-up effectively. Migraine sufferers are lost to care through under-consultation, under-diagnosis and under-treatment of their attacks.[5–10]



A range of initiatives has been set up to improve migraine care, by encouraging migraine patients to consult their physicians and for physicians to improve their diagnostic and treatment strategies. Several of these involve assessing the impact of migraine on sufferers' lives, and using this information to facilitate management strategies. This article reviews the rationale for, and development of, tools that assess migraine impact and their potential roles in general practice.

Research into the impact of migraine

In some instances, the impact of migraine can be considered as the objective effects of the illness on sufferers' lifestyles, including their work and leisure activities, rather than subjective effects expressed as symptoms and HRQoL. Impact has great similarities to the *World Health Organization's* definition of disability: "a restriction or lack (resulting from an impairment) of ability to perform an activity in the manner or within the range considered normal for a human being".[11] Studies from the USA, Canada and Japan have shown that migraine causes significant disability in its sufferers, with two thirds or more reporting at least mild disability and one third or more reporting moderate to severe disability.[4,12,13] In a UK study, two thirds of migraine sufferers reported that migraine disrupted their lives, with three quarters having to lie down during attacks (Table 1).[14] A second study indicated that between one third and two thirds of migraine sufferers in the UK (an estimated 1.9–3.8 million people) felt that they were not in control of their migraine and the way it affected their day-to-day lives.[9]

Table 1. Migraine-related disability reported from a study conducted in the United Kingdom.[14]

Disability	Proportion of sufferers
Physical functioning	
Always have to lie down	76
Not in control of life	34
Disruption of life	67
Employment	
Usually miss work	50
Difficulty performing work	72
Cancel appointments/meetings	67
Rely on other people	45
Perceived effect on promotion	15
Unpaid work	
Postpone household chores	90
Family and leisure activities	
Relations with family and friends affected	54

The consequences of migraine impact are seen in patients' lifestyles, including employment, unpaid work and family and leisure activities. The loss of these activities has been quantified in a series of studies. In the USA, each working migraine sufferer missed an average of 4.4 days of work per year and the equivalent of 12 further days due to reduced productivity during attacks.[15] In the UK, half of sufferers reported missing work and over two thirds reported difficulty performing work during attacks (Table 1).[14] Migraine may even lead to unemployment. In a Health Maintenance Organisation in the USA, the unemployment rate was 2- to 4-fold higher in severely affected migraine sufferers than in the general population.[16] School and college work is also affected in young migraine sufferers. In a Scottish study, children with migraine were absent from school for significantly longer periods than those without migraine (7.8 days *versus* 3.7 days per year, $P<0.0001$).[17] This personal burden of migraine is reflected in an economic burden on society. Indirect costs (due to work absence and reduced work productivity) are very large for migraine, being estimated at £1 Billion or more in the UK.[18] These costs are very much higher than the direct costs due to medical care, last estimated at £23 million in 1990.[19] Although direct medical costs for migraine have increased since 1990, partly due to the introduction of the triptan drugs, indirect costs still provide the main economic burden of the illness.

Migraine also affects unpaid work and family and leisure activities. In a UK study, 90% of migraine sufferers reported that they postponed their household work during an attack (Table 1).[14] Several studies have shown that migraine attacks commonly result in the cancellation of social events, and affect relationships with partners, children, friends and other people.[14,20,21]

Migraine is therefore a remarkably disabling condition, with most sufferers reporting significant impact associated with their attacks in all areas of their lifestyles. Recent research has focused on the use of impact assessments to measure the severity of migraine in comparison with other assessments.

Assessing the impact of migraine

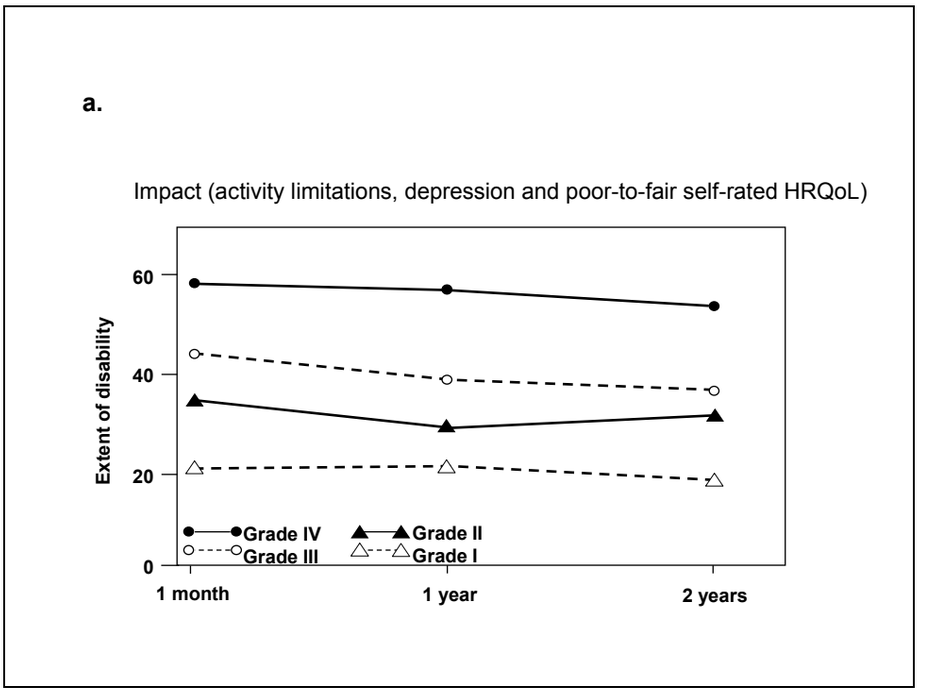
Migraine attacks vary in severity from moderate pain, with no activity limitations, to severe pain with prolonged incapacitation.[4] To measure the impact of migraine, parameters must be defined that capture the personal burden on the sufferer and the economic burden on society. Following this, a scientifically valid tool needs to be developed to capture this information in a way that is simple to use and clinically relevant.

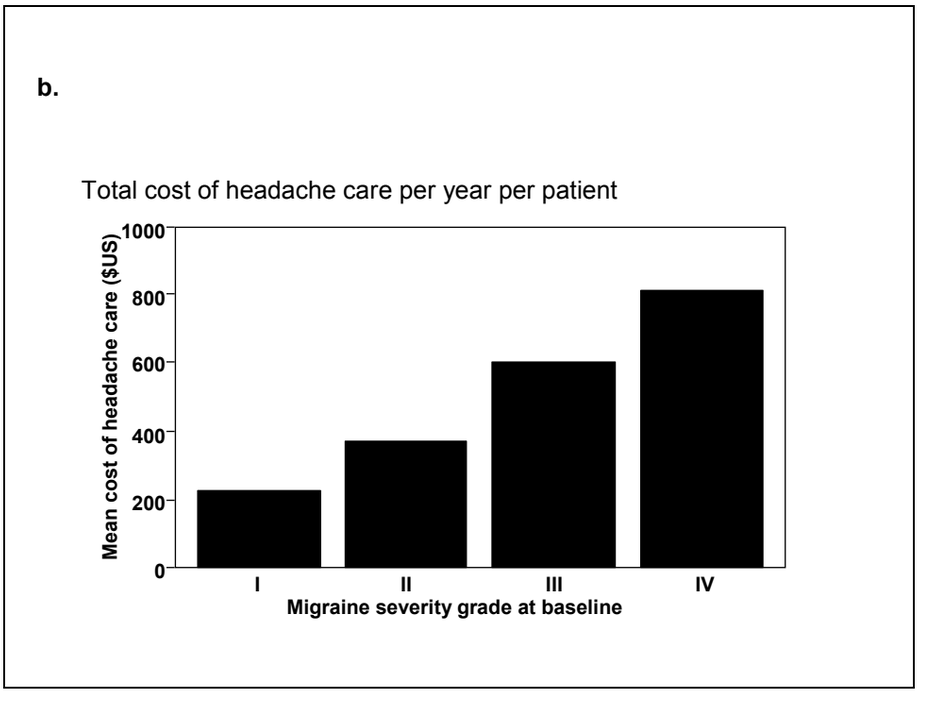
Rationale for using impact tools

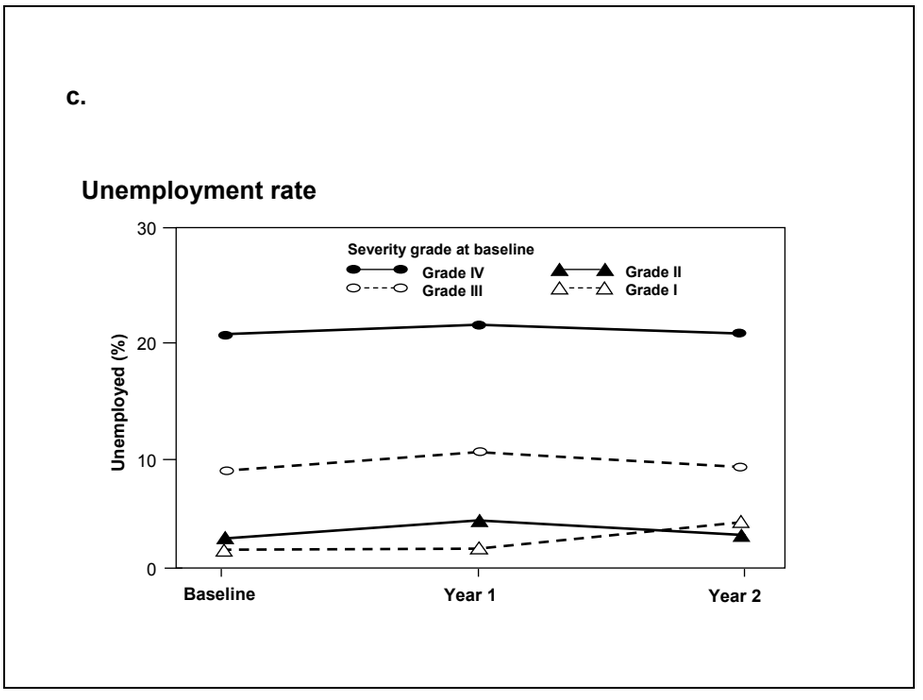
Pain intensity is the most important aspect of migraine to the individual sufferer. Sufferers report headache pain more frequently than all other migraine symptoms and most patients consulting their physicians do so for pain relief.[12] However, economic studies have shown that headache-related disability is the most important determinant of migraine's societal impact in economic terms.[22] Assessments of pain and disability were therefore included in initial studies assessing the impact of migraine.

The Chronic Pain Index (CPI) was developed to measure the severity of a number of pain conditions, including headache, in primary care patients.[16] Results showed that pain intensity and disability measures formed a reliable hierarchical scale whereby pain intensity scaled the lower range and disability the upper range of severity. Four severity grades were identified that covered the whole pain spectrum. When the CPI was tested on 740 primary care headache patients over a 2-year period, the severity grade was directly related to the impact of the headache on the individual and the direct and indirect economic costs (Figure 2).[16,23] There was approximately 3–4 fold greater individual impact, direct costs and indirect costs (assessed as the unemployment rate) for patients in the highest severity grade compared with those in the lowest grade. These results were confirmed in a study conducted in migraine patients who assessed the pain and disability associated with their most recent attack.[4]

Figure 2. Relationship of the Chronic Pain Index severity grade to the individual and societal costs of headache when tested on a group of 740 primary care headache patients over 2 years. a. Pain impact on the individual assessed as a composite of activity limitations, depression and poor-to-fair self-rated HRQoL. b. Impact on society assessed as direct medical costs of care per year. c. Impact on society assessed as indirect costs over 2 years (assessed as the unemployment rate).[16,23] Grade I = low pain intensity and low disability; Grade II = high pain intensity and low disability; Grade III = high disability which was moderately limiting; Grade IV = high disability which was severely limiting.







Using the CPI as a model, the Headache Impact Questionnaire (HImQ) was developed to measure headache impact. This was a relatively complex, 16-item questionnaire assessing headache frequency, pain intensity and disability, the latter measured as total lost time in employment, household work and non-work activities. Studies showed that the HImQ was a scientifically reliable and valid measure of migraine severity. [24,25] However, it was complex to score, requiring mathematical equations, and was not intuitive to use as it was based on a composite of pain, frequency and disability measures. It was therefore not suitable for use in primary care, but has proved to be an excellent research tool.

This research did indicate that it was possible to assess the impact of migraine using scientifically valid questionnaires. The next challenge was to develop simple but accurate and comprehensive questionnaires that could be used in the primary care setting.

Development of impact tools for use in primary care

Two tools have been developed to assess the impact of migraine, both partly based on the HImQ. However, they use quite different strategies to achieve their goals. The Migraine Disability Assessment (MIDAS) Questionnaire assesses impact as a static measure of disability, while the Headache Impact Test (HIT) uses a global assessment of impact, including headache-related disability. It should be noted that both questionnaires assess headache in general, rather than migraine specifically, and so have potential application to the whole field of headache management.

The Migraine Disability Assessment (MIDAS) Questionnaire

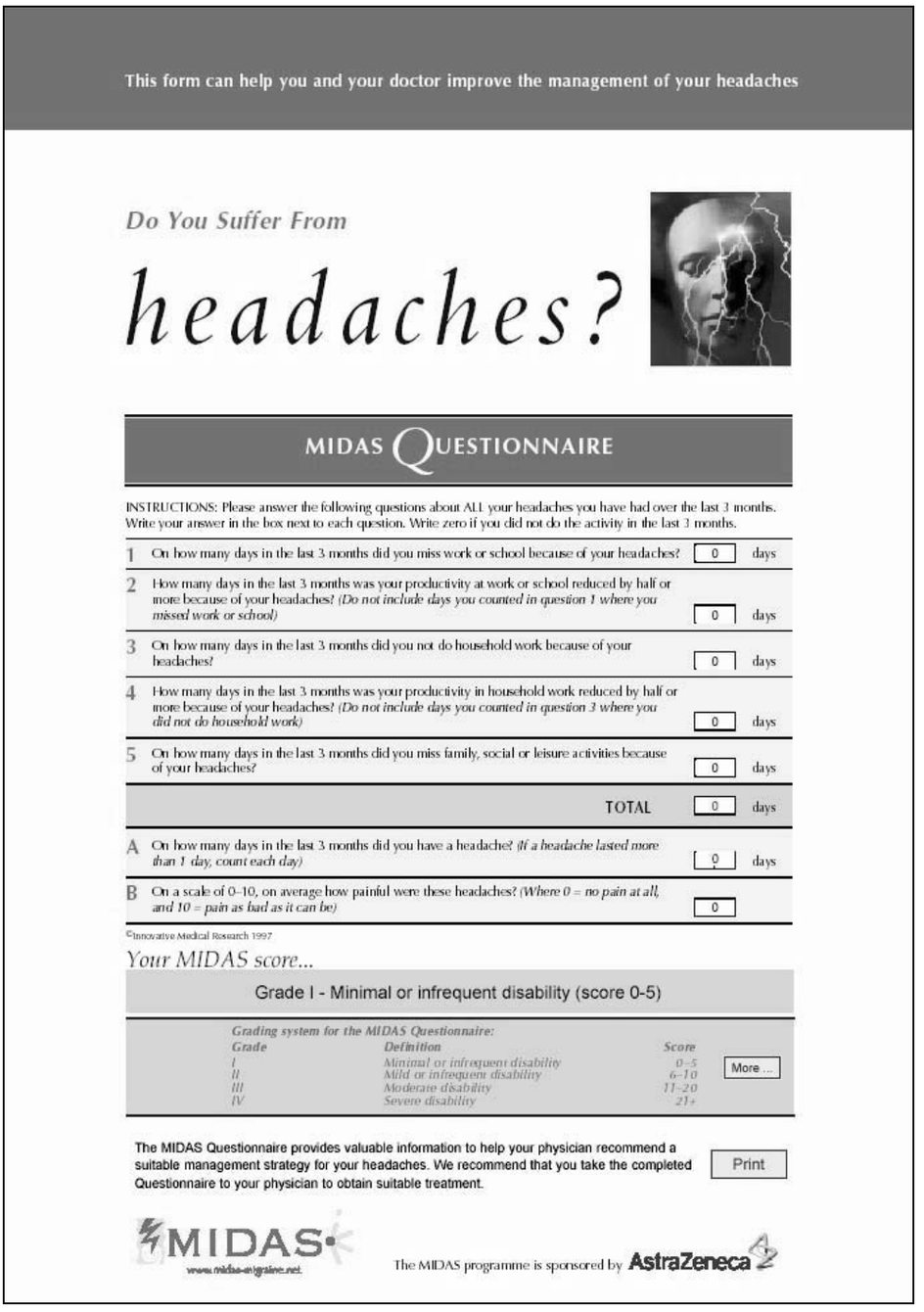
MIDAS is a paper-based questionnaire, designed to be accessible at physicians' surgeries and pharmacies. Headache sufferers answer five questions in three activity domains covering the previous 3-month period (Figure 3).[26] They score the number of lost days due to headache in employment, household work and family and social activities. Sufferers also report the number of additional days with significant limitations to activity (defined as at least 50% reduced productivity) in the employment and household work domains. The total MIDAS score is obtained by summing the answers to the five questions as lost days due to headache. This can sometimes be higher than the actual number of lost headache days due to any one day being counted in more than one domain. The score is categorised into four

severity grades: Grade I = 0–5 (defined as minimal or infrequent disability); Grade II = 6–10 (mild or infrequent disability); Grade III = 11–20 (moderate disability); Grade IV = 21 and over (severe disability); Two other questions (A and B) are not scored, but were designed to provide the physician with clinically relevant information on headache frequency and pain intensity. Information on MIDAS can be accessed at www.migraine-disability.net.

MIDAS was tested extensively and shown to have face validity (i.e. meets physicians' conceptions of important clinical criteria) and to be reliable, accurate, easy to use and score and intuitively meaningful to physicians.[27–29] These features support its suitability for use in clinical practice. MIDAS has been proposed as an aid to communication between patients and healthcare professionals, as an aid to referral for primary care physicians, as a means of specifying treatment by using it to stratify patients according to their treatment needs, as an outcome measure and as a public health initiative to coordinate public policies for migraine management.[8]

The MIDAS Questionnaire has several strengths. It has proved to be an effective aid to communication between physicians and their migraine patients with regard to disability, a subject often overlooked in conventional consultations.[30] MIDAS is now widely used for this purpose by headache specialists and neurologists. Clinical studies have shown that MIDAS is sensitive to change, and can be used as an outcome measure in the follow-up of patients with migraine or CDH during treatment.[31,32] However, these data require corroboration in large scale clinical trials.

Figure 3. The Migraine Disability Assessment (MIDAS) Questionnaire.[26] The MIDAS Program was developed by Innovative Medical Research Inc, with sponsorship and assistance from AstraZeneca.



This form can help you and your doctor improve the management of your headaches

Do You Suffer From

headaches?

MIDAS QUESTIONNAIRE

INSTRUCTIONS: Please answer the following questions about ALL your headaches you have had over the last 3 months. Write your answer in the box next to each question. Write zero if you did not do the activity in the last 3 months.

1	On how many days in the last 3 months did you miss work or school because of your headaches?	0	days
2	How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? *(Do not include days you counted in question 1 where you missed work or school)*	0	days
3	On how many days in the last 3 months did you not do household work because of your headaches?	0	days
4	How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches? *(Do not include days you counted in question 3 where you did not do household work)*	0	days
5	On how many days in the last 3 months did you miss family, social or leisure activities because of your headaches?	0	days
	TOTAL	0	days
A	On how many days in the last 3 months did you have a headache? *(If a headache lasted more than 1 day, count each day)*	0	days
B	On a scale of 0–10, on average how painful were these headaches? *(Where 0 = no pain at all, and 10 = pain as bad as it can be)*	0	

©Innovative Medical Research 1997

Your MIDAS score...

Grade I - Minimal or infrequent disability (score 0-5)

Grading system for the MIDAS Questionnaire:

Grade	Definition	Score
I	Minimal or infrequent disability	0–5
II	Mild or infrequent disability	6–10
III	Moderate disability	11–20
IV	Severe disability	21+

More...

The MIDAS Questionnaire provides valuable information to help your physician recommend a suitable management strategy for your headaches. We recommend that you take the completed Questionnaire to your physician to obtain suitable treatment.

Print

MIDAS www.midas-migraine.net

The MIDAS programme is sponsored by AstraZeneca

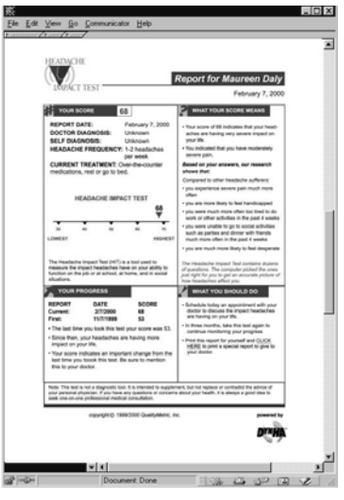
However, MIDAS also has several weaknesses. It does not assess the full spectrum of headache, covering only about 35% of the range between moderate and severe intensity.[33] This may be due to its reliance on a single measure (disability). Additionally, the MIDAS grade score may not indicate the true medical need of patients. In the author's clinical practice, many needy patients scored as Grade I, theoretically with little disability. A US study has shown that about 10% of MIDAS Grade I headache sufferers had more than six severely painful headaches per year.[34] On the other hand, patients with frequent headaches, e.g. chronic daily headache, tend to all score as Grade IV. Some physicians have suggested that

MIDAS is weighted towards the measurement of headache frequency over disability. Relatively few physicians currently use MIDAS as a tool to specify treatment according to the patient's disability grade, despite some evidence for this from a large clinical trial.[35]

The Headache Impact Test (HIT)

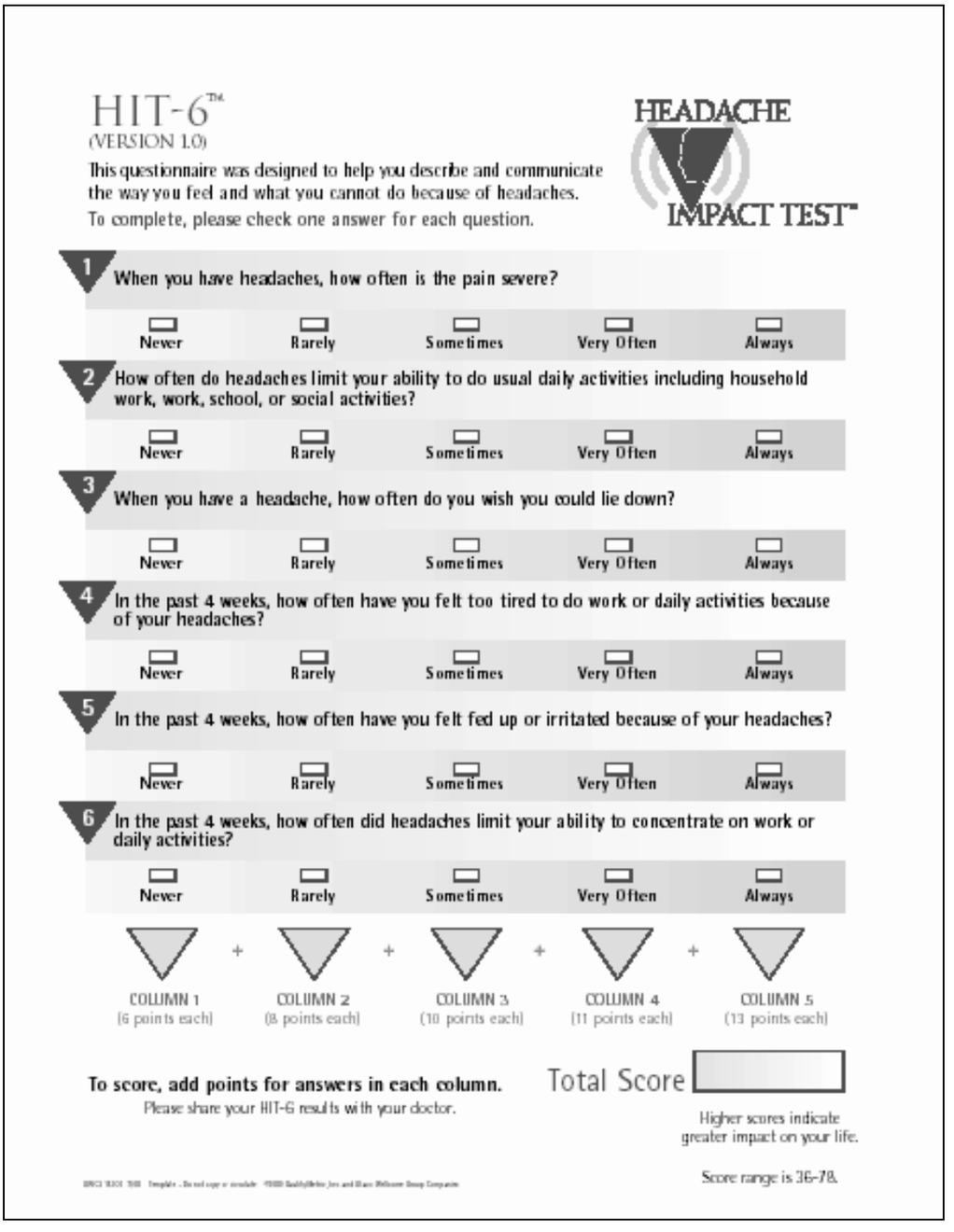
HIT was first developed as a web-based test, designed to be accessible to all physicians and headache sufferers through the Internet (at www.headachetest.com and www.amlhealthy.com). Questions are not printed on forms in advance. Rather, it is a dynamic questionnaire (Figure 4), with items derived from four validated headache questionnaires sampling all areas of headache impact (the Headache Disability Inventory [HDI], the HImQ, the MIDAS Questionnaire and the Migraine-Specific Quality of Life Questionnaire [MSQ]).[36] Patients are questioned until clinical standards of score precision are met. Internet-HIT matches the questions asked to each patient's severity level. In practice, five questions are sufficient to grade the majority of headache sufferers.[36] Clinical standards of accuracy were met by 98% of migraine sufferers, and 97%, 87% and 61% of people with severe, moderate and mild headaches, respectively, completing five or fewer questions. In an extensive testing study in over 19,000 headache sufferers in the USA, Internet-HIT was shown to be reliable and valid, and covered the whole spectrum of headache.[33,37,38] Coverage was similar to that reported for HImQ and much greater than that of MIDAS.[33] Results showed that migraine had greater impact on sufferers' lives than most other headaches.[37] Internet-HIT differentiated sufferers on the basis of diagnosis and characteristics such as headache severity and frequency.[37] It took only 1–2 minutes to complete, and its use motivated headache sufferers to seek medical care and facilitated headache-related communication between patients and their physicians.[39]

Figure 4. The web-based Headache Impact Test (Internet-HIT).[36,37] HIT was developed by QualityMetric Inc and GlaxoSmithKline.



HIT-6 is a paper-based, short-form questionnaire based on the Internet-HIT question pool, designed for people without access to the Internet (Figure 5). Six questions cover pain severity, loss of work and recreational activities, tiredness, mood alterations and cognition. Each question is scored on a five-point scale, with the scores being added to produce the final score.[40] HIT-6 scores are categorised into four grades, representing minimal, mild, moderate and severe impact due to headache. Studies have shown that HIT-6 is reliable and valid,[40] and can be used to help diagnose headaches and select management strategies according to headache severity.[41,42] Also, HIT-6 scores were directly related to self-reported hours of workplace productivity loss due to headache.[43] Internet-HIT and HIT-6 scores compared well to each other when the two forms of the questionnaire were tested on a group of headache sufferers.[44]

Figure 5. The paper-based short form Headache Impact Test (HIT-6).[40] HIT was developed by QualityMetric Inc and GlaxoSmithKline.



HIT-6™
(VERSION 1.0)

HEADACHE IMPACT TEST™

This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.
To complete, please check one answer for each question.

1 When you have headaches, how often is the pain severe?

☐ Never ☐ Rarely ☐ Sometimes ☐ Very Often ☐ Always

2 How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?

☐ Never ☐ Rarely ☐ Sometimes ☐ Very Often ☐ Always

3 When you have a headache, how often do you wish you could lie down?

☐ Never ☐ Rarely ☐ Sometimes ☐ Very Often ☐ Always

4 In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?

☐ Never ☐ Rarely ☐ Sometimes ☐ Very Often ☐ Always

5 In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?

☐ Never ☐ Rarely ☐ Sometimes ☐ Very Often ☐ Always

6 In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?

☐ Never ☐ Rarely ☐ Sometimes ☐ Very Often ☐ Always

COLUMN 1 (6 points each) + COLUMN 2 (8 points each) + COLUMN 3 (10 points each) + COLUMN 4 (11 points each) + COLUMN 5 (13 points each)

To score, add points for answers in each column.
Please share your HIT-6 results with your doctor.

Total Score ☐

Higher scores indicate greater impact on your life.

Score range is 36–78.

Both the MIDAS and HIT tools provide scientifically reliable and valid measures of headache impact, and show great promise for wide utility in clinical practice. However, both forms of HIT appear to have certain advantages over MIDAS. HIT has the brevity of a short-form questionnaire but has the accuracy required for measuring individual patients at all levels of impact. This may be due to its wider range of questions compared to MIDAS, which scores time lost due to headache only. HIT is also more widely accessible than MIDAS, designed to be used by everyone through the Internet and as a paper-based form. However, HIT was developed more recently than MIDAS and has so far not been used in clinical practice to the same extent. So far, only MIDAS has exhibited sensitivity to change and can therefore be used to monitor the outcome of therapy.[31,32] HIT has not been tested for this, but may be expected to also have this feature. Future work will define further the place of each of these impact tools in primary care, and such studies are currently underway with HIT.

Strategies for managing migraine using impact measures

Although impact measures for migraine are a recent development, they have been adopted widely by many opinion leaders in the field of headache. Both MIDAS and HIT have been proposed to have a wide potential for use in clinical practice, to improve communication between physicians and their patients, to assess illness severity and as public health measures.[8,39,41,42] Impact measures have been incorporated in several initiatives to develop guidelines for the management of migraine in primary care, including those issued by the Migraine in Primary Care Advisors (MIPCA) in the UK[45] and the Headache Consortium[46] and the Primary Care Network[47] in the USA.

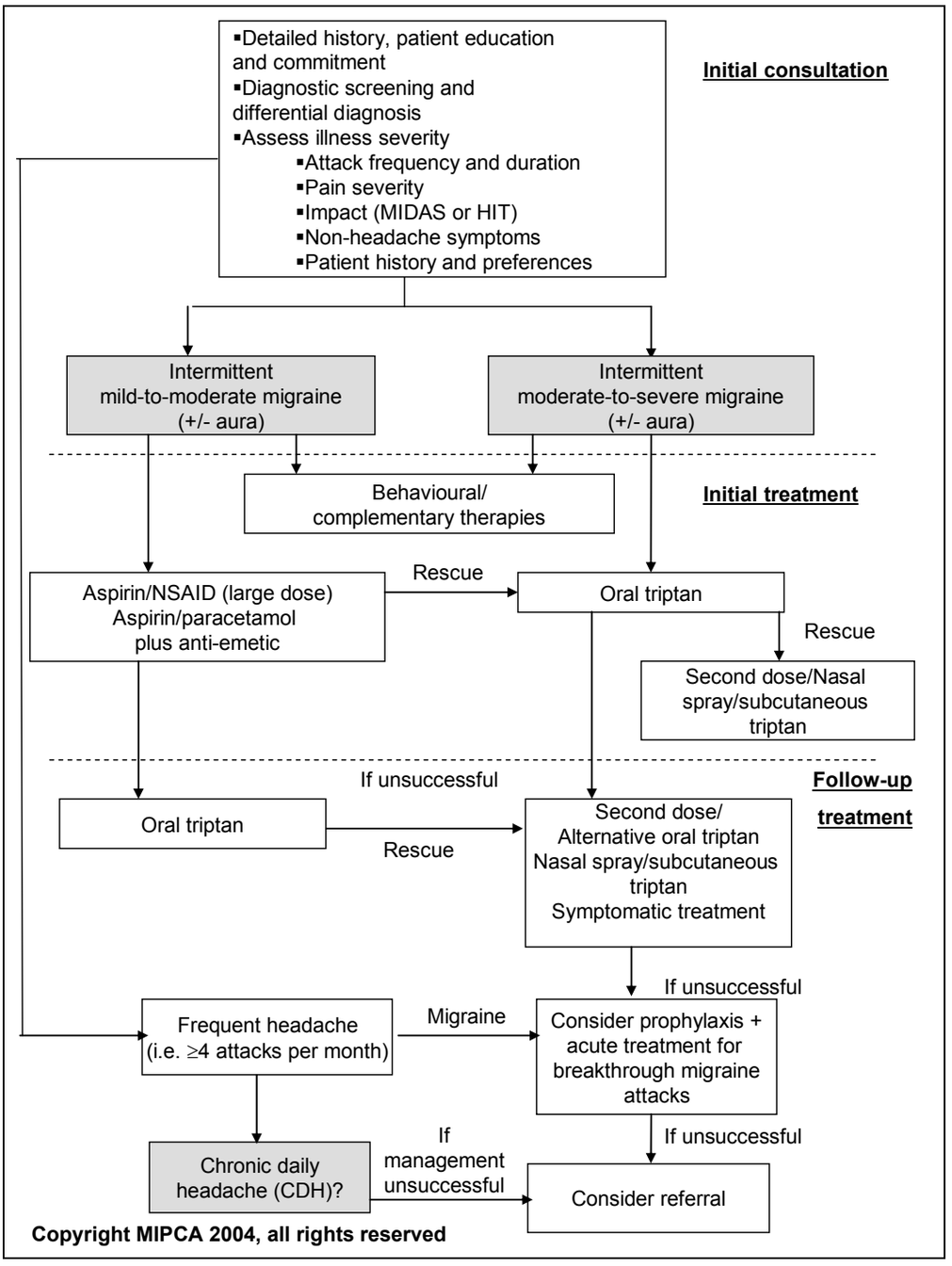
These three sets of guidelines have several features in common. They use assessments of migraine impact or disability in the initial evaluation of patients and recommend that treatment should be tailored to the patient's individual needs. Additionally, patients who have disabling migraine are recommended to have access to migraine-specific therapies from the outset. Assessing migraine impact has obvious applications in these areas of management and future migraine guidelines are likely to incorporate impact tools significantly.

The Migraine in Primary Care Advisors' (MIPCA) Guidelines

In 1997, MIPCA was the first organisation to advocate assessing the impact of migraine as part of its management strategy, before clinically valid impact tools had been developed. Fully revised and evidence-based guidelines were published in 2002,[45] and updated in 2004.[48] MIPCA advocates an individualised approach to care, treatment being prescribed according to each patient's needs. Factors considered include the nature of the patient's attacks, the impact of headache on the individual's life and the demands of the patient's lifestyle.

The MIPCA guidelines are illustrated in Figure 6. At the initial consultation, the physician is recommended to conduct a diagnostic assessment and to take a careful history covering the nature of the headaches, previous treatments taken and the impact on the patient's life. Patients who experience up to four attacks per month are given acute therapy with a simple analgesic, with or without an anti-emetic (for mild-to-moderate migraine) or an oral triptan (for moderate-to-severe migraine). Rescue medication is also given for when the initial treatment fails. Nasal spray or subcutaneous triptan formulations may be considered if the patient has difficulties with oral therapies or requires a fast therapeutic effect due to the demands of their lifestyle.

Figure 6. The MIPCA management guidelines for migraine in the UK.[45]



If the initial therapy is unsuccessful, an alternative therapy should be provided. For patients who fail on multiple acute therapies, and for migraine patients with four or more headaches per month, prophylactic treatment is recommended, together with additional acute treatment for breakthrough attacks. Migraine patients who fail on this treatment, and those diagnosed with chronic daily headache (CDH), may require referral to a specialist physician.

Commentary

Migraine is a remarkably disabling condition, but is not always managed effectively in primary care. Barriers to migraine care exist for both general practitioners (GPs) and patients, leading

to under-consultation, under-diagnosis and under-treatment. Patients often do not rate non-headache symptoms as medical and tend not to communicate the disability they suffer. In two studies with a total of 105 physicians in North America and Europe, only about one third of patients were reported to volunteer information about their headache-related disability.[30] It can be difficult for the physician to go through protocols with patients. Headache diaries, though useful, need reinforcement with other measures and GPs need to know that migraine causes disability. In the same North American / European studies discussed above,[30] physicians reported that they recorded symptoms related to diagnosis (e.g. pain intensity and associated symptoms) rather than information on headache-related disability. Similar results have been reported from the UK. In a recent study of 33 UK GPs, only 54% took the impact of migraine into consideration on diagnosis as opposed to 81% who assessed family history, 93% who assessed symptomatology and 90% who assessed trigger factors (AJ Dowson, unpublished results). Only 24% of the physicians felt that migraine always had an impact on the patient's life. Such assessments of impact were subjective, as none of the GPs was aware of the MIDAS or HIT impact tools. Overall, measuring the impact of migraine is likely to aid the initial assessment of migraine, and improve treatment delivery.

Research has shown that the impact of migraine and other headaches can be measured using assessments of some or all of pain severity, headache frequency, limitations to work and leisure activities, tiredness, mood alterations and cognition. Tools that address headache impact are now available and are being brought into clinical use. The MIDAS Questionnaire assesses disability only, as lost time in employment, unpaid work and family and leisure activities, whereas HIT assesses a global range of impact, including pain intensity, disability and other items, which can be tailored to the individual in Internet HIT.

Neither MIDAS nor HIT is used widely in UK general practice. MIDAS is used in specialist practices, where it has proved to be effective in improving communication between physicians and their patients, and as a measure of treatment outcome. However, it has not proved as useful when tested in UK general practice, partly due to the overlapping nature of the questions. Patients too, are unsure of it. Little or no feedback was received from Migraine Action Association (MAA: the UK headache patient support group) members when MIDAS was published in the MAA Newsletter and tested in pharmacies in the UK. HIT has not been used significantly to date in UK clinical practice.

An impact tool can be recommended for the primary care of migraine and its desirable attributes identified. It should be a self-administered form that is able to be summarised briefly. Open questions should be used, rather than a 'ticking boxes' approach. The tool should be used in the physician's initial assessment to aid in the initiation of appropriate management strategies. It should also be able to measure the efficacy of medications and needs to be discriminating, e.g. impact testing may be used as a tool to measure if a treatment is working for a patient, rather than merely if it is not. If the treatment is working, the patient should remain on that same treatment. In practice, the impact tool should be integrated with other assessments of migraine symptoms. Finally, impact tools need to be refined and shown to work in general practice, where they can be used to review patient costs and potential cost savings of treatments. From the patients' viewpoint, it is important to ask questions about migraine impact, but this should be taken as part of the whole clinical judgement of patients' needs.

Migraine impact is probably the most important headache assessment for the patient. Impact tools should therefore be widely accessible to patients at home, in pharmacies and GPs' waiting rooms and with nurse consultants, e.g. in well woman clinics. They should also have positive effects on the GP's practice, highlighting that migraine is a disabling illness and raising its profile in primary care. However, education of both patients and physicians on migraine impact and the use of impact tools will be necessary for their successful

introduction. The initial launch of impact tools is probably best achieved through headache clinics and GPs with an existing interest in treating headache.

Both MIDAS and HIT meet many of the above desirable attributes for an impact tool suitable for use in primary care. They are both brief, simple to use and score, and have demonstrated scientific validity and clinical utility. HIT has greater accessibility (by design for use on the internet and as a paper-based form) and a greater coverage of the spectrum of headache patients, irrespective of their illness severity. MIDAS is sensitive to change and is increasingly being used as an outcome tool in clinical studies.[31,32] However, with MIDAS, there is the possibility of patients with infrequent but disabling headache being categorised as having minimal disability, and so being overlooked.

Recently published guidelines for the management of migraine have included assessments of migraine impact in the evaluation of migraine severity and treatment choice, in conjunction with traditional history taking and symptom evaluation. These guidelines advocate an individualised approach to care, where patients are managed according to their illness severity and lifestyle needs. Patients are educated and encouraged to play a key role in the care decisions made. However, previously published guidelines for migraine management in many countries, including the UK,[49] USA[50] and Germany[51] make no mention of assessing migraine impact in the evaluation of patients. Nevertheless, impact assessments have a central role in the management of migraine and should be used in the development of new guidelines for primary care in the UK.

In conclusion, the assessment of migraine impact is important in UK primary care. The use of impact tools can improve communication between physicians and their patients, aid in the assessment of migraine severity and the production of an individualised treatment plan in concert with other clinical assessments, and in the monitoring of the response to therapy. In the future, impact tools will be used in generalised headache management guidelines for the UK. As yet, it is not possible to unequivocally recommend the optimal impact tool, but it should be usable by GPs, pharmacists, nurses and patients, and should also be useful for purposes of research.

Acknowledgements

This paper was presented at a meeting of the Migraine in Primary Care Advisors (MIPCA) on 14 June 2001 at the Berystede Hotel, Ascot, Berkshire, UK, sponsored by GlaxoSmithKline. Meeting attendees were Dr Tony Bland, Chester, UK; Dr Sue Bradford, Sheffield, UK; Dr Frances Carter, London, UK; Dr Heather Fearon, Runcorn, UK; Dr Ahmet Fuat, Darlington, UK; Dr Trevor Rees, Solihull, UK; Ms Heather Spitall, Birmingham, UK; Ms Ann Turner, Migraine Action Association, Northampton, UK; Dr David Watson, Aberdeen, UK. The author thanks all the meeting attendees for their valuable contributions to the issues discussed in this article

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4.2

The outcome of headache management following nurse intervention: assessment in clinical practice using the Migraine Disability Assessment (MIDAS) Questionnaire*

Abstract

Objectives: This audit assessed the outcome of a nurse intervention strategy in patients presenting with headache to a primary care surgery.
Methods: All patients aged 18–65 years attending the surgery who reported headache in the previous 3 months were assessed by a nurse and completed a Migraine Disability Assessment (MIDAS) Questionnaire and a questionnaire investigating headache features and physician consultations. All patients were given oral and written advice on headache management by the nurse. Patients of MIDAS Grade I/II (minimal-mild disability) with severe or frequent headaches and all Grade III–IV (moderate-severe disabling headache) patients were also offered an appointment with a headache specialist physician. Patients were reviewed after 3 and 6 months with the same questionnaires.
Results: A total of 195 patients took part in the study. At baseline, 136 (69.7%) were MIDAS Grade I/II and 59 (30.3%) were Grade III/IV. Compared with baseline, patients reported significant mean reductions at 6 months in: total MIDAS scores (5.9 *versus* 9.6; $p = 0.014$); headache frequency (MIDAS A score: 7.0 *versus* 12.6; $p = 0.009$); headache severity (MIDAS B score: 5.0 *versus* 6.0; $p = 0.003$); and physician consultations for headache (3-month period: 0.05 *versus* 0.30; $p = 0.05$).
Conclusions: Advice on headache management given by a nurse can potentially lead to significantly improved patient outcomes. MIDAS appeared to be a sensitive outcome measure for reduction in disability in headache sufferers. These results warrant further investigation in randomised, controlled clinical studies.

** Edited from the full published article: Dowson AJ, Salt R, Kilminster S. The outcome of headache management following nurse intervention: assessment in clinical practice using the Migraine Disability Assessment (MIDAS) Questionnaire. Headache Care 2004;1:177–81.*

Introduction

Headache management is currently suboptimal in primary care. Migraine patients remain under-diagnosed and under-treated, with many patients not consulting a physician for care,[1] and this state has improved little over the past decade or more.[2] Patients with chronic daily headache (CDH) are frequently not managed in primary care, but are referred to specialist headache clinics.[3] Sufferers of tension-type headache rarely consult a physician for care.[4] Recently published guidelines for migraine management in the UK advocate a primary care team approach to headache management, utilising practice nurses and other healthcare professionals, as well as the physician.[5] A UK pilot study has suggested that headache education provided by nurses can be effective in reducing the severity of headaches.[6] Following advice given by a primary care nurse to a group of headache sufferers, the severity of headache and associated disability declined over a 6-month period compared to a control group who did not receive this advice. In addition, a retrospective study in the USA indicated that the provision of headache advice by Advanced Practice Nurses resulted in improved quality of life in adult migraine patients.[7]

The practice nurse may therefore have a key role to play in the management of headache patients. This audit was set up to investigate the outcome of a nurse intervention strategy in patients presenting with headache to a primary care clinic. The main outcome measure used was the Migraine Disability Assessment (MIDAS) questionnaire. MIDAS assesses the disability associated with headache, by measuring the days lost over a 3-month period in employment or education, unpaid work and family and leisure activities.[8] MIDAS is a reliable and valid measure of disability,[9] and has been shown to be sensitive to changes in outcome in clinical studies.[10,11] MIDAS is scored as the number of days of missed activity and scores are categorised as Grade I (score 0–5; minimal or infrequent disability), Grade II (score 6–10; mild or infrequent disability), Grade III (score 11–20; moderate disability), or Grade IV (score over 20; severe disability).[9]

Patients and methods

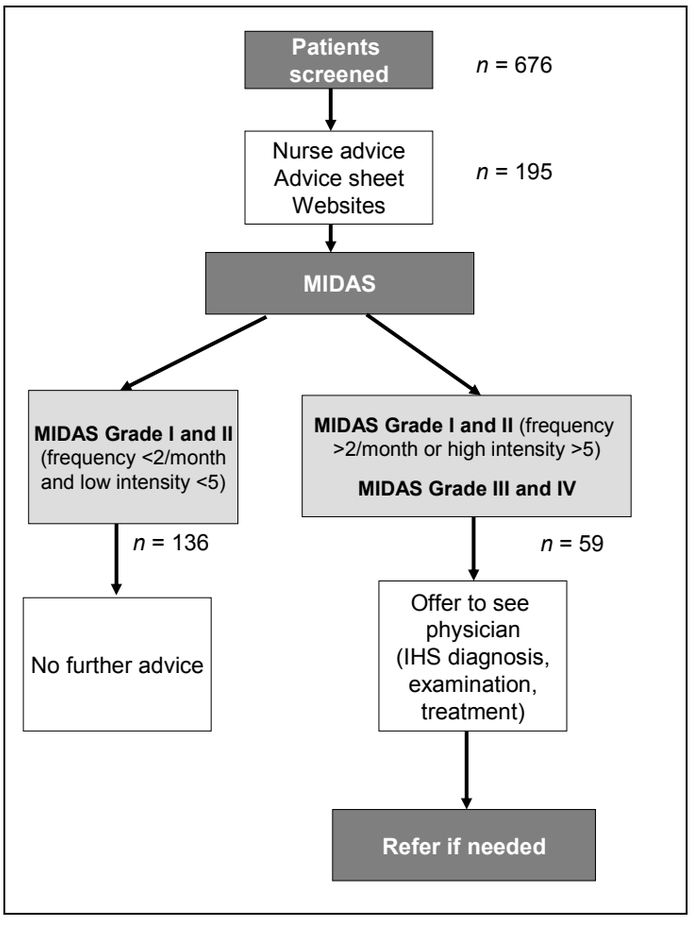
All patients aged 18–65 years attending the primary care Merrow Park Surgery in Surrey, UK for any reason were interviewed. Those who reported headache in the previous 3 months were eligible for inclusion in the audit. Patients were assessed by a primary care nurse with experience in headache (RS) and completed a MIDAS Questionnaire and a questionnaire investigating headache features and physician consultations (Table 1).

Table 1. Nurse-administered questionnaire investigating patients' headache features and physician consultations.

1. In the last 3 months how many times have you consulted your GP?
2. How many of these consultations were specifically about headaches?
3. Do you think your headaches affect your mood?
4. Do you think your headaches make you tired or lethargic?
5. Do you feel an improvement in your headaches compared with 3 months ago?
6. Do you feel that overall you need to see your GP less now?

The design of the audit is illustrated in Figure 1.

Figure 1. Design of the audit: management decisions during the study.
IHS = International Headache Society.



All patients were given oral and written advice on headache management by the nurse, covering trigger factors, use of acute medications, treatment targets, prevention of frequent attacks and consulting with a physician if chronic daily headache was suspected. Patients were referred to the UK patient support group, The Migraine Action Association, for further information. Patients with MIDAS Grades I–II (minimal or mild disability), with infrequent and low intensity attacks, received no further specific headache management advice. However, patients with MIDAS Grades III–IV (moderate-severe disabling headache), plus those with MIDAS Grades I–II and either frequent or severe intensity attacks, were offered an appointment with a headache specialist physician (AJD), for diagnosis and appropriate interventions. Patients were further reviewed by the nurse after 90 and 180 days, when they again completed the MIDAS questionnaire and the questionnaire investigating headache features and physician consultations (Table 1).

Endpoints from the audit included:

- The total MIDAS score (days lost from daily activities over the previous 3-month period).
- MIDAS Question A score (headache frequency over the previous 3-month period).
- MIDAS Question B score (average headache severity over the previous 3-month period, using a 10-point scale where 0 = no pain and 10 = pain as bad as it can be).
- Patients' headache features and physician consultation (from the questionnaire in Table 1).

Summary statistics were calculated as changes from baseline at 90 and 180 days for each item and were analysed by *t*-tests for dependent samples. The definition of significance was set at $p \leq 0.05$. Additional non-parametric analyses, using Wilcoxon rank tests, were also conducted on these data. This was required, as MIDAS data are not necessarily normally distributed due to floor effects (patients can score 0 on the questionnaire).[12]

Results

Baseline characteristics

A total of 676 patients were interviewed by the nurse, of whom 477 did not report headaches, 195 (28.8%) had headaches and took part in the audit, and four declined to participate. At baseline, 136 patients (69.7%) were MIDAS Grade I/II with low headache severity and frequency and 59 (30.3%) were Grade I/II with high headache severity and frequency or Grade III/IV. These 59 patients were offered an appointment with the headache specialist, but only 17 actually had the consultation. One hundred and ninety four patients had a recorded MIDAS score at baseline, and this number decreased to 87 and 70 patients at 90 and 180 days, respectively.

Changes in outcome scores at 90 and 180 days

Figures 2–5 illustrate the changes from baseline in the audit endpoints after 90 and 180 days. The MIDAS items all cover the 3-month period immediately preceding completion of the questionnaire. Compared with baseline, patients reported significant mean reductions in total MIDAS score at 180 days (5.9 *versus* 9.6 days; $p = 0.014$, Figure 2). Compared with baseline, patients reported significant mean reductions in headache frequency (MIDAS Question A score) at 180 days (7.0 *versus* 12.6 headaches; $p = 0.009$, Figure 3). Compared with baseline, patients reported significant mean reductions in headache severity (MIDAS Question B score) at 180 days (5.0 *versus* 6.0; $p = 0.003$, Figure 4). Similar results were reported when the data were analysed non-parametrically.

Compared with baseline, patients reported no significant changes at 90 and 180 days in the total number of times they consulted a GP, but did report significant mean reductions in the number of consultations for headache in the previous 3-month period at 180 days (0.05 *versus* 0.30 consultations; $p = 0.05$, Figure 5). Similar results were reported when the data were analysed non-parametrically.

Figure 2. Total MIDAS scores (total activity days lost due to headache in the previous 3 months) at baseline (n = 194), and 90 (n = 87) and 180 (n = 70) days. Results are presented as means, ± SE (boxes) and ± 1.96 SE (bars).

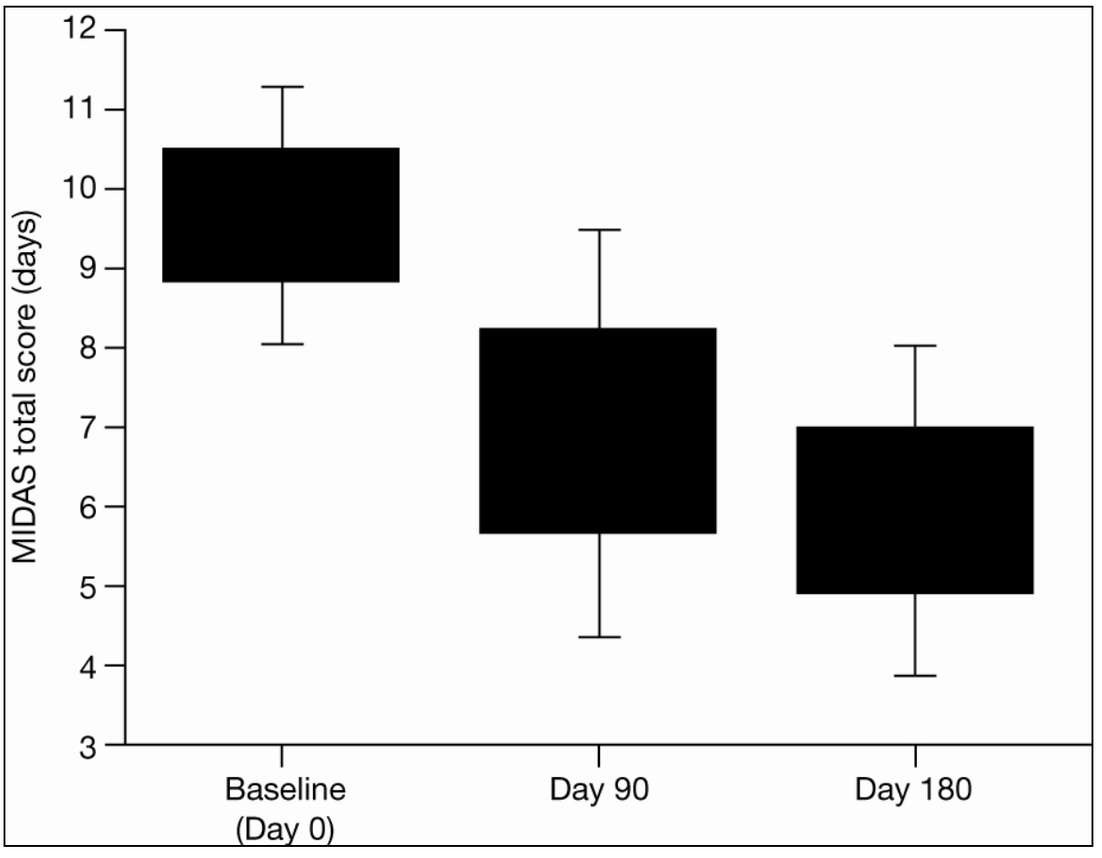


Figure 3. MIDAS Question A scores (number of days with headache in the previous 3-month period) at baseline (n = 192) and at 90 (n = 86) and 180 (n = 68) days. Results are presented as means, ± SE (boxes) and ± 1.96 SE (bars).

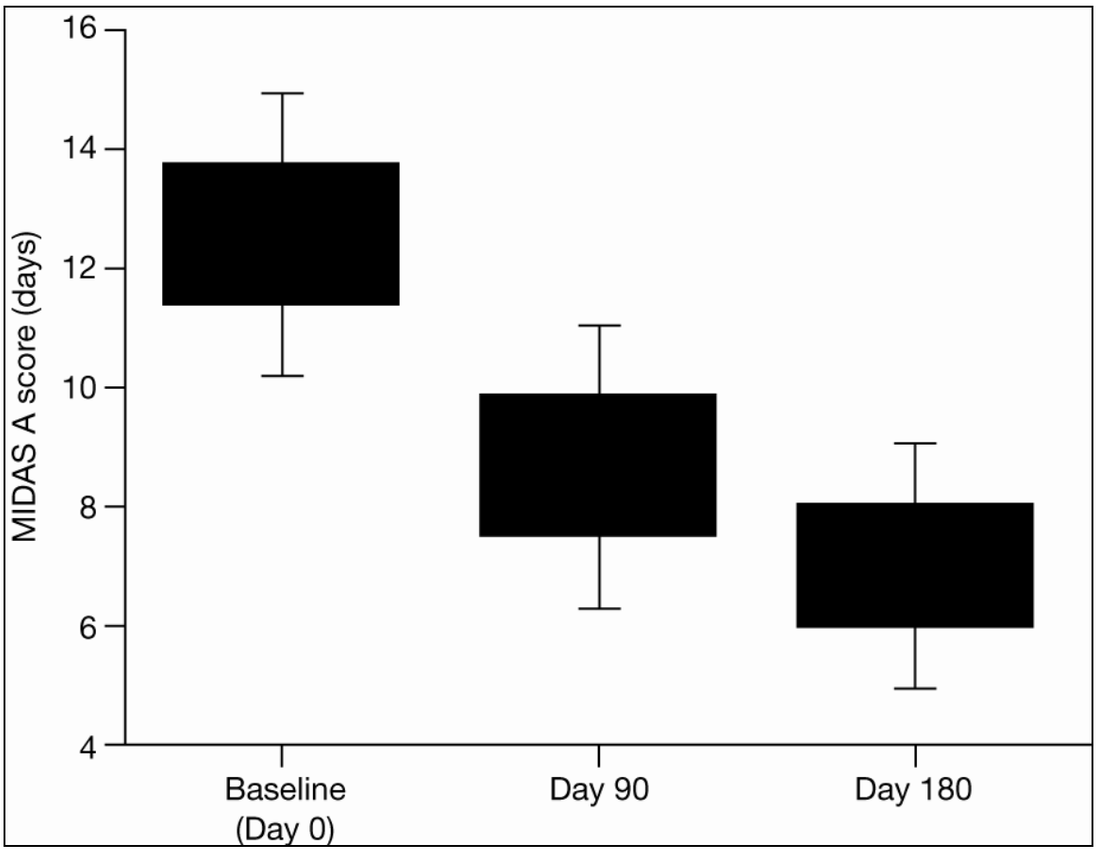


Figure 4. MIDAS Question B scores (average headache severity in the previous 3 months, where 0 = no pain at all, and 10 = pain as bad as it can be) at baseline (n = 194) and at 90 (n = 87) and 180 (n = 68) days. Results are presented as means, ± SE (boxes) and ± 1.96 SE (bars).

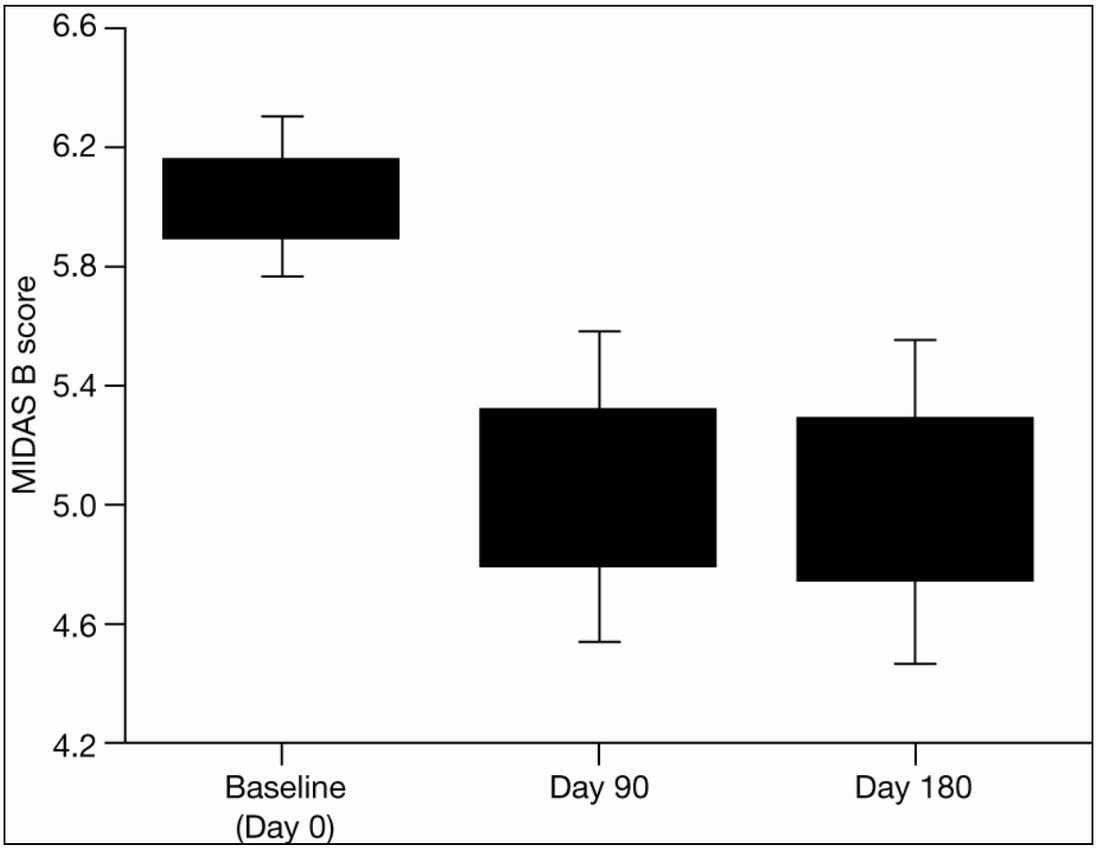
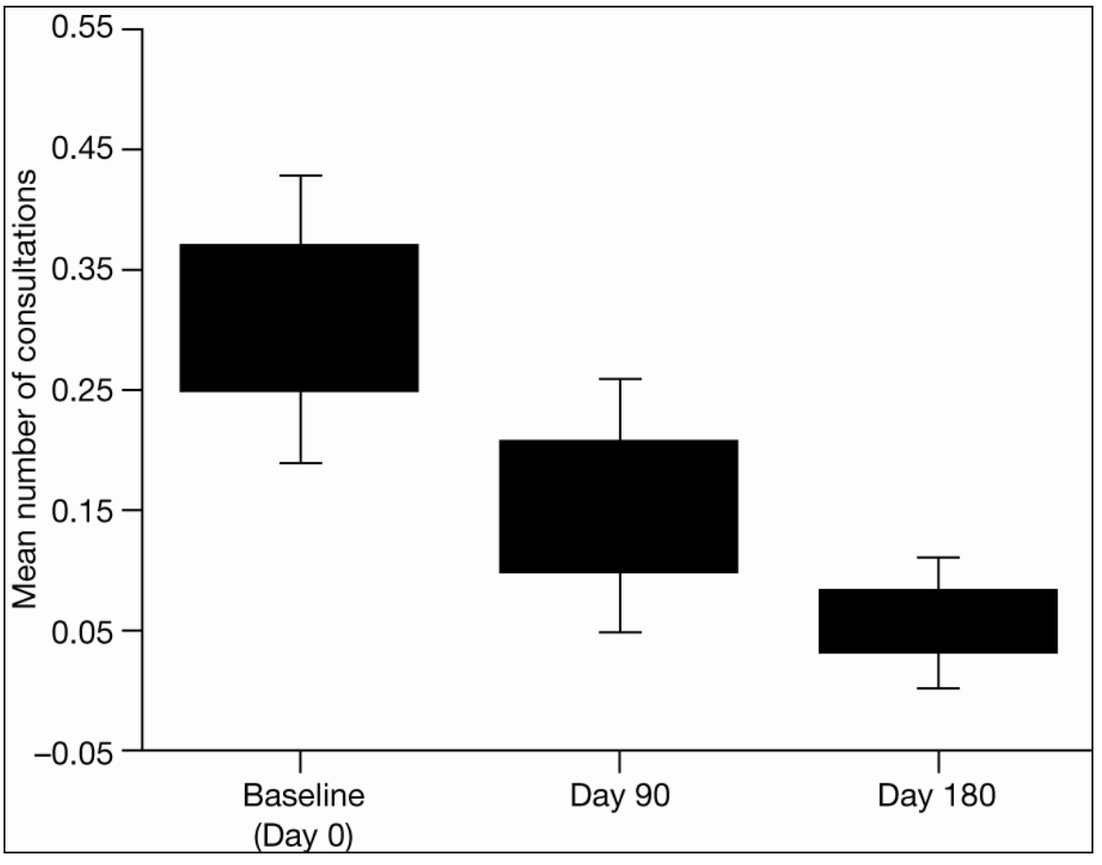


Figure 5. Average number of consultations for headache per patient in the previous 3-month period: data for baseline (n = 194), and 90 (n = 85) and 180 (n = 70) days. Results are presented as means, ± SE (boxes) and ± 1.96 SE (bars).



Throughout the study, approximately 90% of patients self-reported that headaches affected mood and resulted in feelings of tiredness or lethargy. However, patients reported some improvement in headaches and the need to see their GP at 90 and 180 days compared with baseline (Table 2). However, no significant changes were reported in any of these items during the study (Table 2).

Table 2. Patient perceptions of headaches at baseline, and 90 and 180 days: percentage of patients reporting 'Yes' to the questions.

	Percentage of patients		
Question	**Day 0**	**Day 90**	**Day 180**
Do you think your headaches affect your mood?	91.2	87.8 (NS)	90.0 (NS)
Do you think your headaches make you tired or lethargic?	90.2	87.1 (NS)	93.1 (NS)
Do you feel an improvement in your headaches compared with 3 months ago?	38.2	38.3 (NS)	45.6 (NS)
Do you feel that overall you need to see your GP less now?	NA	48.5	62.5 (NS)

NA = Not applicable
NS = not significant

Discussion

Results from this audit illustrate the positive role that the practice nurse can have in the management of headache in primary care. Recent UK guidelines provide clear roles for nurses in the screening and follow-up of migraine patients.[5,13] Recommendations state that nurses should undertake information dissemination and recording of data using headache history and impact questionnaires and headache diaries. Previous, small studies have indicated that the provision of information by nurses can have a positive effect on headache, even when no other interventions are provided.[6,7]

Patients who took part in the audit were markedly affected by headaches, with approximately 90% reporting that headaches affected mood and caused tiredness. The baseline mean MIDAS score was 9.6, indicating mild to moderate headache-related disability. On average, patients experienced about 4 headaches per month. These patients had significantly improved headache outcomes at 180 days compared with baseline, in terms of headache-related disability, headache frequency and severity. Additionally, they perceived an improvement in headache and reported a reduced need for consulting a physician for headache. As very few patients consulted a physician during the audit, this improvement can be attributed with a reasonable degree of confidence to the advice given by the nurse on headache management.

MIDAS has been shown to be an accurate measure of headache severity[9] and to be sensitive to interventions, with drug treatments resulting in significant reductions in total MIDAS score.[10,11] In this audit, the mean MIDAS score was significantly reduced after 180 days, indicating headache improvement, which in turn correlated with the patients' self reporting of headache improvement and a reduced need to consult with a GP. MIDAS therefore seems to be a sensitive outcome measure for headache sufferers.

The audit does have certain shortcomings. As no control group was included, the reductions in MIDAS and other items could be due to a placebo effect. However, there was good evidence of significant improvements in MIDAS items and significant reductions in headache consultations, as parametric and non-parametric analyses exhibited the same patterns of results. Also, the numbers of patients were reduced due to drop outs as the visits proceeded, which may have caused some bias. The expected bias would result in an improvement. This is because, psychologically, patients are more likely to continue with an investigation if they are generally feeling well or better. Overall, this was an interesting exploratory study that

provided positive results. It paves the road for future randomised, controlled studies investigating the role of nurses in headache management.

In conclusion, this audit indicated that advice on headache management given by a nurse could potentially lead to significantly improved patient outcomes. MIDAS appeared to be a sensitive outcome measure for reduction in disability in headache sufferers.

Acknowledgement

This audit was sponsored in part by an unrestricted educational grant from AstraZeneca.

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4.3

Outcome measures compared: Headache Impact Test (HIT) and Short Pain Inventory© (SPI)*

Summary

The psychometric properties of the Headache Impact Test (HIT-DYNA®) were compared with the 17-item Short Pain Inventory (SPI©) in 75 patients presenting to primary care with tension-type headache, migraine or chronic daily headache. Also compared were the abilities of the SPI and HIT in terms of discriminating headache severity and diagnosis.

The HIT score correlated 0.28 with the severity of the headaches whereas the SPI correlated 0.76 on its Total Mood Disturbance score. The correlations of the HIT items with pain severity never rose above 0.26 whereas the correlations of the SPI items were all typically about 0.7. The SPI significantly discriminated with headache severity levels (none, mild, moderate, severe, extreme), with *t* values of 2–20. The HIT scores were far less powerful at discriminating severity, with *t* test values from 2–5. HIT scores at screening significantly discriminated with diagnosis, with the resolution between tension-type headache and chronic daily headache reaching 1/100 million. The SPI summary scores and subscales did not discriminate with diagnosis. These differences between HIT and SPI were confirmed by factor analysis.

The results showed the HIT to be poorly related to the severity of the pain but very closely related to the diagnostic label. In contrast to this, the SPI was very closely related to severity but not related to diagnosis.

** Summarised and edited from the published article: Kilminster SG, Dowson A, Bundy M. The Headache Impact Test® and the Short Pain Inventory©: Outcome measures compared. Int J Pharm Med 2003;17:23–32.*

Introduction

Pain outcome measures for clinical trials are broadly of two types; scales that measure the functional impact of the specific disease entity, and scales that index the general pain experience. The Oswestry Back Pain Questionnaire,[1] and the Headache Impact Test (HIT®)[2] typify questionnaires of the former type whereas the McGill Pain Questionnaire (MPQ)[3] and the Short Pain Inventory (SPI©)[4] represent the latter. Whatever methods used, and no matter how clever and complex their psychometric development, tests must be reliable and valid under specified conditions. The basic requirements include published internal reliability in the form of Cronbach alpha, split-half reliability, and test-retest reliability under specified time intervals. Additionally, the test should state clearly if it measures the here and now (state), the general (trait), or the retrospective (over the preceding weeks or months). The test should be able to discriminate and resolve fine detail on a scale of what it purports to measure (validity). The test data should show empirically whether it is a valid diagnostic or severity measure.

The HIT is a retrospective (4-week window) tool to measure the impact headaches have on a person's ability to function in their everyday activities.[5,6] The Dynamic Headache Impact Test (HIT-DYNA®) was designed to be administered via the Internet and was developed from questions included in four widely-used measures of headache impact (the Migraine-Specific Quality of Life Questionnaire [MSQ]; the Headache Disability Index [HDI]; the Headache Impact Questionnaire [HImQ] and the Migraine Disability Assessment Questionnaire [MIDAS]) using item response theory psychometric methods.[7] The MSQ, HDI, HImQ and MIDAS are all well referenced and psychometrically robust tests.[8–11] From a dynamic computerised HIT scoring system available on the web, in a few minutes the programme yields a description of the impact headaches are having on a patient's life and their ability to function.[12] Many of the items on the HIT are clearly retrospective, relating to the previous 4 weeks. In general, only five questions are required to obtain a HIT score.

The SPI is a prospective 17-item self-rating questionnaire dedicated to measuring any pain, not only headache. Patients rate each item on a five point Likert scale: *not at all, a little, moderately, very much so and extremely.* Five subscales measuring sedation, social interaction, anxiety, sadness and anger have been fine-tuned by emphasising items that were specific to pain. The SPI takes about one minute to complete and assesses the headache as it is at the time of completion. A scale of Total Mood Disturbance (TMD) can be summated from the SPI which measures the subtle mood changes that specifically covary with mild to severe pain. As the physical severity of pain worsens so generally does each of the emotional components.[4,13,14] If a patient's emotional score is exaggerated or flattened relative to the normative values, then a coping score can also be given as to how well a patient is coping with their pain, relative to others at the same physical level of pain. This can be very useful in the individual management of patients. Testing showed the SPI to be psychometrically robust.[4,13,14]

The psychometric properties of the computerised HIT (HIT-DYNA) were compared with the 17-item SPI in patients presenting to primary care with headache. Also compared were the severity of the headaches and the diagnostic labels given by a specialist neurologist, with the ability of the SPI and HIT in terms of discriminating between diagnoses and headache severity.

Methods

Patients

Patients who took part in the study were attending a general practice headache clinic at Cranleigh Health Centre, Surrey, UK (Dr Bundy). The study was approved by the South West Surrey Local Research Ethics Committee.

Design

This was a within-group comparative study carried out at one general practice (Cranleigh Health Centre headache clinic) comparing the discriminant validity of the computerized HIT (HIT-DYNA) and the SPI. The questionnaires were administered by a psychologist (SGK). A specialist neurologist (AD) provided a diagnosis for each patient based on the *International Headache Society* (IHS) criteria pertaining at the time,[15] and on his own clinical experience. The neurologist or his nurse supervised the Internet testing for the HIT evaluation. The SPI was self-completed at home at the following times:

1. Practise session at the practice.	Day 0
2. Within 1 hour after starting headache or on waking.	Day 1
3. Just after pain is worst (peak)	Day 1
4. 1 hour after headache has gone or on waking	Day 1
5. 24 hours after headache started.	Day 2
6. Evening of Day 2 about 8 pm	Day 2
7. Days 3–7 inclusive about 8 pm	Days 3-7

Explanation on how to complete the questionnaires was kept to a minimum and all spoiled forms were entered into the analysis on an intention-to-treat basis. This was done so as to reduce the administrator bias and evaluate the SPI as it would be used realistically in clinical screening settings.

Statistical methods

Analysis was by discriminant function analysis, simple *t*-tests, and test-retest Pearson product moment correlation coefficients. Statistical analysis was carried out on a Power Macintosh G4/400/200 machine with Statistica V4. All data points were double-validated against source forms. The analysis was carried out by a medical statistician (SGK).

For the discriminant validity analysis, the SPI recorded headache severity ('pain right now') as no pain (0), mild pain (1), moderate pain (2), severe pain (3), and extreme pain (4). Thus pain groups were divided by pain severity as screening samples. The SPI raw scores were used for the summary and components. The diagnostic labels derived from the IHS classification were dummy-coded. Summary and derivative SPI measures were then used as dependent variables in simple *t*-tests. Discriminant function analysis is the same as simple *t*-tests in this case where there is only one independent and one dependent variable. Factor analyses with orthogonal and Varimax rotation of the principal components was carried out to examine the structure and redundancy of the two tests.

Results

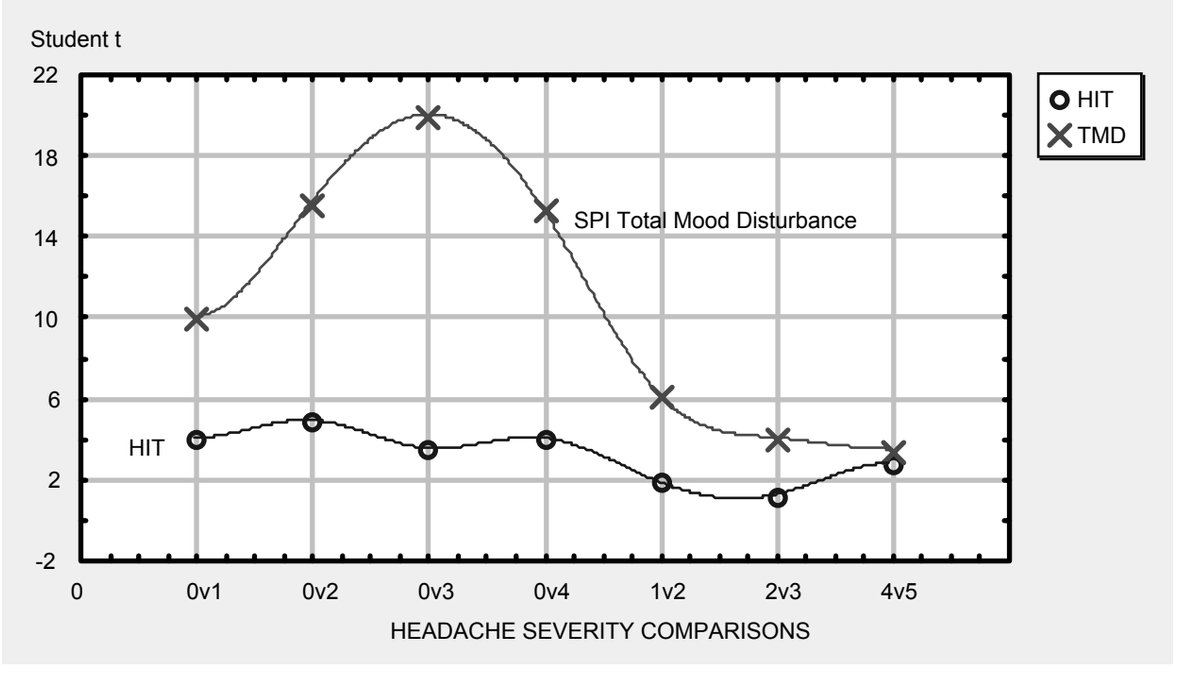
Demography

A total of 75 patients were recruited to the study, diagnosed with episodic TTH (15 patients [20%]), migraine (41 patients [54.7%]) and CDH (19 patients [25.3%]). The mean age of the patients was 44.3 (SD 9.8). The majority (73, 97.3%) were women. At screening, extreme pain (4) was reported by two patients (2.6%), severe pain (3) by six (8.2%), moderate pain (2) by eight (10.5%), mild pain (1) by 26 (34.2%) and no pain by 33 (44.7%). Forty two patients returned the completed questionnaires within 6 weeks Six of these patients had TTH (14.3%), 23 had migraine (54.8%) and 13 had CDH (31.0%). Drop outs (n = 33) were mostly due to patients not experiencing a headache during the 6-week window.

Differentiation of pain severity by HIT and SPI

Figure 1 shows the student *t* tests computed for headache severity comparisons of all headaches for the summary SPI TMD and HIT scores. As headache severity increased from none (0) to extreme (4) there was a highly significant increase in SPI TMD ranging from 4–20. There was a relative diminishment of *t* for 0 v 4 compared to 0 v 1, 0 v 2 and 0 v 3. This is probably explained by the low number of patients with extreme pain (*n* = 2). Nevertheless, the results showed the SPI TMD score had excellent discrimination at resolving the fine detail differences in pain severity. The HIT scores were far less powerful at discriminating headache severity, with *t* test values from 2–5 only.

Figure 1. Discriminant t-values of the SPI Total Mood Disturbance (TMD) and HIT at resolving the differences in pain severity (0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain; 4 = extreme pain).



The best correlation of the HIT with headache severity was 0.28. The relationship was much stronger with all of the SPI subscales and the correlation of the TMD score was 0.76.The nature of these relationships is also displayed in Figures 2 and 3. Similar results to the SPI TMD score were observed for SPI social interaction, sedation, sadness, anger and anxiety sub-scores.

Figure 2. Dynamic HIT scores relationship to headache pain severity (0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain; 4 = extreme pain)..

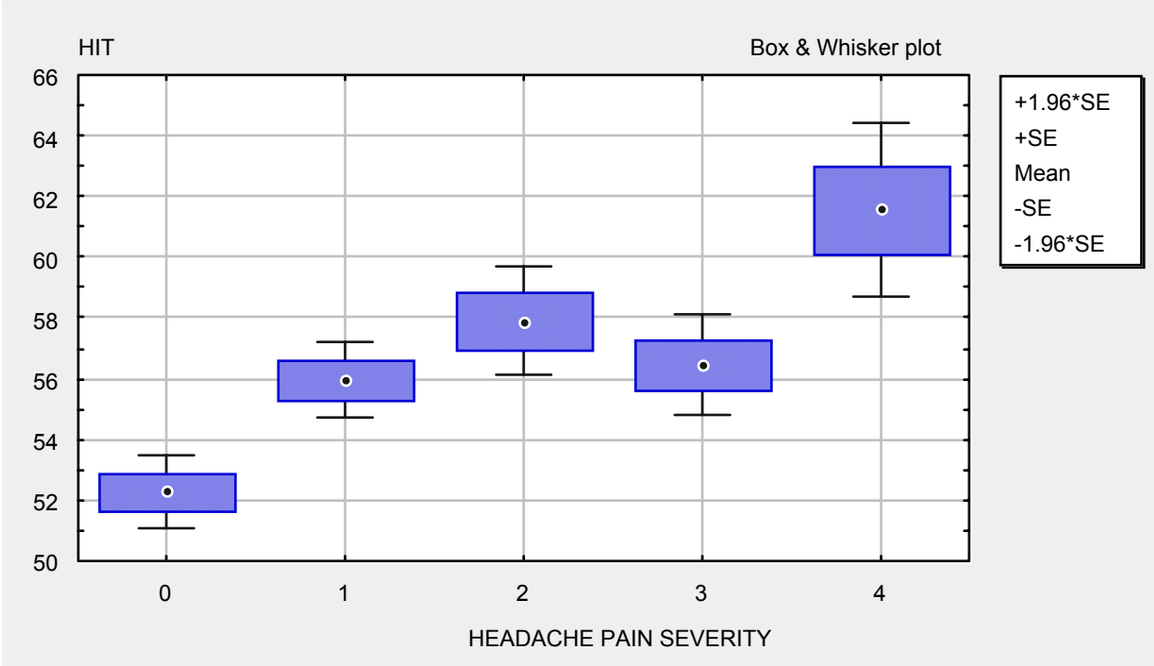
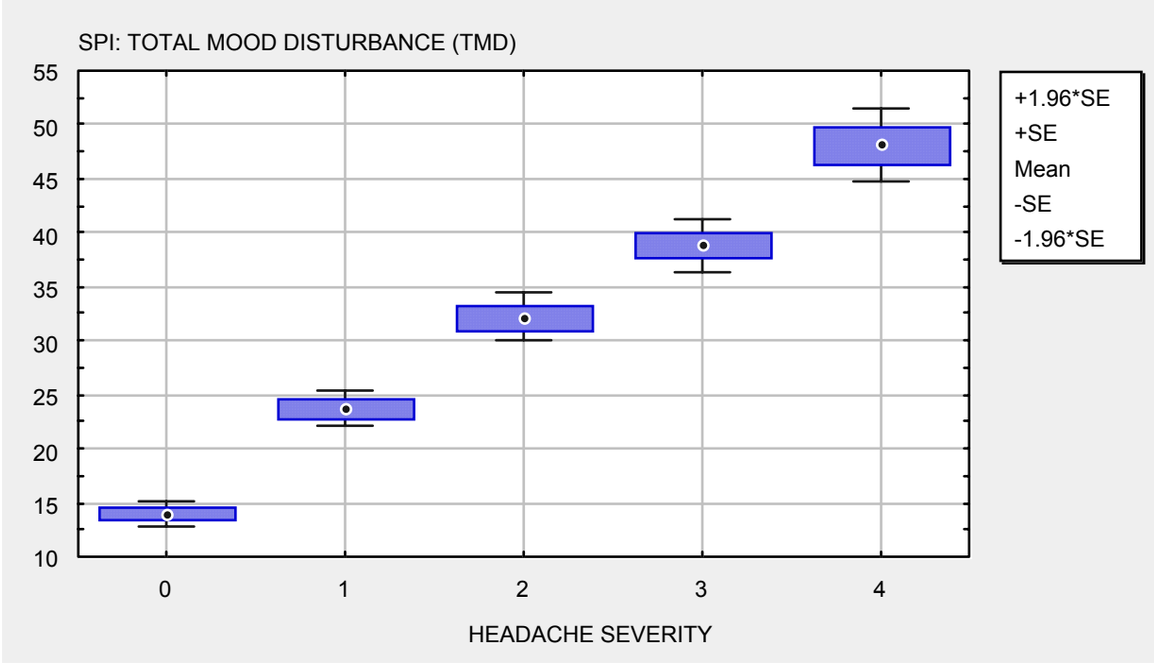


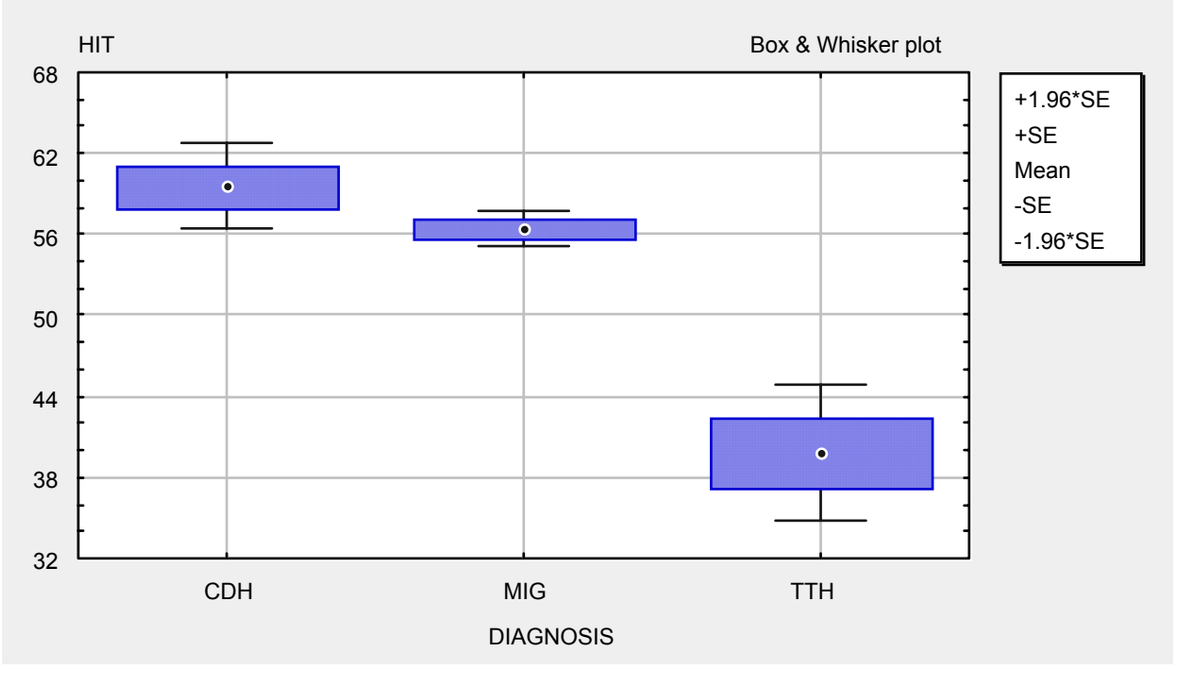
Figure 3. SPI Total Mood Disturbance (TMD) scores relationship to headache pain severity (0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain; 4 = extreme pain)..



Differentiation of diagnosis with HIT and SPI
There were originally four main groups diagnosed by the neurologist: chronic daily headache (CDH), high-frequency migraine (MIG-H), low-frequency migraine (MIG-L) and tension-type headache (TTH). However this was simplified into CDH, TTH and total migraine (MIG) groups due to sample size limitations.

The study used *t* tests to see if the HIT or SPI scores could reveal a statistically significant difference between the neurologist-validated diagnoses of CDH, TTH and migraine on the initial screening visit. There was significant relationship ($p < 0.05$) between the HIT score and diagnosis (Figure 4), but this was not observed with the SPI.

Figure 4: HIT relationship with diagnosis (CDH = chronic daily headache; MIG = migraine; TTH = episodic tension-type headache).



Factor structure of the outcome measures and diagnosis
The independence of the HIT and SPI were checked by Quartimax and Varimax factor analyses. Various analyses gave strikingly the same factor structure. The factor structure revealed that the major variance was accounted for by the SPI Total Pain Disturbance. All the SPI mood subscales also loaded highly on the first factor as did the physical severity of the headache, with an explained variance of 58%. The HIT score and the diagnosis (even if it included high or low migraine frequency) did not relate to the Total Pain Disturbance.

The second smaller factor which accounted for only 22% of the variance was a diagnostic variable and loaded highly with the HIT.

Discussion

The results of this study indicate that the HIT is very good at measuring the diagnosis and is superior in this to the SPI. The SPI is very good at indexing the severity of the pain experience, while the HIT is relatively poor at this. These data show the HIT and SPI to be complementary in measuring headache.

Clinicians should be vigilant in conceptualising the difference between a diagnostic and a severity scale. The SPI measures the mood disturbance and social interaction associated with the physical severity of pain. This 17-item tool is a state-dependent test which measures the here and now. It does not rely upon the retrospective recollections of the past as do tests like the MIDAS and HIT. The SPI measures the pain now; it does not enquire as to the cause of the pain but into its effects. Beyond this, the SPI does not have intentions to give causal statements about the medical or biological derivatives of pain.

The HIT is a tool to measure the impact headaches have on a person's ability to function at work, at home, at school and in social situations. It only purports to measure headache as an outcome measure and clearly states it is not a diagnostic. As a retrospective view of the patient it probably does measure headache outcome, but it is a blunt measure of severity. It is perhaps best used before long term anti-migraine treatments are initiated and again at the end of an extended treatment session. However, it cannot be used for point assessments of efficacy.

The HIT did not correlate well with headache severity nor was it as powerful as SPI at resolving differences in the fine gradations of headache severity. The SPI was more closely correlated with headache severity and each of the subscales showed excellent discrimination between the small changes in severity (Figure 1). The HIT does not capture emotional or sedation status of the patient, both of which are important aspects to the patient. The SPI is clearly not a diagnostic tool, but is a measure of headache severity. However, the HIT scores were closely associated with the headache diagnosis at screening. Various factor analyses were carried out to examine the factor structure and redundancy of the SPI and HIT. Two factors were identified

1) Headache severity, best measured by the SPI
2) Diagnosis, best measured by a neurologist or the HIT.

The study has limitations, mostly related to the relatively small numbers of patients analysed. For example, in the analysis of discriminant *t* values (Figure 1) there was a relative diminishment of *t* for none *versus* extreme headache as compared to none *versus* mild, none *versus* moderate and none *versus* severe, where the relationship was approximately linear. This was probably explained by the low number of patients with extreme pain (n = 2). It is therefore probably best to consider the statistical analyses as exploratory, requiring confirmation in a large study with equivalent numbers of patients in each severity group.

The HIT does discriminate between headache subtypes very well and, should a neurologist be not available at screening, this is a rather good diagnostic test. The SPI is not a diagnostic test but is a very discriminating outcome measure of headache severity and the consequential emotional impact. Accordingly, the data support using the HIT and SPI in different ways. As outcome measures, the HIT and SPI are very different and in some sense complementary. Clinical trialists should take care choosing and using their outcome measures appropriately.

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4.4

Development and validation of the Headache Diagnostic Screening Questionnaire (DSQ): a new questionnaire for the differential diagnosis of headache for use in primary care*

Abstract

This prospective, open investigation was set up to validate the 8-item Headache Diagnostic Screening Questionnaire (DSQ), containing questions screening for possible sinister symptoms, and evaluating headache impact, frequency and duration, the use of symptomatic medications and the presence of migraine aura symptoms. Patients completed the DSQ on their own and with a pharmacist's help. The same pharmacist, a GP and a headache specialist conducted a differential headache diagnosis according to their usual practices. Diagnoses were deduced from the DSQ using an algorithm by a healthcare professional, who was blind to the other diagnoses. The primary endpoint was the sensitivity of the DSQ, measured as the proportion of correct diagnoses assessed from the patient, pharmacist and GP responses, compared with the gold standard of specialist diagnosis, for each headache subtype. Eighty seven patients (80.5% women, mean age 52.9 years) completed the study, all completing the questionnaire without help within a few minutes. Most patients were diagnosed by the specialist with migraine (with or without aura) or chronic daily headache (with or without medication overuse headache [MOH]). The overall sensitivity of the patient-completed DSQ was good (59.3%) and similar to the pharmacist-completed DSQ (66.6%) and GP diagnosis (59.4%). The accuracy of the DSQ-derived diagnoses was greatest for total migraine, migraine with aura, MOH and migraine without aura. The accuracy of the pharmacists' headache diagnosis was improved markedly when they used the DSQ, particularly with regard to diagnosing migraine with and without aura and MOH. In conclusion, the Headache DSQ is a brief, rapid to use and accurate diagnostic screening questionnaire for headache, and is especially sensitive for migraine and MOH. It can be recommended for screening new headache patients at and below the primary care level.

** Edited from the published article: Dowson AJ, Turner A, Kilminster S et al. Development and validation of the headache Diagnostic Screening Questionnaire (DSQ): a new questionnaire for the differential diagnosis of headache for use in primary care. Headache Care 2005;2:111–18.*

Introduction

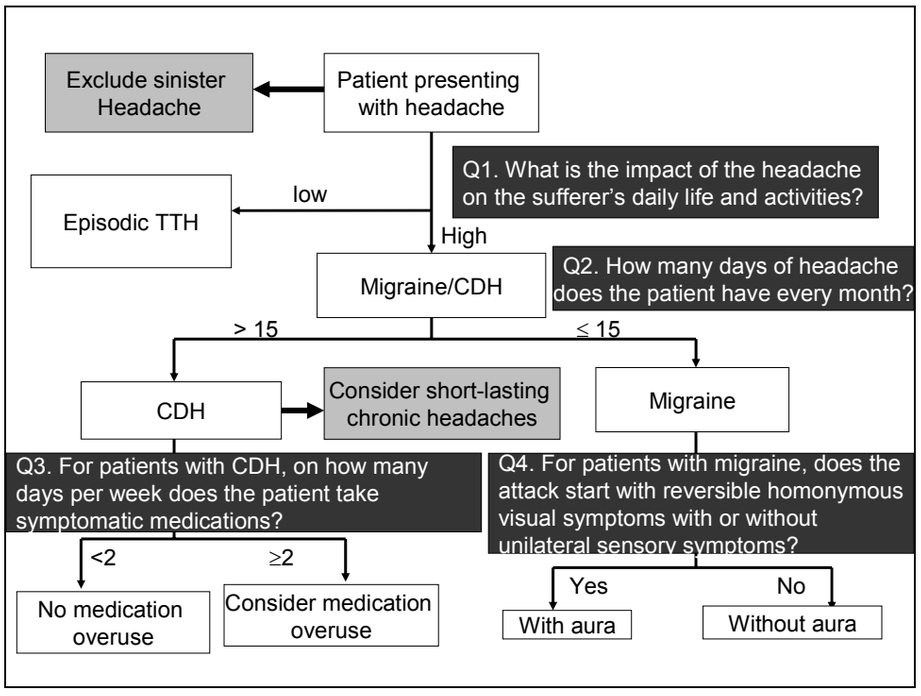
Despite the many recent advances in drug therapy, management of migraine remains suboptimal in primary care. Patients frequently do not consult with a physician for treatment, and physicians in turn often fail to make a correct diagnosis and prescribe appropriate treatments.[1,2] The result is that sufferers end up receiving little medical care, relying on over-the-counter medications, which are often ineffective.[3] This situation has not improved markedly over the past decade or so.[2,4]

Improving the differential diagnosis of headache is one potential way of improving headache management. The International Headache Society (IHS) publishes criteria for headache diagnosis that are comprehensive, but too lengthy for everyday clinical use.[5] Recently, brief screening questionnaires for migraine have been developed, which are accurate and rapid and easy to use, but are specific for migraine only.[6,7] What is needed in primary care is a brief, easy to use questionnaire which screens for the constellation of headache subtypes. The diagnosis can then be confirmed if necessary by additional questioning.

The UK Migraine in Primary Care Advisors (MIPCA) primary care group have developed evidence-based guidelines for migraine and chronic headache management in primary care.[8,9] As part of these initiatives, a 4-item diagnostic questionnaire was developed to screen patients for the common headache subtypes of migraine with and without aura, episodic tension-type headache (TTH), chronic daily headache (CDH) and medication overuse headache (MOH), while features of potential secondary (sinister) headaches and cluster headache are elicited by additional questioning. Figure 1 shows the questionnaire and the diagnostic algorithm derived from it. The questions are all based on the IHS classification criteria[5] and other evidence sources:

1. Episodic TTH typically has low impact on patients' daily activities, while migraine and CDH have high impact. Studies have indicated that any high-impact, episodic headache can be given a default diagnosis of migraine.[10]
2. Chronic headaches are defined as those occurring on > 15 days per month, while episodic headaches occur on ≤ 15 days per month.[5] Chronic headaches of duration > 4 hours are generally classified as CDH, while shorter-duration headaches may be classified in several subtypes (including cluster headache), depending on their duration and presenting symptoms.[5] CDH is defined arbitrarily as any headache of duration > 4 hours that occurs on > 15 days per month. In the new IHS classification, these headaches equate to chronic migraine, chronic TTH, hemicrania continua and new persistent daily headache.[5] In practice, patients are often seen with symptoms of mixed chronic migraine and chronic TTH.
3. CDH can be categorised as MOH if it is associated with the overuse of symptomatic medications (e.g. analgesics, ergots or triptans) on ≥ 10 days per month.[5]
4. Attacks of migraine with aura are associated with reversible sensory symptoms (mostly visual) which occur immediately before the headache starts.[5]

Figure 1. The MIPCA diagnostic screening questionnaire for headache and its associated diagnostic algorithm.[8]



In an initiative to improve headache diagnosis, MIPCA and the Migraine Action Association (MAA: the UK patient support group) have jointly developed a checklist designed for use by people with headaches that aims to help the GP diagnose and manage the presenting headache subtype. This checklist has been modified slightly for use by pharmacists to help them with the diagnosis and processing of patients with headache. However, the first eight questions for the patient and pharmacist questionnaires are identical and act as a diagnostic screen. The questions are closely based on the MIPCA 4-item questionnaire. This diagnostic screen needs to be validated before it can be recommended for use in everyday clinical practice. The objective of the current investigation was to validate the 8-item Headache Diagnostic Screening Questionnaire (DSQ), comparing data from completions of the questionnaire by patients and pharmacists with a conventional GP diagnosis and the gold standard of diagnosis by a headache specialist.

Patients and methods

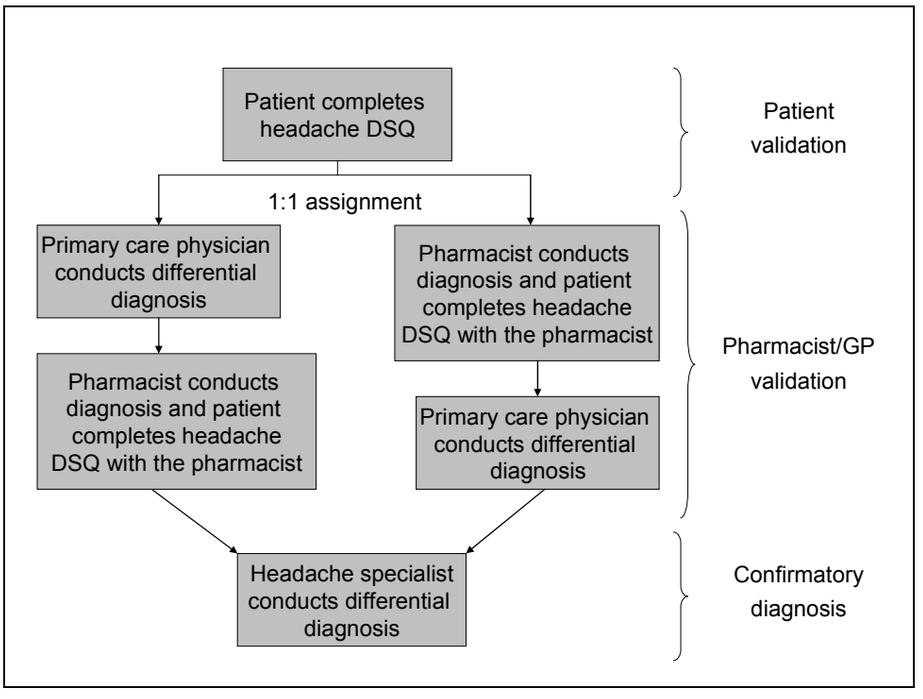
Patient population

The aim was to enrol 100 patients with migraine, episodic TTH, CDH (with or without MOH) and cluster headache. Patients living local to the Surrey area were recruited from the MAA database and from those attending Dr Dowson's own specialist clinic patients. Patients were men or women who had at least a 1-year history of headache. Patients were excluded if they had a history of significant psychiatric or any other major illness, or a history of abuse of alcohol or other recreational drugs. All patients provided their written consent before participating in the investigation, by signing an informed consent form.

Design of the investigation

This was an open, prospective, single-visit investigation, conducted in a single centre in the UK. The investigational design is shown in Figure 2.

Figure 2. Design of the investigation.



Patients completed the DSQ twice, once on their own and once in conjunction with a pharmacist. Patients also underwent a differential diagnosis procedure with the pharmacist and a GP. Alternate patients saw the pharmacist first then the GP, or the GP first and then the pharmacist, in a non-randomised sequential fashion. Finally, a confirmatory diagnostic procedure with a headache specialist was conducted. Table I shows the 8-item Headache DSQ, and the algorithm used to define the diagnosis that is deduced from it.

Table 1. The MIPCA/MAA 8-item headache diagnostic screening questionnaire (DSQ).

1. Are all the headaches usually similar in their symptoms, frequency and duration?
   Yes / No
2. Have you had headaches for longer than 6 months?
   Yes / No
3. Are you aged between 5 and 50 years?
   Yes / No
4. Does the headache interfere to a noticeable extent with your normal daily life (work, education and social activities)?
   Yes / No
5. On average, how many days with headache do you have per month?
   Less than 1 / 1 / 1–4 / 5–15 / 15–30 / Every day
6. On average, how long do your headaches last?
   Less than 15 minutes / 15 minutes to 1 hour / 1–2 hours / 2–4 hours / over 4 hours / My headaches are always there
7. On average, on how many days per week do you take analgesic medications?
   Less than 1 / 1 / Up to 2 / 2 or more / Every day
8. Do changes in your senses (sight, taste, smell or touch) occur before the headache starts?
   Yes / No

NB. If the patient answers <u>No</u> to any of Questions 1, 2, or 3, they may possibly have sinister headache. They should be advised to seek immediate medical advice from their GP.
If the patient answers <u>Yes</u> to questions 1, 2 and 3, they should complete the remainder of the questionnaire.

Diagnostic algorithm

- A 'no' answer to Questions 1, 2 or 3 indicates the possibility of secondary (or sinister) headaches. These patients should be investigated further and do not complete the remaining questions.

For patients who answer 'yes' to Questions 1–3:

- **Question 4:**
  - 'No' = episodic tension-type headache
  - 'Yes' = migraine or chronic headache
- **Question 5:**
  - <1; 1; 1–4 and 5–15 days = migraine
  - 15–30 days and every day = chronic headache
- **Question 6:** For patients with chronic headaches only:
  - <15 minutes = investigate further
  - 15 minutes to 1 hour = possible cluster headache
  - 1–2 and 2–4 hours = investigate further
  - Over 4 hours and my headaches are always there = chronic daily headache (CDH)
- **Question 7:** For patients with CDH only:
  - <1; 1; up to 2 = CDH without medication overuse
  - 2 or more and every day = CDH with medication overuse (MOH)
- **Question 8:** For patients with migraine only:
  - Yes = migraine with aura
  - No = migraine without aura.

At baseline, patients completed an informed consent form and a demography questionnaire (age, gender and race). They then completed the DSQ, without help or any divulging of the purpose of the questionnaire (*patient-completed DSQ*). Each patient was then assigned in a 1:1 ratio to see a pharmacist or GP. Consecutive patients were assigned to see the pharmacist or GP first, before seeing the other healthcare professional. The pharmacist conducted a diagnostic assessment of the patient, without using the DSQ (*pharmacist diagnosis*). They then completed the DSQ with the patient, with additional questioning and advice where necessary (*pharmacist-completed DSQ*). The GP conducted a standard differential headache diagnostic procedure with the patient (*GP diagnosis*), and were provided with summaries of the IHS criteria for the diagnosis of migraine, episodic TTH, CDH, MOH and cluster headache. Finally, the patient consulted with a headache specialist (*specialist diagnosis*), who conducted a confirmatory diagnostic procedure (the gold standard diagnosis). The patients remained blind throughout the investigation to the purpose of these assessments, and the evaluators were all blinded to the results of each others' assessments.

Endpoints

All DSQs and pharmacist, GP and specialist diagnoses were collected. The returned DSQs were assessed by a trained healthcare professional, who was blind to the pharmacist and physician diagnoses and provided diagnoses according to the DSQ algorithm (Table 1). The primary endpoint was the sensitivity of the DSQ, measured as the proportion of correct diagnoses assessed from the patient, pharmacist and GP responses, compared with the gold standard of specialist diagnosis, for each headache subtype. Sensitivity is defined as the proportion of those patients with the illness correctly identified as positive by the test. Specificity was not assessed in the investigation.

Statistical analyses

Introduction

This investigation was designed to assess the accuracy (validity) of the 8-item DSQ when used by the patient alone, or by the patient in consultation with a pharmacist. Diagnostic data derived from the completions of the checklist were cross-tabulated with those from diagnoses deduced by the pharmacist, GP and headache specialist. All data were 100% triple validated against source documents. The analyses were conducted using the Statistica V4 (Tulsa USA) statistical package.

Analyses

Baseline demographic assessments were analysed as descriptive statistics only. The deduction of DSQ-based diagnoses was conducted by a trained professional using the diagnostic algorithm (Table 2). These diagnoses were formally validated against the gold standard diagnosis. The accuracy of diagnoses derived from the DSQ was analysed by cross-tabulating diagnostic labels on the following data sets:

- Patient-completed DSQ *versus* pharmacist diagnosis
- Patient-completed DSQ *versus* pharmacist-completed DSQ
- Patient-completed DSQ *versus* GP diagnosis
- Patient-completed DSQ *versus* specialist diagnosis
- Pharmacist diagnosis *versus* GP diagnosis
- Pharmacist diagnosis *versus* specialist diagnosis.
- Pharmacist-completed DSQ *versus* pharmacist diagnosis
- Pharmacist-completed DSQ *versus* GP diagnosis
- Pharmacist-completed DSQ *versus* specialist diagnosis
- GP diagnosis *versus* specialist diagnosis.

The different diagnostic sensitivities were compared using the Wilcoxon matched-pairs test, as 'Z' scores and 'T' statistics, with the level of significance set at $p < 0.05$.

The study statistician (SK) calculated that a sample size of 100 patients (assuming 25 per diagnostic group [migraine, episodic TTH, CDH and cluster headache]) was appropriate to assess sensitivity, as it is similar to the numbers used in other studies of this design.

Results

Patient characteristics

Eighty seven patients took part in the investigation, 44 who saw the pharmacist first and 43 who saw the GP first. All patients completed the five diagnostic procedures. Most patients were women (*n* = 70, 80.5%), all were Caucasian in racial origin and the mean age was 52.9 years (range 23–77 years). The vast majority of the patients were diagnosed by the specialist with migraine (with and without aura; *n* = 48, 55.2%) or CDH (with and without MOH; *n* = 32, 36.8%). Only four patients were diagnosed with cluster headache and one with TTH. All patients completed the DSQ without help within a few minutes.

Sensitivity analysis

Sample sizes were adequate for the patients with migraine (*n* = 48) and total CDH (*n* = 32), but were very small for those with episodic TTH (*n* = 1) and cluster headache (*n* = 4). The sensitivity analyses are shown in Table 2. Overall, the pharmacist diagnoses had the poorest sensitivities across all diagnostic groups (29.3% sensitivity). However, the pharmacist-completed DSQ sensitivity was markedly higher, at 66.6%, and similar to that of the patient-completed DSQ (59.3%) and GP diagnoses (59.4%). The diagnostic sensitivity for 'total migraine' was high in all groups (83.3%–93.8%) and similar, although lower, for 'total CDH' (43.8–50.0%). The sensitivity for diagnosing migraine with aura, migraine without aura and MOH was substantially higher in the DSQ groups (patient-completed and pharmacist-completed) than in the pharmacist and GP diagnosis groups. There were too few patients in the episodic TTH and cluster headache categories for analysis.

Table 2. Sensitivity of each diagnostic assignment analysed from the patient-completed DSQ, pharmacist-completed DSQ, pharmacist diagnosis and GP diagnosis for episodic TTH, CDH, MOH, migraine and cluster headache compared with the gold standard specialist assignment.

		Sensitivity Number of patients (%)			
Diagnosis	**Number of patients**	**Patient-completed DSQ**	**Pharmacist-completed DSQ**	**Pharmacist diagnosis**	**GP diagnosis**
TTH	1	1 (100.0)	1 (100.0)	0 (0)	1 (100.0)
CDH	17	2 (11.8)	2 (11.8)	4 (23.5)	5 (29.4)
Migraine with aura	11	9 (81.8)	10 (90.9)	1 (9.1)	7 (63.6)
Migraine without aura	32	19 (59.4)	21 (65.6)	0 (0)	16 (50.0)
MOH	15	9 (60.0)	11 (73.3)	0 (0)	2 (13.3)
Total CDH (CDH + MOH)	32	15 (46.9)	16 (50.0)	14 (43.8)	16 (50.0)
Total migraine*	48	43 (89.6)	44 (91.7)	40 (83.3)	45 (93.8)
Cluster headache	4	1 (25.0)	2 (50.0)	3 (75.0)	3 (75.0)
Mean		**59.3**	**66.6**	**29.3**	**59.4**

* The ‘migraine with aura’ and migraine without aura’ groups do not add up to the ‘total migraine’ group because a group labelled ‘migraine’ was only identified by the specialist, GP and pharmacist diagnoses, and was included in the overall ‘total migraine’ group.

Analysis of the Wilcoxon matched-pairs tests of the different diagnostic groups is shown in Table 3. The data was organised so as to match pairs of diagnostic groups, validated with the specialist diagnosis. The diagnosis from the patient-completed DSQ was significantly less accurate than that from the pharmacist-completed DSQ (p = 0.03). However, there were no significant differences between the patient-completed DSQ and the pharmacist and GP diagnoses. Both were equally good by reference to the gold standard (specialist). The only variation to this was that CDH was diagnosed less accurately on the pharmacist-completed DSQ.

Table 3. Analysis of the Wilcoxon matched-pair tests for accuracy from the patient-completed DSQ, pharmacist-completed DSQ, and pharmacist, GP and specialist diagnoses.

Wilcoxon comparison	**Wilcoxon T statistic**	**Wilcoxon Z score**	***p*-value**
Patient-completed DSQ *versus* pharmacist diagnosis	7.00	1.54	0.12
Patient-completed DSQ *versus* pharmacist-completed DSQ	0.00	2.20	0.03
Patient-completed DSQ *versus* GP diagnosis	12.50	0.25	0.80
Pharmacist-completed DSQ *versus* pharmacist diagnosis	5.00	1.82	0.07
Pharmacist-completed DSQ *versus* GP diagnosis	6.50	0.84	0.40
GP diagnosis *versus* pharmacist diagnosis	0.00	2.37	0.02
Specialist diagnosis *versus* patient-completed DSQ	0.00	2.37	0.02
Specialist diagnosis *versus* pharmacist-completed DSQ	0.00	2.37	0.02
Specialist diagnosis *versus* pharmacist diagnosis	0.00	2.52	0.01
Specialist diagnosis *versus* GP diagnosis	0.00	2.20	0.03

There was a trend for the pharmacist-completed DSQ to be more accurate than the pharmacist diagnosis, although the difference did not reach statistical significance (p = 0.07). The pharmacist-completed DSQ was of similar accuracy to that of the GP diagnosis. The GP diagnosis was significantly more accurate than the pharmacist diagnosis (p = 0.02). The patient-and pharmacist-completed DSQ (p = 0.02 for both analyses), the pharmacist diagnosis (p = 0.01) and the GP diagnosis (p = 0.03) were all significantly less accurate than the specialist diagnosis (the gold standard used in this study).

Discussion

The 8-item DSQ was designed to be a diagnostic aid for headache to be used at the patient’s first consultation with a healthcare professional, who may be a GP, nurse, pharmacist or other practitioner (e.g. opticians and dentists often see people with headache). Its principal use is proposed to be an aid to deciding the appropriate first management decisions. The questionnaire was designed to be brief and simple to use, so that patients could complete it on their own. Although the design of the DSQ was based on sound theoretical criteria,[5] it had

to be demonstrated to be accurate in terms of diagnostic sensitivity before being recommended for general use.

The patients who took part in the investigation were mostly women, and were somewhat older than those recruited in most migraine studies.[11] This may be due to the high proportion of CDH sufferers recruited, whose age distribution tends not to be skewed as is the typical young to middle-aged migraine sufferer.[12,13] Both migraine and CDH are more prevalent in women than in men.[12,13] All the patients completed the initial patient-completed DSQ with little difficulty within a few minutes, and all questions were answered. This demonstrates the general ease of use of the questionnaire.

Overall, both the patient- and pharmacist-completed DSQs exhibited good sensitivity, of around 60% for both measures, values very similar to that of the GP diagnosis. The best sensitivity was demonstrated for total migraine (about 90%), migraine with aura (about 80–90%), MOH (about 60–75%) and migraine without aura (about 60–65%). The sensitivity for total CDH (CDH with and without MOH) was somewhat lower at about 50%, driven by a poor sensitivity for CDH without MOH (about 12%). Results for episodic TTH and cluster headache could not be interpreted due to the small number of patients with these conditions. These results indicate that the DSQ is an effective tool for the differential diagnosis of headache. Interestingly, the accuracy of the pharmacists' headache diagnosis was improved markedly when they used the DSQ, particularly with regard to diagnosing migraine with and without aura and MOH. It would be interesting to see if GPs' diagnostic accuracy could improve to the specialist level if they had access to the DSQ.

As would be expected, all groups were significantly less accurate in diagnosis than the headache specialist diagnoses. However, when pharmacists had access to the DSQ, their diagnostic accuracy was significantly greater than that of patients using the DSQ and approached that of the GP diagnosis. These results indicate that, with this aid, pharmacists can diagnose headache accurately, which is of clinical importance as they may see more headache sufferers than do GPs.[1] Use of the DSQ therefore has the potential to improve headache management in the pharmacy setting, from which many effective medications are available without a prescription. In turn, the burden of managing headache on busy GPs may be relieved.

Some weaknesses were observed in the results. The study was not properly randomised, with consecutive patients being openly assigned to seeing the pharmacist or GP first. The study was not large enough to determine whether the order of seeing these healthcare professionals had any effect on the results. However, the pharmacists and GPs were blind to each other's assessments. The entry criteria for numbers of patients with episodic TTH and cluster headache were not met by the patients recruited from the databases of the MAA and Dr Dowson. For this reason the specificity of the DSQ was not assessed. The lack of patients with TTH and cluster headache is perhaps not surprising bearing in mind what we know about these headaches. Cluster headache is an uncommon condition, affecting < 0.5% of the population,[14] and is not seen often in general practice. Episodic TTH is very common, but sufferers rarely consult for the condition, preferring to self-treat with OTC medications.[3] Such sufferers are, however, very likely to consult pharmacists. It would be useful to repeat this validation exercise in a specialist headache clinic (where cluster headache patients are more common) and in a pharmacy (where episodic TTH sufferers may be encountered frequently). The accuracy of the DSQ for CDH without MOH was poor, and patients tended to underestimate the duration and/or the frequency of their headaches. Additionally, migraine patients sometimes confused aura symptoms with prodromes when answering question 8. Based on feedback from patients who took part in the study, we suggest that the following small changes to the questions may help to improve the accuracy of the DSQ:

- Question 1: *Has the pattern of your headaches been generally stable (i.e. no change or only small changes in frequency and severity) over the past few months?*

- Question 6: On average how long do your headaches last, *if left untreated*?
- Question 8: Do changes in your senses (sight, taste, smell or touch) occur *in the period immediately* before the headache starts?

Table 4 shows the revised DSQ, including these changes. Future testing of the DSQ for sensitivity and specificity should use this version of the questionnaire.

Table 4. The revised 8-item headache diagnostic screening questionnaire (DSQ) produced following completion of the investigation.

1. Has the pattern of your headaches been generally stable (i.e. no change or only small changes in frequency and severity) over the past few months?
   Yes / No
2. Have you had headaches for longer than 6 months?
   Yes / No
3. Are you aged between 5 and 50 years?
   Yes / No
4. Does the headache interfere to a noticeable extent with your normal daily life (work, education and social activities)?
   Yes / No
5. On average, how many days with headache do you have per month?
   Less than 1 / 1 / 1–4 / 5–15 / 15–30 / Every day
6. On average, how long do your headaches last, if left untreated?
   Less than 15 minutes / 15 minutes to 1 hour / 1–2 hours / 2–4 hours / over 4 hours / My headaches are always there
7. On average, on how many days per week do you take analgesic medications?
   Less than 1 / 1 / Up to 2 / 2 or more / Every day
8. Do changes in your senses (sight, taste, smell or touch) occur in the period immediately before the headache starts?
   Yes / No

NB. If the patient answers No to any of Questions 1, 2, or 3, they may possibly have sinister headache. They should be advised to seek immediate medical advice from their GP.
If the patient answers Yes to questions 1, 2 and 3, they should complete the remainder of the questionnaire.

The DSQ has considerable potential clinical utility in the management of headache in primary care. Patients should be able to obtain a copy at their first point of care, whether a GP surgery, pharmacist, optician, dentist or other provider. They can complete the DSQ, either at home by themselves or with the help of the practitioner. Both patients and pharmacists find the questionnaire easy to complete. The practitioner should review the DSQ and provide appropriate advice. Episodic TTH can usually be managed successfully by the sufferer or by a pharmacist.[15] Patients with migraine and CDH probably need to be advised to see a GP for care, although the pharmacist may be able to manage those with uncomplicated, mild-to-moderate migraine symptoms.[8,9] Using the questionnaire, there is the potential for earlier and better headache diagnoses. Following pharmacist intervention, patients should be empowered to obtain help from the GP sooner rather than later. Improved migraine management has the potential to reduce the high economic cost of the illness to society.[16]

It is interesting to compare the DSQ with other screening questionnaires that have been recently developed for headache. Migraine was diagnosed sensitively and specifically using three questions on headache-related disability, nausea and sensitivity to light,[6] or three questions on disability, headache duration and the lack of new-onset headaches in the previous 6 months.[7] Both these questionnaires restricted themselves to diagnosing migraine

only. Maizels and Burchette have developed the Brief Headache Screen to diagnose different headache subtypes.[17] Migraine, daily headache syndromes and medication overuse could be distinguished using three questions: the frequency of disabling headache, the presence of other, mild headaches and the use of symptomatic medications. There is considerable overlap between the DSQ and these other questionnaires in terms of assessing disability, headache frequency and duration, and the use of headache medications, which reinforces the validity of these assessments.

In conclusion, the headache DSQ is a brief, rapid to use and accurate diagnostic screening questionnaire for headache, and is especially sensitive for migraine and MOH. It can be recommended for screening new headache patients at and below the primary care level.

Acknowledgements

We are especially grateful to the patients who gave their time and commitment to take part in this investigation. We are also pleased to acknowledge the help of the GPs (Drs Susan Boucher, Michael Bundy, Annette de la Court, Frances Edgar, Helen Grisewood, Trevor Rees and David Watson) and pharmacists (Ms Gillian Donkin, Alison Ranftler and Victoria Withington) who conducted the diagnostic assessments. This investigation was sponsored in part by an unrestricted educational grant from AstraZeneca.

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4.5

Identifying patients who require a change in their current acute migraine treatment: the Migraine Assessment of Current Therapy (Migraine-ACT) questionnaire*

Abstract

Background: Currently available measures of the efficacy of acute migraine medications are not frequently used in primary care. They may be too burdensome and complicated for routine use.

Objectives: To design and test a new, easy to use, 4-item assessment tool, the Migraine Assessment of Current Therapy (Migraine-ACT) questionnaire for use by clinicians, to quickly evaluate how a recently prescribed acute medication is working, and to identify patients who require a change of their current acute treatment.

Methods: A 27-item Migraine-ACT questionnaire was developed by an international advisory board of headache specialists. Questions were formulated in four domains: headache impact, global assessment of relief, consistency of response and emotional response. All these are clinically important measures of migraine severity and treatment outcome. All questions were dichotomous and answered by yes or no. Patients (n = 185) attending secondary care headache clinics who were diagnosed with migraine according to International Headache Society criteria entered a multinational, prospective, observational study to investigate the test-retest reliability and construct validity of the 27-item Migraine-ACT. Patients completed the Migraine-ACT on two occasions, separated by a 1-week interval, and test-retest reliability was assessed by Pearson product moment and Spearman rank measures. Construct validity was assessed by correlating patients' answers to the 27-item Migraine-ACT with those to other questionnaires (individual domains and total scores) conceptually related to it; the Short-Form 36 quality of life questionnaire (SF-36), the Migraine Disability Assessment (MIDAS) questionnaire and the Migraine Therapy Assessment Questionnaire (MTAQ). Discriminatory t-tests were used to identify the four Migraine-ACT questions (one in each domain) which discriminated best between the domains of the SF-36, MIDAS, and MTAQ. These four items constituted the final 4-item Migraine-ACT.

Results: The test-retest reliability of the 27 Migraine-ACT questions ranged from good to excellent, and correlation coefficients were highly significant for all items. The consistency of reporting the yes and no answers was also excellent. Correlations of Migraine-ACT items with SF-36 and MIDAS items and SF-36, MIDAS and MTAQ total scores indicated that the following were the most discriminating items, in the respective four domains, and constitute the final Migraine-ACT questionnaire:

- Consistency of response - **Does your migraine medication work consistently, in the majority of your attacks?**
- Global assessment of relief - **Does the headache pain disappear within 2 hours?**
- Impact - **Are you able to function normally within 2 hours?**
- Emotional response - **Are you comfortable enough with your medication to be able to plan your daily activities**

The 4-item Migraine-ACT was shown to be highly reliable (Spearman / Pearson measure r = 0.82). The individual questions, and the total 4-item Migraine-ACT score, showed good correlation with items of the SF-36, MIDAS and MTAQ questionnaires, particularly with the total MTAQ and SF-36 scores.

Conclusions: The 4-item Migraine-ACT questionnaire is an assessment tool for use by primary care physicians to identify patients who require a change in their current acute migraine treatment. It is brief and simple to complete and score, and has demonstrated reliability, accuracy and simplicity. Migraine-ACT can therefore be recommended for everyday clinical use by clinicians.

** Edited from the published article: Dowson AJ, Tepper SJ, Baos V, Baudet F, D'Amico D, Kilminster S. 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 2004;20:1125–35.*

Introduction

The Migraine Assessment of Current Therapy (Migraine-ACT) is designed to be a brief assessment tool used in initial assessments and follow-up to help the clinician determine quickly and easily whether a change in the acute therapy of their migraine patients is required. The 27-item version was developed by an advisory board of headache specialists from the UK, Germany, Italy, Spain and the USA. This paper describes an international study designed to assess the test-retest reliability and construct validity of the items constituting the 27-item Migraine-ACT, and use these data to select the four items that will constitute the final questionnaire.

Several recent initiatives have resulted in the development of novel questionnaires that can be used to assess the efficacy of migraine therapies:

- Impact tools, e.g. the Migraine Disability Assessment (MIDAS) Questionnaire[1] and the Headache Impact Test (HIT).[2]
- Quality of Life (QOL) questionnaires, which can be generic or migraine-specific.[3]
- Disease management tools, e.g. the Migraine Therapy Assessment Questionnaire (MTAQ).[4]

All these questionnaires have been shown to be reliable and valid tools in populations of headache sufferers, and all have potential in assessing the outcome from interventions.[4–6] However, experience from clinical practice has demonstrated some problems with the questionnaires that have that limited their uptake there:

- Patients often find them too complicated to use without supervision.
- Physicians are frequently unaware of the questionnaires, and find them too long and unwieldy for everyday use.
- Both MIDAS ands HIT-6 are brief questionnaires,[1,2] but both patients and physicians require education for their use, which is generally not available.
- When asked, many physicians state that they prefer to ask a single question on impact, rather than a series of questions.

There is a clear need for a brief, simple, patient-friendly, re-evaluation tool to be used in triage and as a good means of evaluating the efficacy of medications used for the management of migraine in primary care. Such simple screening tools have proved valuable in other therapy areas. The CAGE alcohol dependence questionnaire contains only four yes/no type questions, with two 'yes' responses constituting a positive screening test result.[7] A three-question yes/no type questionnaire was developed for asthma to provide the patient and physician with a rapid assessment of outcome, and as a trigger for intervention.[8] We set out to develop a similar questionnaire for migraine, the Migraine Assessment of Current Therapy (Migraine-ACT). As originally developed by an international advisory board (AJD, SJT and VB), Migraine-ACT consisted of 27 questions (Table 1) in four domains selected from a much larger question pool on the basis of consensus and the group's extensive clinical experience to be of significant importance on the basis of clinical evidence: impact;[9,10] global assessment of relief;[11,12] consistency of response;[12,13] and emotional response.[14] Questions are answered by the patient as yes or no. The aim is to produce a 4-item test, with one question in each of the four domains above.

Table 1. The initial 27-item Migraine Assessment of Current Therapy (Migraine-ACT) questionnaire.

Each question starts with the text 'When you take your treatment'

Impact

Question	Code	Yes	No
When you take your treatment: Is the impact of the headache significantly relieved within 2 hours?	IMP 1		
Is the disability caused by the headache significantly relieved within 2 hours?	IMP 2		
Are you able to resume your normal activity (i.e. work or family-leisure-social activity, etc.) within 2 hours?	IMP 3		
Are you able to function normally within 2 hours?	IMP 4		
Do you usually not need to lie down after 2 hours?	IMP 5		
Can you get back to what you were doing within 2 hours?	IMP 6		
Are you able to experience normal enjoyment of your daily life within 2 hours?	IMP 7		
Are you able to cope normally with everyday life within 2 hours?	IMP 8		
Are you able to concentrate normally within 2 hours?	IMP 9		
Do you feel that your sense of emotional well-being returns to normal within 2 hours?	IMP 10		
Have any feelings of tiredness, irritability, sadness, anger and anxiety disappeared within 2 hours?	IMP 11		

Global assessment of relief

Question	Code	Yes	No
When you take your treatment: Does the headache pain disappear within 2 hours?	GAR 1		
Is the headache pain relieved after 2 hours?	GAR 2		
Does the headache pain disappear within 2 hours and not return within 24 hours?	GAR 3		
Does the headache pain disappear within 2 hours and not return within 48 hours?	GAR 4		
Does the headache pain start to disappear within 30 minutes?	GAR 5		
Do your non-headache symptoms (e.g. nausea and sensitivity to light, sound or smells) disappear within 2 hours?	GAR 6		
Are your non-headache symptoms (e.g. nausea and sensitivity to light, sound or smells) relieved within 2 hours?	GAR 7		
Are you clear of all your symptoms within 2 hours?	GAR 8		
Does your migraine headache pain stop within 2 hours?	GAR 9		

Consistency of response

Question	Code	Yes	No
When you take your treatment: Does your migraine medication work attack after attack?	CONS 1		
Does your migraine medication work reliably in the majority of your attacks?	CONS 2		
Does your migraine medication work consistently, in the majority of your attacks?	CONS 3		

Emotional response

Question	Code	Yes	No
When you take your treatment: Does your migraine medication work consistently enough that you can plan your future activities?	EMOT 1		
Are you confident that the migraine medication you are taking will treat the next attack effectively?	EMOT 2		
Are you comfortable enough with your medication to be able to plan your daily activities?	EMOT 3		
Do you feel in control of your migraine enough so that you feel there will be no disruption to your daily activities?	EMOT 4		

Patients and Methods

Patients

Patients at five secondary care headache centres, in the UK, Spain, Germany, Italy and the USA, took part in the study. All patients were attending the centres for migraine treatment. Each centre enrolled 40 patients with migraine diagnosed according to the International Headache Society (IHS) criteria.[15,16] Eligible patients were men or women aged between 18–65 years, with at least a 1-year history of migraine, experiencing on average 1–4 attacks per month, and a minimum of 24 hours between each attack. Patients were able to distinguish migraine attacks from other types of headache. Patients were excluded from the study if they had a history of significant psychiatric illness, or any other illness that could affect the interpretation of the results, e.g. major depression or anxiety disorder, or had a history of abuse of alcohol, or other recreational drugs.

Study design

This was an open, prospective, multinational, observational, two-visit study, conducted in the UK, Spain, the USA, Germany and Italy, using questionnaires which were translated into the local languages. Patients were assessed at baseline and completed a series of outcome questionnaires; the 27-item Migraine-ACT, the Short Form-36 (SF-36) quality of life (QOL) questionnaire,[3] the MIDAS Questionnaire[1] and the MTAQ Questionnaire.[4] The validity of the Migraine-ACT Questionnaire was assessed from the responses to these questionnaires. Additionally, we evaluated test-retest reliability, thus the same patients completed the 27-item Migraine-ACT Questionnaire again 1 week later.

Patients provided their written consent before participating in the study, by signing a consent form. The study was conducted in accordance with the Declaration of Helsinki, as revised by the most recent meetings of the World Medical Assembly. The study was conducted in the spirit of, and according to, the principles of Good Clinical Practice (GCP), as embodied in the ICH Harmonised Tripartite Guideline for GCP.

Study procedures

Migraine patients (*n* = 200; 40 per centre) attended the clinic, or were contacted by telephone, for demography baseline assessments (age, gender, race, weight and height) and completion of the outcome questionnaires: 27-item Migraine-ACT; SF-36 QOL questionnaire; MIDAS Questionnaire; and the MTAQ Questionnaire (Visit 1). All patients (*n* = 40 per centre) who completed the 27-item Migraine-ACT attended the clinic or were contacted by telephone 1 week later to complete the Migraine-ACT Questionnaire for a second time (Visit 2). During this time, no changes were allowed in the patients' migraine treatments. Any patients who withdrew from the study were recorded, and the reasons for withdrawal noted. Patients who withdrew were included in the analyses of results.

Endpoints

The primary study endpoints were test-retest reliability (a comparison of the Migraine-ACT data from the 27 individual questions from Visits 1 [baseline] and 2 [1 week]), and construct validity (a comparison of the Migraine-ACT data from the 27 individual questions with relevant data from the SF-36 and MIDAS (domains and total scores) and MTAQ questionnaires (total score only) at Visit 1 [baseline]). The construct validity data were used to identify the four items (one in each domain) to be contained in the final Migraine-ACT questionnaire.

Statistical analyses

Introduction

This study was designed to assess the test-retest reliability and construct validity of the 27 items constituting the original Migraine-ACT questionnaire. These data were then used to construct the final 4-item version of the questionnaire. Test-rest reliability was assessed by

comparing patients' responses to the individual Migraine-ACT questions when completed at baseline (Visit 1) and 1 week later (Visit 2). Validity was assessed by comparing patients' responses to the individual Migraine-ACT questions at baseline (Visit 1) with those to components of questionnaires related to the conception of Migraine-ACT, i.e. the SF-36, MIDAS and MTAQ questionnaires. All analyses were conducted with Statistica (Tulsa, USA) software with statistical hypotheses tested for two-tailed tests of type 1 error at 0.05. Data were 100% validated against source documents.

Baseline analyses
All baseline demographic assessments were analysed as descriptive statistics only (means and standard deviations).

Test-retest reliability
Test-retest reliability of the individual Migraine-ACT questions was assessed using Pearson's product moment and Spearman rank measures. A minimum test-retest product moment of $r = 0.30$ (detected statistically at alpha2 $p = 0.05$) would be $n = 40$ per centre. A test–retest or r statistic of 0.75 or over represents excellent agreement, 0.40 to 0.75 represents intermediate to good agreement, and below 0.40 represents poor agreement.[17] The whole process was repeated and confirmed on the summed 4-item score.

Construct validity
To assess the construct validity of the individual Migraine-ACT questions, the associations were determined between patients' responses to the individual Migraine-ACT questions and instruments related conceptually to the Migraine-ACT questionnaire. Correlations were made between Migraine-ACT and the MIDAS, SF-36 and MTAQ questionnaires (criterion variables). Discrimination was analysed by simple t-tests of means from dichotomised Migraine-ACT item scores. Factor analysis was used to identify and score the key features of the criterion variables and the Migraine-ACT questions were correlated and discriminated with these factors. Separate analyses checked for centre effects (i.e. within each centre [country]), and for the total scores derived from all countries combined (i.e. overall analysis).

Item selection
The questions to be included in the final 4-item Migraine-ACT questionnaire were identified from the correlation coefficients and discrimination of all 27 questions with summary and derived subscale scores and factor analysed criterion scores from MIDAS, MTAQ and SF36. In addition, the questions all had to exhibit at least good test-retest reliability. Regression was used to compare the summation of the individual final four items *versus* weighted items. Summation of the best four items was made after various analyses to find the best structure and redundancy of terms from the MIDAS, MTAQ and SF36.

Orthogonal and Oblique rotations of the principal components derived the maximum variance factors associated with a reduced data set. Regression-derived new composite variables were constructed from the factor analyses.

Results

Demography and baseline characteristics
One hundred and eighty five patients took part in the study. All patients were assessed at Visit 1, with 143 (77%) completing the questionnaire on both occasions. The majority of the patients (68%) were women. All but one of the patients was of white racial origin. The mean age was 44 years (range 14 to 87 years), with the vast majority (172, 93%) aged 18–65 years.

Test-retest reliability

Spearman rank order measures for all 27 Migraine-ACT items are shown in Table 2. The analyses were nonparametric and pairwise deleted. There were few dropouts; between 176 and 185 of the 185 patients taking part in the study provided data at Visits 1 and 2. Spearman rank order measures ranged from 0.54 to 0.79 for the individual 27 Migraine-ACT items, indicating good-to-excellent reliability. Summated Spearman measures for the impact (IMP1–11), global assessment of relief (GAR1–9), consistency of response (CONS 1–3) and emotional response (EMOT1–4) items exhibited excellent reliability, and the total summation of all 27 items was extremely reliable, at $r = 0.99$ (Table 2).

Table 2. Test-retest reliability of the 27-item Migraine-ACT Questionnaire. Spearman rank order measures are shown below for all 27 Migraine-ACT items. Analyses were nonparametric and pairwise deleted.

Migraine-ACT questions	***n***	***r***	**t (*n* - 2)**	***p*-value**
IMP1	184	.68	12.67	<.0001
IMP2	182	.61	10.23	<.0001
IMP3	182	.77	16.25	<.0001
IMP4	185	.72	13.96	<.0001
IMP5	183	.54	8.61	<.0001
IMP6	181	.79	16.96	<.0001
IMP7	184	.73	14.31	<.0001
IMP8	182	.70	13.10	<.0001
IMP9	182	.74	14.76	<.0001
IMP10	183	.62	10.66	<.0001
IMP11	183	.62	10.64	<.0001
GAR1	181	.58	9.44	<.0001
GAR2	183	.63	11.04	<.0001
GAR3	179	.61	10.18	<.0001
GAR4	179	.58	9.44	<.0001
GAR5	183	.60	10.15	<.0001
GAR6	182	.60	10.15	<.0001
GAR7	182	.62	10.56	<.0001
GAR8	179	.58	9.53	<.0001
GAR9	177	.72	13.68	<.0001
CONS1	182	.68	12.43	<.0001
CONS2	184	.70	13.15	<.0001
CONS3	182	.61	10.30	<.0001
EMOT1	180	.74	14.76	<.0001
EMOT2	179	.77	16.04	<.0001
EMOT3	178	.78	16.40	<.0001
EMOT4	176	.62	10.56	<.0001
Total IMPACT (IMP 1–11)	168	1.00	137.78	<.0001
Total GAR (GAR 1–9)	164	.78	16.08	<.0001
Total CONS (CONS 1–3)	180	.73	14.33	<.0001
Total EMOT (EMOT 1–4)	172	.80	17.41	<.0001
TOTAL Migraine-ACT (27 items)	143	.99	75.62	<.0001

Analyses of consistency of response were conducted to investigate the reliability data further. The proportion of patients who consistently answered ‘yes’ or ‘no’ at both Visits 1 and 2 is shown in Table 3. The consistency of response was excellent for all 27 Migraine-ACT items. Similar consistency was shown in the distribution of ‘yes’ and ‘no’ answers over the two visits.

Table 3. The consistency of the 'yes'/'no' responses between Visit 1 and Visit 2 for the 27 Migraine-ACT items: proportion of patients who responded 'yes' or 'no' at Visit 1 who had the same responses at Visit 2.

	Consistency of response (% patients)	
Migraine-ACT item	**'No' answers**	**'Yes' answers**
IMP 1	76.74	90.28
IMP 2	75.00	84.00
IMP 3	87.14	87.07
IMP 4	83.15	85.86
IMP 5	66.67	83.04
IMP 6	77.78	93.50
IMP 7	84.85	84.27
IMP 8	80.49	85.58
IMP 9	88.07	81.82
IMP 10	80.00	78.21
IMP 11	88.43	69.23
GAR 1	79.75	73.83
GAR 2	83.33	88.89
GAR 3	90.43	62.32
GAR 4	86.07	67.21
GAR 5	83.58	75.47
GAR 6	77.91	79.80
GAR 7	71.43	88.81
GAR 8	86.40	66.10
GAR 9	85.06	82.11
CONS 1	82.54	83.06
CONS 2	78.79	93.78
CONS 3	70.00	86.86
EMOT 1	84.75	85.83
EMOT 2	83.08	81.36
EMOT 3	84.00	89.55
EMOT 4	79.79	75.56

Construct validity and item selection

Discriminatory t-test scores between the individual 27 Migraine-ACT questions and 15 items contained within the SF-36, MIDAS and MTAQ questionnaires are shown at the end of the article in Table 4. Eleven items related to the SF-36 questionnaire (physical function, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental heath, total physical, total mental and total SF-36 scores). Three items related to the MIDAS questionnaire (MIDAS A score [headache frequency], MIDAS B score [headache severity] and total MIDAS score [time lost for everyday activities]) and one item related to the MTAQ score (total MTAQ score). Finally, the total score from all 15 variables was correlated with the four best Migraine-ACT items. A t-discrimination score of ≥ 2 indicates a significant correlation.

Correlations of Migraine-ACT items with SF-36 and MIDAS items and SF-36, MIDAS and MTAQ total scores indicated that the most discriminating items in the four domains of the Migraine-ACT questionnaire were IMP 4, GAR 1, CONS 3 and EMOT 3. The discriminating factors for these four items were all highly significant. The best correlation was observed between the Migraine-ACT items and the MTAQ total score. These data indicate that the four items constituting the final Migraine-ACT questionnaire should be:

- Impact: **Are you able to function normally within 2 hours?** (IMP 4)

- Global assessment of relief: **Does the headache pain disappear within 2 hours?** (GAR 1)
- Consistency of response: **Does your migraine medication work consistently, in the majority of your attacks?** (CONS 3)
- Emotional response: **Are you comfortable enough with your medication to be able to plan your daily activities?** (EMOT 3)

The results showed that the four items in the Migraine-ACT discriminated most with the MTAQ score, and to a slightly lesser degree with the total SF-36 score. Factor analysis showed that four items described most of the variance in the data: the total SF-36 score described 42.01%; the SF-36 role emotional score described 9.49%; the total MTAQ score described 8.93%; and the MIDAS B score (pain severity) described 6.96%. Mean t-discrimination scores from the 15-item analysis above were compared with those from the factor analysis (Table 5), and were very similar, indicating a high level of correlation.

Table 5. Discrimination analysis (discriminatory t-tests) of the four items constituting the final Migraine-ACT Questionnaire: comparison of t-test values calculated from all 15 items contained within the SF-36, MIDAS and MTAQ questionnaires, and the four items derived from factor analysis.

	Mean t-discrimination	
Migraine-ACT item	**Total score derived from all 15 SF-36, MIDAS and MTAQ items**	**Total score derived from factor analysis**
IMP 4	3.07	3.97
GAR 1	2.70	3.14
CONS 3	2.08	2.71
EMOT 3	3.16	4.18

Analysis of the 4-item Migraine-ACT questionnaire

The 4-item Migraine-ACT questionnaire was further analysed in several ways. The individual questions, and the total Migraine-ACT score, were correlated with subscales and total scores of the SF-36, MIDAS and MTAQ questionnaires using Pearson product moment measures (Table 6). The Migraine-ACT items and total score correlated well with the other items, particularly so with the total MTAQ and SF-36 domain and total scores. Regression of MTAQ and total SF-36 on Migraine-ACT were both highly significant (MTAQ: beta = -0.58, SE = 0.06, $p < 0.0001$; SF-36: beta = 0.36, SE = 0.07, $p < 0.0001$). The 4-item Migraine-ACT questionnaire was examined for test-retest reliability, and was shown to be very reliable by the Pearson and Spearman measures ($r = 0.82$ for both calculations).

Table 6. Analysis of the 4-item Migraine-ACT questionnaire: calculation of Pearson product moment measures with the SF-36, MIDAS and MTAQ questionnaires.

	Pearson product moment measures				
	IMP4	**GAR1**	**CONS3**	**EMOT3**	**Total Migraine-ACT score**
SF-36 Bodily Pain	0.345	0.24	0.25	0.33	0.38
SF-36 General Health	0.18		0.15	0.25	0.24
SF-36 Vitality	0.22	0.25		0.22	0.28
SF-36 Social Functioning	0.31	0.30	0.21	0.34	0.38
SF-36 Mental Health	0.20	0.21		0.21	0.25
SF-36 Total Physical	0.31	0.25	0.20	0.29	0.34
SF-36 Total Mental	0.27	0.27	0.18	0.29	0.33
SF-36 Total	0.31	0.28	0.20	0.31	0.36
MIDAS B score	-0.24	-0.20	-0.18	-0.18	-0.26
Total MIDAS score	-0.28	-0.29		-0.31	-0.32
Total MTAQ score	-0.50	-0.39	-0.38	-0.59	-0.60

In scoring the Migraine-ACT questionnaire, it is desirable to produce simple cut-off points that facilitate interpretation and use. The simplest scoring method is to score all 'yes' answers as '1' and all 'no' answers as '0', and sum the answers. This produces a 5-item score, ranging from 0–4. A score of '4' might indicate that the patient has no medication needs, while a score of '0' may indicate very high medication needs. Alternatively, the items can be individually weighted, resulting in a more complex scoring scheme. However, regression analysis indicated that weighting the scoring only increased its discriminatory power by 3% as compared to the MTAQ questionnaire. The simpler method was therefore practically as good as a more complicated weighting method. Table 7 shows how the simple version Migraine-ACT scores compare with those of MIDAS, MTAQ and SF-36 total scores. A decreasing Migraine-ACT score (indicating increased medication needs) correlated with increasing MIDAS and MTAQ scores (indicating increased management needs) and a decreasing SF-36 score (indicating reduced quality of life). The mean Migraine-ACT score for patients (n = 181) participating in this study was 2.55 (SE = 0.11).

Table 7. Interpretation of the total Migraine-ACT score: relation to MIDAS, MTAQ and SF-36 scores

Migraine-ACT score	**MIDAS score**	**MTAQ score**	**SF-36 score**
4	16	2.25	54
3	22	2.95	48
1	34	4.37	46
0	40	5	44

MIDAS scores range from 0 to over 100. There are four grades: I = no or minimal disability (score 0–5); II = mild disability (score 6–10); III = moderate disability (score 11–20); and IV = severe disability (score > 20). Most migraine sufferers score as Grade III or IV.[1]
MTAQ scores range from 0–8, with a higher score indicating an increasing number of management issues.[4]
SF-36 scores range from 0–100, with increasing score correlating with better health. A score of 50 is the average for the US population.[23]

Discussion

Any new tool assessing clinically important endpoints needs to exhibit good test-retest reliability and validity before it can be recommended for use. Good test-retest reliability means that the tool assesses the data consistently over time. Validity denotes the accuracy of the tool in assessing what it is meant to measure. Validity is commonly assessed by criterion (gold standard) or construct validity (comparing the accuracy of the new tool compared to other tools that are related to the same disease area). Additional attributes are necessary if a tool is designed for use in primary care. The tool needs to be brief, and simple to complete and score. It should also exhibit face validity, being intuitively meaningful to the target audience. All these factors were included in the design and testing of the Migraine-ACT questionnaire.

Migraine-ACT was designed from the outset to have high face validity. The question domains were chosen to be clinically relevant. Migraine impact, the global response to medication, consistency of response and the emotional component of the headache are all important in assessing the severity of illness and the response to treatment.[9–14] The questionnaire was also designed to be brief, with only four questions, one in each domain. Simplicity was assured by ensuring that all questions were answered by 'yes' or 'no'.

The individual 27 Migraine-ACT questions all exhibited good-to-excellent test-retest reliability. However, additional analyses of reliability were required due to the variables being dichotomous (yes/no) rather than continuous, with resultant low degrees of freedom in the analyses. We therefore analysed the consistency of response in the patients' answers at the two study visits. Analyses of consistency (the proportion of patients who answered 'yes' or 'no' at both study visits and the proportion of 'yes' and 'no' answers for each question at the study visits) provided a high consistency in the responses (typically over 80% agreement). Taken together with the good test-retest reliability data, it can be concluded that the Migraine-ACT questions are highly reliable. While the 1-week gap between the first and second completions of the questionnaire may be considered to be short, this was done to minimise potential changes in the patients' migraine attacks, which could have altered the results.

For the assessment of construct validity, the 27 items constituting the original Migraine-ACT were correlated with a series of questionnaires that have been shown to be sensitive to outcome in headache. SF-36 is a generic QOL questionnaire that can be used for any illness state. It has been shown to accurately assess the severity of migraine, and effective treatment results in an increased score, indicating improved QOL.[18] MIDAS is a headache-specific questionnaire that assesses disability as time lost from daily activities, as well as the headache frequency and severity.[1] It is a reliable[1,19] and valid[20] measure, and is a sensitive outcome measure in migraine and other headaches.[21,22] MTAQ is a migraine-specific questionnaire that is a reliable and valid screening tool,[4] although its utility as an outcome measure has not yet been demonstrated. Discriminatory t-tests showed that many of the Migraine-ACT items correlated well with the total SF-36 score and some of its subscales, the MIDAS total score and MIDAS B scores, and the total MTAQ score. Of all these items, Migraine-ACT items correlated best with the total SF-36 and MTAQ scores. The four items constituting the final Migraine-ACT questionnaire were selected on the basis of those items (one in each domain) that correlated best with the total score from all 15 items from the SF-36, MIDAS and MTAQ variables. Factor analysis confirmed these data.

The four-item Migraine-ACT questionnaire is shown in Figure 8 at the end of this article. The order of the questions is designed so that migraine and headache items are introduced first, while the more generic questions are answered later. Each 'yes' answer is scored as '1' and each 'no' answer as '0'. The total Migraine-ACT score is achieved by summing the answers

to the four items. We suggest that a score of 4 corresponds to the physician not needing to re-evaluate the patient while 0 corresponds to a very high need for re-evaluation. However, further studies are required to confirm this relationship and define the cut-off point that indicates the need for evaluation and/or a change in treatment. Regression analysis showed that there was no significant advantage in weighting the answers, which would have increased the complexity of the questionnaire markedly. The result is a questionnaire that is intuitive and simple to complete and score, yet correlates highly with both generic (SF-36) and disease-specific (MTAQ) measures of health status. Further testing showed that the 4-item Migraine-ACT is highly reliable and valid.

We envisage the main use of the Migraine-ACT as a rapid and accurate screener to identify patients whose current acute treatment regimen needs to be changed. It is intended for use by the primary care physician or clinician in everyday clinical practice. Currently-used tools do not fulfil this role because they are too complex for routine use.[1–4] There were clear but opposite relationships between the 4-item Migraine-ACT with the SF-36 general health measure, and the headache-specific MIDAS and the highly migraine-specific MTAQ. This would be expected, as illness and health are opposite constructs. The 4-item Migraine-ACT score ranges from 0–4 and indexes a window into the total SF-36 score ranging from 44–54. The higher the score, the better off is the patient. Similarly the specific MIDAS and MTAQ measure illness with higher scores being worse for the patient. The 4-item 0–4 score indexes a window into MIDAS from 16–40 and into MTAQ ranging from 2–5. The MIDAS scores, ranging from mid-Grade III to high Grade IV are what would be expected in a population of secondary care patients having significant headache-related disability.[1] The 4-item Migraine-ACT is appreciably shorter, simpler and easier to complete than any of the three other questionnaires above.

Further studies are required to define the clinical utility of Migraine-ACT, to define the score that indicates a change in treatment is needed, and to investigate its sensitivity to change for use as an outcome tool in comparison to changes in SF-36, MIDAS and MTAQ. This study was conducted in secondary care referral centres. Studies in primary care practice are therefore particularly needed to demonstrate its utility in the everyday management of migraine. However, we believe that the main use of Migraine-ACT will be in clinical practice, and naturalistic studies conducted in this domain will determine the true utility of the questionnaire.

Conclusions

The 4-item Migraine-ACT questionnaire is a rapid, reliable, brief, simple to complete and score assessment tool, which can be recommended for everyday clinical use by the clinician to identify patients who require a change in their current acute migraine treatment.

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Table 4. Construct validity of the 27-item Migraine-ACT questionnaire: discrimination analysis (discriminatory t-tests) between the 27 Migraine-ACT items and the 15 items contained within the SF-36, MIDAS and MTAQ questionnaires.

	Mean t-discrimination															
Migraine-ACT question	SF-36 Physical Function	SF-36 Role-Physical	SF-36 Bodily Pain	SF-36 General Health	SF-36 Vitality	SF-36 Social Functioning	SF-36 Role Emotional	SF-36 Mental Health	SF-36 Total Physical	SF-36 Total Mental	SF-36 Total	MIDAS A Score	MIDAS B Score	Total MIDAS Score	Total MTAQ Score	Total score from all 15 variables
IMP 1	-0.00	0.51	3.15	1.72	2.16	3.38	-0.89	1.63	2.28	2.19	2.17	-1.11	-2.12	-2.63	-5.06	1.98
IMP 2	1.08	0.61	3.07	2.52	1.77	2.67	0.61	1.76	2.69	2.50	2.63	-1.57	-2.30	-3.05	-6.17	2.24
IMP 3	1.20	0.85	3.72	2.96	2.45	3.91	0.98	3.19	3.38	3.89	3.77	-0.99	-4.42	-3.61	-6.75	2.96
IMP 4	-1.06	-1.53	-5.04	-2.39	-3.05	-4.48	-1.05	-2.70	-4.16	-3.61	-4.15	1.17	3.37	3.62	7.31	3.07
IMP 5	2.15	-1.18	0.52	0.22	-0.27	-0.17	-0.57	0.18	0.56	-0.09	0.35	-1.22	-0.28	1.53	0.66	0.69
IMP 6	-0.07	0.50	3.21	2.07	1.28	3.69	0.59	2.43	2.07	2.75	2.60	-0.81	-3.39	-2.39	-6.09	2.17
IMP 7	0.18	-0.68	-3.57	-2.07	-3.10	-3.50	-1.71	-2.81	-2.68	-3.59	-3.13	0.92	2.79	3.10	5.81	2.56
IMP 8	0.55	0.86	3.84	0.93	1.81	4.42	0.86	2.88	2.11	2.70	2.57	-1.09	-2.91	-3.22	-5.76	2.39
IMP 9	0.096	-0.82	-3.87	-1.72	-2.58	-3.30	-0.43	-2.38	-2.54	-2.84	-2.75	1.29	3.06	4.02	4.92	2.35
IMP 10	0.30	-1.58	-3.36	-1.21	-2.71	-3.71	-2.41	-4.25	-2.19	-3.59	-3.23	1.69	2.34	3.52	5.94	2.67
IMP 11	-0.27	-1.71	-2.37	-2.37	-3.85	-3.87	-1.72	-4.49	-2.98	-4.04	-3.45	1.04	3.55	2.90	4.06	2.76
GAR 1	0.57	1.11	3.37	1.93	3.44	4.32	0.72	2.82	3.28	3.67	3.74	-1.77	-2.70	-3.76	-5.40	2.70
GAR 2	-1.57	0.30	1.20	-0.10	-0.23	1.49	-2.18	0.45	-0.15	-0.21	0.03	0.16	0.00	-0.96	-4.30	0.84
GAR 3	1.86	0.11	-2.31	-1.32	-2.05	-1.54	0.67	-1.55	-1.21	-2.14	-1.92	0.87	2.26	2.28	3.21	1.62
GAR 4	-0.80	-0.22	2.47	2.61	2.13	2.21	0.50	2.28	1.75	2.85	2.51	-1.94	0.39	-2.15	-4.62	1.98
GAR 5	0.75	0.23	2.02	2.24	2.37	2.00	0.44	1.03	3.19	2.78	3.10	-0.48	-1.60	-2.67	-4.45	1.86
GAR 6	0.22	0.14	2.13	1.44	2.11	2.51	0.42	2.36	2.15	2.33	2.43	-2.25	-1.45	-2.61	-4.07	1.83
GAR 7	-0.48	0.85	0.92	-0.15	0.39	1,51	-0.60	2.04	0.44	0.71	0.93	-1.94	-1.21	-0.50	-3.21	1.04
GAR 8	0.27	-1.29	-3.40	-1.99	-2.37	-2.79	-1.19	-2.74	-2.36	-3.09	-2.96	1.07	3.90	3.38	4.52	2.33
GAR 9	0.61	0.04	2.46	1.21	2.13	2.92	-0.66	2.11	1.98	2.17	2.30	-0.49	-2.67	-2.99	-4.35	1.89
CONS 1	-0.15	0.63	3.35	1.33	2.19	2.44	0.90	2.08	1.97	2.26	2.12	-1.73	-2.66	-2.05	-4.90	2.06
CONS 2	1.13	0.20	2.84	2.22	1.26	2.88	0.15	1.75	2.19	1.75	1.98	0.27	-2.96	-1.94	-5.91	1.93
CONS 3	0.29	-1.27	3.53	2.05	1.84	2.88	-0.62	1.91	2.64	2.40	2.62	-1.05	-2.39	-1.27	-5.19	2.08
EMOT 1	-0.09	-0.82	-3.73	-3.26	-2.02	-3.61	-1.01	-2.31	-3.20	-3.43	-3.28	0.10	2.65	3.64	6.44	2.54
EMOT 2	-0.77	0.37	4.24	1.88	0.75	3.34	1.00	1.30	2.29	1.92	2.37	0.03	-2.24	-2.72	-6.25	2.09
EMOT 3	0.04	-0.55	-4.64	-3.41	-2.98	-4.90	-1.10	-2.88	-3.86	-3.98	-4.10	0.71	2.40	4.11	9.10	3.16
EMOT 4	-1.37	-0.78	-6.05	-3.31	-2.86	-4.75	-1.62	-1.90	-4.23	-3.35	-3.55	1.06	1.84	4.80	6.74	3.12

Figure 1. The 4-item Migraine-ACT questionnaire recommended for use in primary care.

Please answer all four questions below, as 'yes' or 'no', by placing a tick in the relevant box.

Question	Yes	No
When you take your treatment: **Does your migraine medication work consistently, in the majority of your attacks?**		
When you take your treatment: **Does the headache pain disappear within 2 hours?**		
When you take your treatment: **Are you able to function normally within 2 hours?**		
When you take your treatment: **Are you comfortable enough with your medication to be able to plan your daily activities?**		
Migraine-ACT Score		

Scoring the Migraine-ACT questionnaire
One or more 'no' answers may indicate the need to change treatment. An increasing number of 'no' answers indicates increasing treatment needs.

4.6

The Migraine Assessment of Current Therapy (Migraine-ACT) questionnaire: investigation of reliability, validity and clinical utility in a multinational study*

Abstract

The 4-item Migraine-ACT questionnaire is an assessment tool for use by primary care physicians to identify patients who require a change in their current acute migraine treatment. It has been shown to be easy to use, and to be reliable and accurate in its assessments. The Migraine-ACT study database was analysed further, providing additional information on the reliability, validity and potential clinical utility of the questionnaire.

Reliability was assessed by recording the distribution of Migraine-ACT scores recorded at baseline and 1 week later (test-retest reliability). Analyses of consistency of Migraine-ACT scores were conducted on the total sample of patients and for the five separate centres (Germany, Italy, Spain, UK and USA), using Pearson and Spearman correlations. Validity was assessed by comparing the t-discrimination values for clinically-relevant questions within domains of the original 27-item questionnaire. Reliability and validity were also assessed by constructing an 'alternative' (Form B) Migraine-ACT questionnaire, derived from an analysis of the second best items in each domain in the original study data. Clinical utility was assessed using Pearson pairwise correlations to compare Migraine-ACT scores with clinically-defined criteria as analysed by the SF-36 Quality of Life questionnaire, the Migraine Disability Assessment (MIDAS) questionnaire and the Migraine Therapy Assessment (MTAQ) questionnaire.

The distribution of Migraine-ACT scores between the two completions of the questionnaire was consistent for the total sample (test-retest reliability r = 0.81) and between the individual countries (r = 0.61–0.92). In this study, the validity (assessed as t-discrimination) of the Migraine-ACT 'impact' and 'global assessment of relief' questions were markedly higher than those of other endpoints used in migraine clinical studies. The Form B Migraine-ACT questionnaire was almost as reliable and accurate as the original Form A questionnaire. The distribution of Migraine-ACT scores was: 0 = 12.6%, 1 = 13.7%, 2 = 14.7%, 3 = 20.5% and 4 = 38.4%. The change in Migraine-ACT score correlated with, and had a linear relationship with changes in SF-36, MIDAS and MTAQ scores, and indicated that a Migraine-ACT score of ≤ 2 corresponded with a need to consider changing the patient's acute medication. About 40% of the migraine patients in the study scored ≤ 2 and may have had significant unmet treatment needs.

These data confirm the good reliability and validity of the Migraine-ACT questionnaire and provide further evidence for its utility in clinical practice.

**Summarised from the article: Kilminster S, Dowson AJ, Tepper S, Baos V, Baudet F, D'Amico D. The Migraine Assessment of Current Therapy (Migraine-ACT) questionnaire: investigation of reliability, validity and clinical utility in a multinational study. Headache 2005; Submitted for publication.*

Introduction

A 4-item questionnaire was developed, the Migraine Assessment of Current Therapy (Migraine-ACT) questionnaire (see Chapter 3.5 and Table 1) as a means to identify patients attending primary care clinics who require a change in their current acute migraine treatment. Four clinically important domains of the migraine experience were assessed: consistency of response,[1,2] global assessment of relief,[2,3] headache impact[4,5] and emotional response.[6] A multicentre, international study was conducted with Migraine-ACT (the original Migraine-ACT questionnaire was developed in English then translated into Spanish, German and Italian for use in the study. The translations were verified by blind back-translation into English). The study demonstrated that Migraine-ACT was easy to use, and was reliable and accurate in its assessments and suitable for use by the primary care physician. Scoring the questionnaire is by simple summing of the 'yes' scores (range 0–4).[7] This article describes further analyses of the Migraine-ACT study database, providing additional information on the reliability, validity and clinical utility of the questionnaire.

Table 1. The 4-item Migraine-ACT questionnaire recommended for use in primary care (Form A).[7]

Please answer all four questions below, as 'yes' or 'no', by placing a tick in the relevant box.

Question	**Yes**	**No**
When you take your treatment: **Does your migraine medication work consistently, in the majority of your attacks?**		
When you take your treatment: **Does the headache pain disappear within 2 hours?**		
When you take your treatment: **Are you able to function normally within 2 hours?**		
When you take your treatment: **Are you comfortable enough with your medication to be able to plan your daily activities?**		
Migraine-ACT Score		

Scoring the Migraine-ACT questionnaire

One or more 'no' answers may indicate the need to change treatment. An increasing number of 'no' answers indicates increasing treatment needs.

Methods

Patients and design

Details of the patient inclusion and exclusion criteria and the overall study design are described in Chapter 3.5.

Reliability

Test-retest reliability was previously assessed by Pearson and Spearman measures.[7] Further analyses of reliability were conducted in terms of the distribution of Migraine-ACT scores recorded at baseline and 1 week later for the total sample of patients and the individual countries. Results were expressed as the proportion of patients at each score. Test-retest reliability was assessed as the Pearson correlation and the Spearman rank correlation for comparisons of data from the total patient sample and the individual countries.

Validity

Construct validity of Migraine-ACT was previously assessed[7] using discriminatory t-tests to relate dichotomous 'yes' and 'no' responses scored 1 and 0 in patients' answers to the 27-item Migraine-ACT with those to the Short-Form 36 quality of life questionnaire (SF-36),[8] the Migraine Disability Assessment (MIDAS) questionnaire[9] and the Migraine Therapy Assessment Questionnaire (MTAQ) [see 'Methods' chapter].[10] Further analyses of validity were conducted in terms of correlating the t-discrimination values for clinically-relevant questions within domains of the original 27-item questionnaire. t-discrimination values were compared for the following items:

- Impact: Are you able to function normally within 2 hours (IMP 4)?; Do you usually not need to lie down after 2 hours (IMP 5)?; Are you able to concentrate normally within 2 hours (IMP 9)?; Have any feelings of tiredness, irritability, sadness, anger and anxiety disappeared within 2 hours (IMP 11)?.
- Global assessment of relief: Does the headache pain disappear within 2 hours (GAR 1)?; Is the headache pain relieved after 2 hours (GAR 2)?; Does the headache pain disappear within 2 hours and not return within 24 hours (GAR 3)?; Does the headache pain disappear within 2 hours and not return within 48 hours (GAR 4)?; Does the headache pain start to disappear within 30 minutes (GAR 5)?; Do your non-headache symptoms (e.g. nausea and sensitivity to light, sound or smells) disappear within 2 hours (GAR 6)?; Are you clear of all your symptoms within 2 hours (GAR 8)?

An 'alternative' Migraine-ACT questionnaire was also constructed, derived from an analysis of the second best items (Form B) for each domain in the original study data. This questionnaire was examined for reliability (Spearman rank correlations) and validity (t-discrimination scores). The overall reliability of the original questionnaire (Form A) and the Form B questionnaire were compared using Pearson pairwise correlations.

Clinical utility

The clinical utility of the Migraine-ACT questionnaire was examined in several ways to relate Migraine-ACT scores to medical need. Firstly, the distribution of Migraine-ACT scores recorded above in the reliability analysis was examined. Secondly, the Migraine-ACT score was correlated to the total scores obtained for the SF-36, MIDAS and MTAQ questionnaires, using Pearson pairwise correlations. Following this, Migraine-ACT scores were compared to clinically-defined criteria as analysed by the SF-36, MIDAS and MTAQ questionnaires.

Results

Reliability

The distribution of Migraine-ACT scores at baseline and 1 week later for the different countries and the total patient population are shown in Table 2. Analyses of these data and the Pearson

and Spearman test-retest correlations (Table 3) showed that the data between the two completions of Migraine-ACT were consistent for the total population and for the individual countries. All correlations were significant to $p < 0.01$. Pearson correlations ranged from 0.61 to 0.92, and similar values were reported for the Spearman rank correlations. The correlation for the total patient population was $r = 0.81$ for both analyses.

Table 2. Consistency of the 4-item Migraine-ACT questionnaire: proportion of patients assigned to each Migraine-ACT score during the two completions of the questionnaire (total sample and data for each country). Scores range from 0 (all answers are 'No') to 4 (all answers are 'Yes').

Total sample

	1st completion (*n* = 190)		2nd completion (*n* = 185)	
Migraine-ACT score	***n***	**Patients (%)**	***n***	**Patients (%)**
4	73	38.4	68	36.8
3	39	20.5	30	16.2
2	28	14.7	36	19.5
1	26	13.7	26	14.1
0	24	12.6	25	13.5

UK

	1st completion (*n* = 40)		2nd completion (*n* = 39)	
Migraine-ACT score	***n***	**Patients (%)**	***n***	**Patients (%)**
4	16	40.0	16	41.0
3	9	22.5	6	15.4
2	5	12.5	7	17.9
1	4	10.0	4	10.3
0	6	15.0	6	15.4

Spain

	1st completion (*n* = 40)		2nd completion (*n* = 40)	
Migraine-ACT score	***n***	**Patients (%)**	***n***	**Patients (%)**
4	15	37.5	14	35.0
3	6	15.0	7	17.5
2	3	7.5	7	17.5
1	5	12.5	3	7.5
0	11	27.5	9	22.5

USA

	1st completion (*n* = 40)		2nd completion (*n* = 40)	
Migraine-ACT score	***n***	**Patients (%)**	***n***	**Patients (%)**
4	20	50.0	18	45.0
3	8	20.0	5	12.5
2	7	17.5	10	25.0
1	5	12.5	5	12.5
0	0	0	2	5.0

Germany

	1st completion (*n* = 30)		2nd completion (*n* = 26)	
Migraine-ACT score	***n***	**Patients (%)**	***n***	**Patients (%)**
4	7	23.3	9	34.6
3	7	23.3	3	11.5
2	7	23.3	4	15.4
1	8	26.7	6	23.1
0	1	3.3	4	15.4

Italy

	1st completion (*n* = 40)		2nd completion (*n* = 40)	
Migraine-ACT score	***n***	**Patients (%)**	***n***	**Patients (%)**
4	15	37.5	11	27.5
3	9	22.5	9	22.5
2	6	15.0	8	20.0
1	4	10.0	8	20.0
0	6	15.0	4	10.0

Table 3. Test-retest reliability of the Migraine-ACT questionnaire: Pearson and Spearman rank correlations for the completions of the Migraine-ACT questionnaire at baseline and 1 week later: analysis by country and for the whole patient sample.

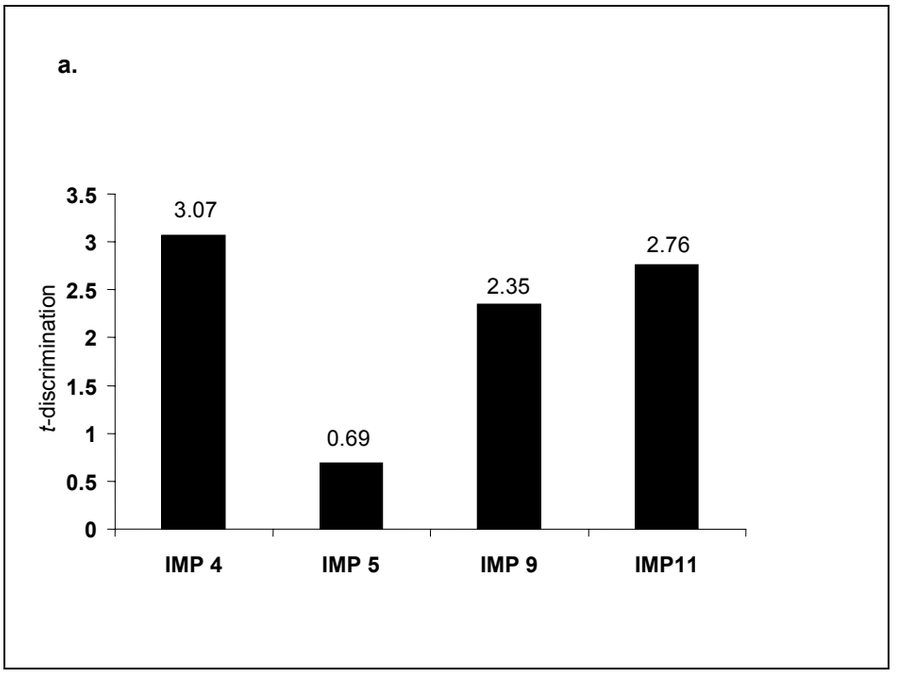
Country	**Pearson correlation**	**Spearman rank correlation**
UK	0.91	0.90
Spain	0.92	0.92
USA	0.61	0.65
Germany	0.74	0.74
Italy	0.75	0.77
Total patient sample	0.81	0.81

All comparisons were significant to $p < 0.01$

Validity

Figure 1 shows the analysis of t-discrimination scores for assessments of impact and the global assessment of relief. In examining the relative discriminatory value of measures of migraine impact, the ability to function normally within 2 hours (IMP 4) was markedly more discriminatory than not needing to lie down after 2 hours (IMP 5), being able to concentrate normally within 2 hours (IMP 9) and the disappearance of emotional symptoms within 2 hours (IMP 11). In examining the relative discriminatory value of measures of global assessment of relief, the assessment of headache pain disappearance at 2 hours (GAR 1) was markedly more discriminatory than that of headache relief at 2 hours (GAR 2), sustained pain-free rates over 24 hours (GAR 3) or 48 hours (GAR 4), early onset of pain disappearance (GAR 5), disappearance of non-headache symptoms (GAR 6) and disappearance of all symptoms (GAR 8).

Figure 1. Comparison of t-discrimination values for Migraine-ACT items equivalent to commonly-used endpoints in migraine studies. ***a. Impact:*** *ability to function normally within 2 hours (IMP 4), no need to lie down after 2 hours (IMP 5), able to concentrate normally within 2 hours (IMP 9) and symptoms of tiredness, irritability, sadness, anger and anxiety disappear within 2 hours (IMP 11).* ***b. Global assessment of relief.*** *pain-free at 2 hours (GAR 1), 24 (GAR 3) and 48 (GAR 4) hours, headache relief at 2 hours (GAR 2), start of headache relief within 30 minutes (GAR 5), free of non-headache symptoms at 2 hours (GAR 6) and clear of all symptoms within 2 hours (GAR 8).*



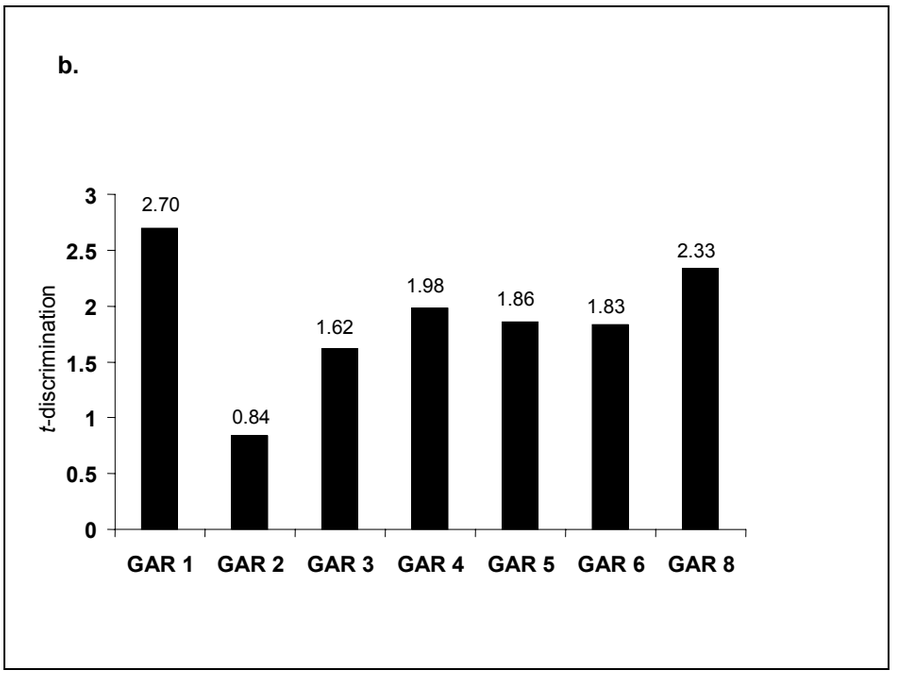


Table 4 shows the 'alternative' (Form B) 4-item questionnaire that was derived from the original 27-item Migraine-ACT by selecting the second most discriminatory question in each domain. Calculated values for reliability (Spearman rank correlation) and validity (t-discrimination scores) for each question were similar to those of the original 4-item questionnaire. Pearson pairwise correlations showed that the overall test-retest reliability of the Form B questionnaire was high, (r = 0.81) and was virtually the same as that of the original Form A questionnaire (r = 0.82). The correlation was significant to $p < 0.01$.

Table 4. An 'alternative' (Form B) 4-item Migraine-ACT questionnaire and its reliability and validity, compared with those of the original questionnaire. Values in parentheses show the equivalent data for the original Migraine-ACT questionnaire (Form A[7]).

Question	Reliability (Spearman rank measure)	Validity (t-discrimination)
When you take your treatment: **Does your migraine medication work attack after attack?**	0.68 *(0.61)*	2.06 *(2.08)*
When you take your treatment: **Are you clear of all your symptoms within 2 hours?**	0.58 *(0.58)*	2.33 *(2.70)*
When you take your treatment: **Are you able to resume your normal activity (i.e. work or family-leisure-social activity, etc.) within 2 hours?**	0.77 *(0.72)*	2.96 *(3.07)*
When you take your treatment: **Do you feel in control of your migraine enough so that you feel there will be no disruption to your daily activities?**	0.63 *(0.78)*	3.12 *(3.16)*

Clinical utility

The distribution of Migraine-ACT scores for the total population was: 0 = 12.6%, 1 = 13.7%, 2 = 14.7%, 3 = 20.5% and 4 = 38.4%. The distribution of scores between the two completions of the questionnaire was consistent between countries (Table 2).

Pearson pairwise correlations for the comparison of Migraine-ACT scores with the total SF-36, MIDAS and MTAQ scores are shown in Table 5. All correlations were significant at $p < 0.05$. The data showed that Migraine-ACT closely correlated with SF-36, MIDAS and MTAQ total scores both times it was completed (at baseline and after 1 week). The tendency was for a greater correlation (stronger relationship) with MTAQ > MIDAS > SF-36. The pattern of correlations showed great construct consistency.

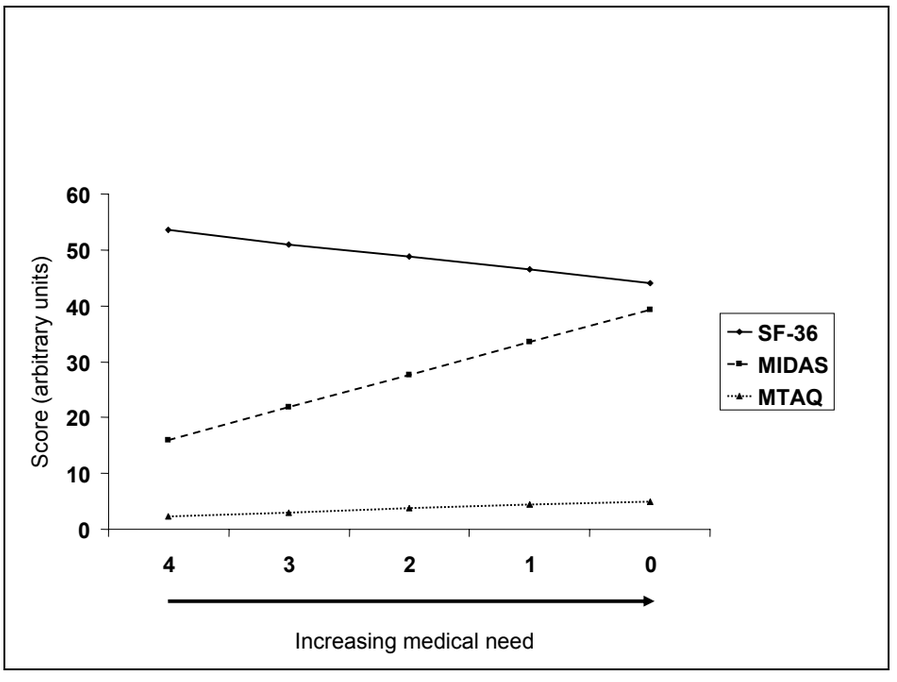
Table 5. Pearson pairwise correlations for the comparisons of Migraine-ACT, SF-36, MIDAS and MTAQ total scores: comparisons of data at baseline and 1 week.

	Total SF-36 score	Total MIDAS score	Total MTAQ score
Migraine-ACT score (baseline)	0.36	-0.32	-0.60
Migraine-ACT score (1 week)	0.34	-0.39	-0.58

All correlations were significant at $p < 0.05$.

Figure 2 shows how the Migraine-ACT scores corresponded to SF-36, MIDAS and MTAQ scores. The relationship was essentially linear in all cases. As the Migraine-ACT score decreased from 4 to 0, the SF-36 score deceased from 53.6 to 44.0, the MIDAS score increased from 16.0 to 39.3 and the MTAQ score increased from 2.3 to 5.0.

Figure 2. Relationship of Migraine-ACT scores to clinically-defined criteria as analysed by scores on the SF-36, MIDAS and MTAQ questionnaires.



Discussion

The aims of this *post hoc* analysis of the original Migraine-ACT study were to provide further data on the robustness of the results, and to give the physician insights into the clinical utility of the questionnaire and how it might best be used in the clinic. To do this, new analyses of reliability and validity were conducted and examined for clinically relevant data.

The original assessments of test-retest reliability used appropriate statistical methodology (Pearson product moment and Spearman rank measures). This methodology has been used in examining the reliability of, among others, the MIDAS Questionnaire, both in its original English version,[5] and in scientific translation into other languages.[11] The 27 items of the original Migraine-ACT questionnaire all exhibited good-to-excellent reliability over 1 week, and the final 4-item Migraine-ACT was a highly reliable measure (r = 0.82).[7] Data presented here demonstrate that there was high consistency in the Migraine-ACT scores reported from the individual countries and the total population. Test-retest reliability ranged from 0.61–0.92 according to country. Additionally, an 'alternative' 4-item Form B questionnaire derived from the same 27 questions was also highly reliable (r = 0.81). These data reinforce the good reliability of the 4-item Migraine-ACT questionnaire.

The assessment of construct validity (accuracy) commonly involves the comparison of data from a new tool with those from standard existing tools ('gold standard' measures).[12] In the original study, Migraine-ACT was compared with the SF-36 QOL questionnaire, the MIDAS disability questionnaire and the MTAQ disease management questionnaire, and was shown to correlate well with these questionnaires, especially with the total MTAQ and SF-36 scores.[7] Data presented here showed that a second Form B 4-item questionnaire could be derived from the original 27 questions in which the questions were almost as accurate as the 4-item Migraine-ACT questionnaire. The two sets of questions exhibited considerable redundancy, indicating that they accurately measured the same specific domains. Additionally, three of the original questions assessing global assessment of relief (GAR 1, 4 and 8) and three of the impact questions (IMP 4, 9 and 11) showed similar levels of discrimination.

This conclusion is reinforced when examining the t-discrimination scores associated with different types of questions used in the 'impact' and 'global assessment of relief' domains. Migraine is associated with different areas of impact, including:

- The ability to function normally, which can be assessed with the MIDAS questionnaire.[13]
- The need to lie down during attacks, which was assessed as important in the studies that developed the Headache Impact Test.[14]
- Cognitive changes, which are frequently reported during attacks, and have been assessed in one study.[15]
- Emotional changes, which have been identified as important components of migraine, tension-type headache and chronic daily headache.[6,16]

The results reported here indicate that assessing the ability to function normally after treatment is markedly more discriminating in assessing impact that the other three measures. Numerous studies have indicated that the disruption of patients' everyday activities is the key measure of illness severity in migraine patients.[4,5,13,17,18]

Over the years, much research has attempted to define the optimal measure of relief of migraine symptoms, usually using a 2-hour endpoint:

- The disappearance of the headache, which is used as the gold standard measure by the *International Headache Society*.[3]
- The relief of headache, defined as an improvement from severe or moderate to mild or none, and used as the primary endpoint in most migraine studies to this day.[19]
- Disappearance of the headache which is sustained for 24 or 48 hours after treatment.[2,20]
- Onset of headache disappearance, usually defined as within 30 minutes after treatment.[21]
- Disappearance of non-headache symptoms of the migraine attack.[19]
- Disappearance of all symptoms of the migraine attack.[20]

The results reported here indicate that assessing the disappearance of the headache at 2 hours after treatment is markedly more discriminating in assessing relief than any of the other measures above. The results therefore agree with recent studies that have indicated the pain-free measure is the most important clinical endpoint in migraine studies.[2,3,20] Migraine-ACT therefore contains two highly valid measures for assessing the efficacy of treatment. Domains of consistency of response and emotional response have not been assessed to anything like the same extent as impact and global response, but are both clinically relevant in assessing the constellation of migraine symptoms.[2,6]

The clinical relevance of these data is considerable. The original Migraine-ACT questionnaire was developed in English then translated into Spanish, German and Italian for use in the study.

The translations were verified by blind back-translation into English. The high values obtained for consistency and reliability in the distribution of the Migraine-ACT grade scores attest to the robustness of the questionnaire for use in different countries. Migraine-ACT has since been translated into Dutch (Appendix 1) and its use is advocated in the Netherlands.[22]

The relationship of Migraine-ACT scores to scores on the SF-36, MIDAS and MTAQ questionnaires provides further evidence of clinical utility. Pearson pairwise correlations confirmed that the Migraine-ACT score was closely related to SF-36, MIDAS and MTAQ total scores. The linear relationship between the range of Migraine-ACT scores and scores for the three other questionnaires is noteworthy and demonstrates an even gradation of Migraine-ACT scoring. The mean SF-36 score in the US population is 50[8] and patients with Migraine-ACT scores of 2, 1 and 0 would therefore seem to have lower quality of life than the general population (SF-36 scores of 48.9, 46.5 and 44.0, respectively). The MIDAS scores ranged from 16.0 (Migraine-ACT score 4) to 39.3 (Migraine-ACT score 0). MIDAS scores of 11–20 (Grade III) equate with moderate disability, while scores of > 20 (Grade IV) equate to severe disability.[9] The mean MIDAS score for migraine patients is typically in the Grade III range.[9] MTAQ scores ranged from 2.3 (Migraine-ACT score 4) to 5.0 (Migraine-ACT score 0). MTAQ scores range from 0–8 depending on the number of management issues identified for the patient. A score of ≥ 2 is used as the threshold for when follow up is warranted.[10]

From these data, it can be deduced that a Migraine-ACT score of 2, 1 and 0 identifies patients for whom a change in acute treatment may be warranted. These patients have reduced quality of life, severe headache-related disability and a considerable number of outstanding management issues. In this study, 41.0% of patients met this criterion, and the results were relatively similar between the countries (UK = 37.5%, Spain = 47.5%, USA = 30.0%, Germany = 53.3%, Italy = 40.0%, Table 2). It might be expected that the proportion of patients presenting to primary care physicians with Migraine-ACT scores of ≤ 2 would be even higher, due to the likelihood of them having received suboptimal care.[23–27]

The general limitations of the Migraine-ACT study are described in Chapter 3.5. From the analyses described here, further work is desirable to investigate the clinical significance of the Migraine-ACT scoring scheme. In addition, further studies are warranted to investigate Migraine-ACT as an outcome tool to monitor the effect of interventions.

In conclusion, these data confirm the good reliability and validity of the Migraine-ACT questionnaire and provide further evidence for its utility in clinical practice. It is suggested that a score of ≤ 2 may indicate that a change in the patient's acute medication is warranted and a score of ≤ 1 may indicate that the change is mandated.

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5

General discussion

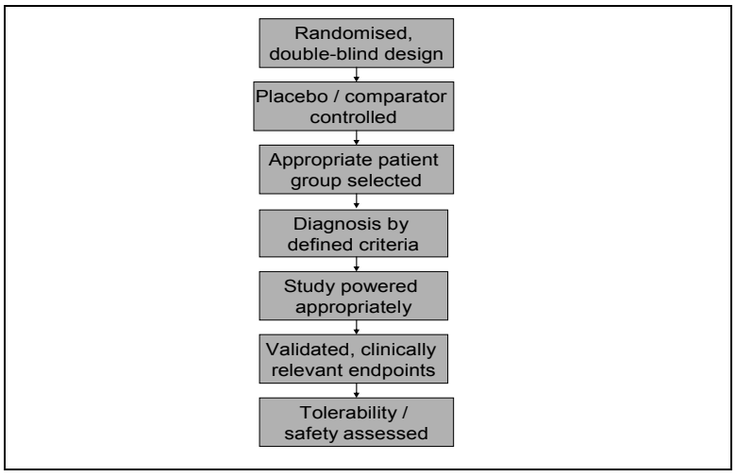
The main aim of these studies was to investigate the clinical significance of headache-related disability and impact; the clinical importance of assessing disability, the means of recognising the patients with severe disability and the development of new ways to assess headache-related disability and their utility in clinical practice. The main methodology used in the thesis was critical reviews of the literature and open, naturalistic studies designed to mimic the situation in everyday primary care clinical practice. In this chapter the main study findings are discussed and related to the published clinical literature. The research and clinical implications deduced from the data are outlined. Finally, the methodology of the studies is criticised and future studies and directions for further research outlined.

5.1 Main results

Clinical importance of assessing headache-related disability

For evidence-based medicine, the randomised, double-blind, controlled clinical study remains the gold standard for evaluating the clinical profile of drugs.[1,2] However, as discussed in Chapter 3.1, several criteria need to be met before the study can be categorised as high quality Grade A clinical evidence. Studies need to be randomised, double-blind and to contain enough patients in each treatment group to allow for sufficient power for the statistical analyses. Patient withdrawals should be low (≤ 10%) and equivalent in the separate treatment groups. Outcome measures should be quantifiable and clinically meaningful, and statistical tests should be appropriate for the populations and endpoints studied.[3] These criteria should be mandatory for all controlled studies (Figure 1). Additionally for headache, a placebo group should always be included to control for the variable placebo response that characterises the condition.[4]

Figure 1. Criteria for the design of Grade A clinical studies.



Not surprisingly, these stringent conditions are not always met, and *post hoc* and meta-analyses are sometimes used if clinical evidence is inconclusive and when comparisons between drugs are desired but a proper controlled study has not yet been conducted. For headache, such analyses have generated controversy, rather than contributing substantially to understanding the efficacy of acute migraine therapies (with inconsistencies in the studies included and analyses conducted).[5–8] Their chief utility should be to suggest avenues for future clinical studies and they should not be used on their own as a means of selecting acute treatments for migraine.[3]

However, even results from double-blind, controlled clinical trials may not always be optimal in terms of reflecting the situation in clinical practice. For example, in migraine controlled clinical studies show only small differences between the oral triptans, whereas patients describe clear, if individual, preferences between them.[3] The conundrum is that individual patients respond differently to medications that have similar efficacy profiles, and reinforce the need for an approach to care that is tailored to the needs of each patient. The basis for these differences in effect may be due to biological (e.g. neuroreceptor profile) and/or clinical (e.g. co-morbidities and the presence of single or multiple headache conditions) factors. Patients differ in how they cope with pain, their sensitivity to pain and in other ways that lead to headache being a heterogeneous rather than an isolated condition. Only very large studies using vast numbers of patients can detect statistically significant differences between treatments in such a heterogeneous environment. However, the differences are often small and not necessarily clinically relevant. This fundamental methodological problem is encountered in other medical fields, e.g. palliative care and psychiatric disorders.

The development of new, more sensitive endpoints to assess migraine relief may therefore be needed. Proposed new endpoints tend to be global measures that combine assessments of efficacy and tolerability, including assessments of patient preference and satisfaction, the impact on patients' daily lives and the patient's quality of life. Of these three types of endpoints, patient preference / satisfaction and headache impact can provide simple and intuitive assessments,[9,10] while quality of life is a more complex measure wherein the units of assessment do not relate directly to clinically meaningful measures.[11] Such endpoints may be more valid and sensitive than the traditional headache-based ones, although this has to be demonstrated in clinical studies.

Assessing patient preference

Chapter 3.2 reviews and discusses the data on using patient preference / satisfaction as an outcome measure in migraine studies.[9] Many studies have used patient preference as secondary analyses of efficacy. Overall, the results show that patients can distinguish differences in efficacy between the triptans and non-triptan medications for migraine, and also between the different triptans.[9] These data are remarkable, as it has proved difficult to show significant differences between acute migraine medications using the usual primary endpoint of relief of headache.[12–20] More limited data for patient satisfaction show similar trends.[9] A limitation of these data is that, as secondary analyses, they were not subject to rigorous statistical analyses.

Patients' assessment of their preference for their migraine treatments may therefore be a valid and sensitive measure of clinical efficacy that is relevant to real-life clinical practice, taking into account both efficacy and tolerability. The results also indicate that patient preference may be a more sensitive measure of efficacy and clinical utility than conventional clinical trial endpoints, although this remains to be proven in rigorously designed clinical studies. Another limitation of the data is that patients' preferences are individual and not predictable beforehand, possibly

being based on individual biological and/or clinical factors.[9] Despite this, physicians should consider using assessments of patient preference when reviewing the efficacy of acute migraine medications, based on the author's clinical experience. It is important that new instruments to assess preference/ satisfaction are appropriately developed and tested. It would be good to have a standard instrument that is used in all studies to make the findings more easily comparable.

Assessing headache-related disability

Headache can be a significantly disabling condition, as defined by the *World Health Organization* as a condition resulting in limitations to daily activities.[21] Migraine is particularly well categorised as being disabling. Numerous studies (reviewed in Chapter 4.1) demonstrate that migraine results in sufferers being unable to conduct their everyday daily activities (employment, household tasks and family and leisure activities) during their attacks.[22] The studies of Lipton, Stewart and colleagues elegantly demonstrate that disability rather than pain severity is the key measure of migraine severity.[23] Tension-type headache (TTH) is generally thought to be a relatively non-disabling condition in terms of pain and headache-related disability.[24] The study assessing emotional impact of headache with the SPI questionnaire (Chapter 3.4) indicated that the pain associated with TTH was indeed transient and mild-to-moderate intensity. However, the results showed a marked chronic sedation associated with TTH[25] that has been noted once before.[26] These data may indicate that the disability associated with TTH is currently under-estimated. The same study showed that chronic daily headache (CDH) was associated with chronic pain and emotional impact that was severe in intensity.[25] These data confirm the well-recognised severe disability associated with CDH,[27] but extend the impact into the emotional domain. From all these data, it is clear that physicians should ask headache patients about their level of disability before deciding on a management plan, although it seems that few currently do so.[28] In fact, information on disability does change the physician's perception of illness severity and subsequent handling of management.[28]

There are currently limited data on the use of disability or impact tools as endpoints in clinical studies. However, two studies have shown that the MIDAS questionnaire is sensitive to change, and can be used to monitor patients with migraine or CDH in the clinic.[29,30] The HIT questionnaire has been much less studied in this regard and, as described in Chapter 4.3, may be more useful as a diagnostic tool than as a measure of headache severity.[31] Both MIDAS and HIT capture retrospective data, over 3 months and 1 month, retrospectively.[22] The SPI questionnaire collects prospective data,[32] and may therefore be a better clinical study endpoint than either MIDAS or HIT, although this can only be demonstrated with further studies.

Recognising headache-related disability

As already described, assessing headache-related disability is important in the clinical evaluation of headache. It is therefore important that the physician is able to recognise patients who are disabled and to manage them accordingly. The level of disability also needs to be monitored over time, and this aspect of recognising disability was assessed in two studies in this thesis:

- Investigating the level of disability associated with headaches occurring inside and outside the menstrual period
- Investigating the emotional impact of different headache subtypes over time.

Disability associated with headaches occurring inside and outside the menstrual period

The study described in Chapter 3.3 provided a snapshot of headache in women attending a primary care clinical practice, and also provided information on their level of depression and bodily pain.[33] Patients who completed an initial questionnaire reported high levels of headache,

depression and bodily pain. About two-thirds of patients reported headache, over 50% symptoms indicative of depression, and about 40% bodily pain. The symptoms were reported across all age groups. Overall, the results indicate that headache, depression and bodily pain are common in the general adult female population and that many patients clearly have multiple symptoms. Physicians would benefit from asking patients about their levels of pain and mood disturbance. Headache is frequently co-morbid with psychiatric disorders (particularly major depression and anxiety),[34] and patients with multiple co-morbidities are likely to require more care than those with a single condition.

Migraine sufferers in this study were invited to complete a disability questionnaire encompassing some of the items now contained in the MIDAS questionnaire over a 2-month period, covering at least a full menstrual period. However, this was not a MIDAS study, being designed before the full development of the MIDAS questionnaire. The data showed that migraine headaches were relatively more frequent inside than outside the menstrual period, while non-migraine headaches were approximately equally distributed inside and outside the menstrual period. This data for the distribution of migraine attacks is in line with recently published data.[35] The study also showed that migraine attacks that occurred inside the menstrual period were somewhat more disabling than those occurring outside the menstrual period in terms of rank sums of the MIDAS items of time lost and time at less than 50% productivity. These results are in line with a recent study indicating that menstrually-associated migraine attacks were only slightly more painful than non-menstrually-associated ones,[36] but not with another study indicating that attacks during menstruation were markedly more disabling than those occurring outside the menstrual period.[35] Results for non-migraine headache were the opposite of those for migraine, with attacks occurring outside the menstrual period scoring numerically, but not significantly, higher than those occurring inside the menstrual period in terms of the rank sums of time lost and time at less than 50% productivity. These data indicate that the pattern of headache-related disability can differ at different time periods in the patient's life and also with respect to the different headache subtypes experienced by the patient. They emphasise the importance of a correct diagnosis (or diagnoses) and the monitoring of patients over time with a headache diary or other form of questionnaire.

The emotional impact of different headache subtypes over time
The study described in Chapter 3.4 categorised the emotional impact of episodic TTH, migraine and CDH with the SPI questionnaire.[25] This allowed the analysis of the emotional 'footprint' of each headache subtype in terms of the emotional experience, associated sedation, disruption to social interactions and the time course of each of these components. Patients recorded their headaches with the SPI at peak intensity and at intervals for 7 days afterwards.

At peak intensity the pain level was mild-to-moderate for episodic TTH, and patients exhibited sedation, disturbances in social interaction, sadness, anxiety and anger. These symptoms all resolved within 24 hours, except for sedation, for which marked levels persisted for most of the following week. Coping scores for sedation were the most disturbed of all the three types of headache, even including CDH. This is surprising, considering the relatively mild intensity of TTH. Sedation may be a precipitating factor for TTH or a feature of the recovery process that is unrelated to the headache severity. Also, coping scores for sadness were sometimes above the normal range for 3 out of the 7 days post-headache. The results indicate that TTH patients have mood lability and may mean that the illness severity of patients is currently underestimated by physicians.

At peak intensity the pain level was moderate-to-severe for migraine and patients exhibited sedation, disturbances in social interaction, sadness, anxiety and anger. In general, the severity

of these emotional components was more intense for migraine than for TTH. All these symptoms typically resolved within 2 days of the headache and coping scores were at normal levels after the headache. These data indicated that the patients coped well with the emotional symptoms, which resulted from the level of physical pain experienced.

At peak intensity the pain level was severe for CDH and patients exhibited sedation, disturbances in social interaction, sadness, anxiety and anger. In general, the severity of these emotional components was more intense for CDH than for TTH. However, these symptoms were maintained over the 7-day period following the headache. Pain remained at a mild-to-moderate level. Marked levels of sedation, disturbed social interaction, sadness, anxiety and anger were also seen during this period. The coping scores for sedation, social interaction and sadness were above the level caused by the pain. The result is that CDH patients are chronically fatigued. CDH is associated with Chronic Fatigue Syndrome[37] and sedation is a major feature of the post-dromal period of CDH. Overall, the level of emotional disturbance experienced by CDH patients was similar to that seen in patients attending chronic pain clinics.[38] An unfortunate feature of CDH patients is that their mood disturbance never returns to normal and patients obtain no respite from the pain and its emotional consequences. This pattern of emotional impact associated with CDH is similar to that reported in a qualitative study.[39]

Overall, patients with TTH, migraine and CDH all had considerable mood disturbances during their headaches. The more severe the pain they experienced, the greater was the level of mood disturbance. The level of mood disturbance was also directly related to the healthcare utilisation of the patients. The pattern of mood disturbance was different for each type of headache, as was the patients' ability to cope with the mood changes. The association of mood disturbances with common headache subtypes may explain in part the reported co-morbidity of headache with psychiatric disorders.[34] Physicians should elicit the emotional needs of their headache patients, which may not be currently appreciated or addressed by healthcare services, as they play no part in the current classification criteria for headache.[24]

Assessing headache-related disability

Chapters 3.3 and 3.4 show that disability is a key feature of headache, and can differ in intensity and quality in different headache subtypes and in individual patients over time.[25,33] Assessing headache-related disability should therefore have utility in monitoring patients, as an outcome measure and possibly for other assessments. A review of the methodological robustness and clinical utility of disability and impact questionnaires was conducted for the thesis (Chapter 4.1)[22] as well as a series of studies investigating the utility of disability questions in diagnosis (Chapters 4.3 and 4.4)[31,40] and as outcome measures for patient assessment (Chapters 4.2, 4.5 and 4.6).[41–43]

Reviewing disability measures for headache

Research (reviewed in Chapter 4.1) has shown that headache-related disability and impact can be measured using assessments of some or all of pain severity, headache frequency, limitations to work and leisure activities, tiredness, mood alterations and cognition. Disability-based measures include the MIDAS, HIT and SPI questionnaires, all of which are now available for clinical use.[22]

The MIDAS questionnaire retrospectively measures headache-related disability as time lost (as the number of days) in employment, unpaid work and family and leisure activities. Numerous studies have shown that it is reliable,[10] valid,[10] sensitive to change[29,30] and exhibits considerable clinical utility in the clinic.[44] HIT (either in the Internet[45] or paper-based HIT-6[46] forms) retrospectively assesses a global range of impact, including pain intensity, disability and other

items. HIT is also reliable and valid,[45,46] and has some evidence of clinical utility for assessing diagnosis and headache severity in the clinic.[47,48] Chapter 4.3 of this thesis indicates that HIT is a good diagnostic tool but a relatively poor tool for assessing headache severity.[31] The SPI questionnaire prospectively assesses pain intensity and emotional impact of the headache over time.[32] It is also reliable and valid,[49] and can distinguish the emotional components of different pain states[50] and, as shown in Chapter 3.4, those of different headache subtypes.[25] Synthesising the available evidence, it would seem that HIT can be used for headache diagnosis, and MIDAS and SPI for assessing headache severity and as outcome measures in clinical studies. MIDAS has been shown to be a useful outcome tool in different headache disorders,[29,30] and we await similar evidence from studies with SPI.

The assessment of headache-related disability is a key item of recently published migraine guidelines in the USA[1] and migraine and CDH guidelines in the UK.[51,52] It is used to improve communication between physicians and their patients and, with other measures, to assess headache severity to tailor treatment to each patient's individual needs. However, although used a lot in specialist clinics, disability tools have not yet penetrated significantly into primary care. They seem to be relatively unknown and the clinical experience of the author shows them to be too complex for patients to complete unaided. Clearly, educational initiatives are needed to promote the use of disability tools in primary care. However, physicians should enquire about disability and a simple question such as: *How do your headaches interfere with your normal daily activities?* may be sufficient to start a discussion and obtain relevant clinical information from the patient.

Utility of disability questions in headache diagnosis
Already discussed are the results from Chapter 4.3 investigating the clinical utility of the HIT and SPI questionnaires. The results showed that the Internet version of HIT is very good at differentiating the diagnosis of TTH, migraine and CDH.[31] HIT was not designed to be a diagnostic tool, but to measure the impact headaches have on a person's ability to function at work, at home, at school and in social situations. Indeed, the developers state that HIT is not a diagnostic tool.[45] We can only speculate on the factors within the HIT questionnaire that are associated with diagnosis. HIT assesses a constellation of factors: headache-related pain severity and disability, the need to lie down, tiredness and mood alterations. As SPI assesses emotional function and is not a diagnostic tool, it seems unlikely that tiredness and mood alterations correlate with diagnosis. However, pain severity[24] and disability[27,47] do differ between the three headache subtypes, and these seem the most likely drivers of diagnosis, at least in the HIT questionnaire. Whatever the case, HIT does discriminate between headache subtypes very well and, should a neurologist be not available, is a good diagnostic test.

Chapter 4.4 describes the development and testing of the 8-item DSQ, designed to be an inclusive diagnostic aid for headache to be used at the patient's first consultation with a healthcare professional.[40] The items assessed were headache frequency, duration and related disability, together with frequency of use of analgesic medications, prevalence of aura symptoms and a series of questions eliciting potential sinister headaches. The study showed that the DSQ was simple to complete, either by the patient on their own or in concert with a healthcare professional. Overall, the DSQ exhibited good diagnostic sensitivity (of about 60%) when completed by the patient or the pharmacist, especially for total migraine, migraine with and without aura and MOH. These results indicate that the DSQ is an effective inclusive tool for the differential diagnosis of headache. Interestingly, the accuracy of the pharmacists' headache diagnosis was improved markedly when they used the DSQ, providing evidence of clinical utility.

Again, it was not possible to identify the DSQ items that correlated best with diagnosis. Compared with the HIT questionnaire, an item on disability was present, while one on pain severity was not. It is tempting to speculate that the assessment of headache-related disability, in concert with other headache features, is the main predictor of diagnosis. Such a pattern is seen in other recently-developed diagnostic questionnaires for headache. With the inclusive Brief Headache Screen, migraine, daily headache syndromes and medication overuse were distinguished using three questions: the frequency of disabling headache, the presence of other, mild headaches and the use of symptomatic medications.[53] Migraine exclusively could be diagnosed sensitively and specifically using three questions on headache-related disability, nausea and sensitivity to light,[54] or three questions on disability, headache duration and the lack of new-onset headaches in the previous 6 months.[55] There is considerable overlap between the DSQ and these other inclusive and exclusive questionnaires in terms of assessing disability, together with other headache features and symptoms, which reinforces the content and external validity of the DSQ questionnaire.[23]

The DSQ is therefore a useful headache screening questionnaire for use when the patient first seeks care for the condition from a healthcare professional, who may be a GP, nurse, pharmacist or other practitioner (e.g. opticians and dentists often see people with headache). Its principal use is proposed to be an aid to deciding the appropriate first management decisions. It may be particularly suitable for use by pharmacists, which is of clinical importance as they may see more headache sufferers than do GPs.[56]

Utility of disability questions as outcome measures for patient assessment
Two studies are included in this thesis investigating the use of disability questions to assess patient outcome.

1. Chapter 4.2: the clinical utility of the MIDAS questionnaire when used by nurses at patient screening[41]
2. Chapters 4.5 and 4.6: the methodological robustness and clinical utility of the Migraine-ACT questionnaire, which contains two items on disability.[42,43]

In Chapter 4.2, the MIDAS questionnaire was used to monitor new patients with mild-to-moderate headache at baseline and for 6 months after being provided with headache advice by a specialist nurse.[41] The patients had significantly improved headache outcomes 6 months later in terms of headache-related disability, headache frequency and severity, all assessed with MIDAS. Additionally, they perceived an improvement in headache and reported a reduced need for consulting a physician for headache. As very few patients consulted a physician during the study, this improvement could be attributed to the advice given by the nurse on headache management, despite the absence of a control group. The study also adds to the published data indicating that MIDAS may be a sensitive outcome measure for headache sufferers.[29,30]

It is worth noting that the simple provision of advice can lead to a sustained significant improvement in headache, although previous small studies have suggested the same effect.[57,58] Recently published headache guidelines have advocated the provision of advice and information to patients at headache screening,[51,52] and this study illustrates how effective this strategy can be. The practice nurse has a positive role in the management of headache in primary care, particularly with respect to screening and follow-up, and guidelines dedicated for nurse use have been published.[59] These recommendations state that nurses should undertake information dissemination and recording of data using headache history and impact questionnaires and headache diaries.

Chapters 4.5 and 4.6 outline the development of a new outcome questionnaire, Migraine-ACT, to assess the need to change a migraine patient's acute medication.[42,43] This somewhat limited functionality is, however, clinically important due to the fact that acute medications are usually under-used, despite the availability of effective treatments today.[60–63] Four clinically-relevant domains were included in the questionnaire: impact,[23,54] global assessment of relief,[5,64] consistency of response[5,65] and emotional response.[25,31] Twenty seven questions were developed and reduced to four (one in each domain) by testing for reliability and validity. The tool was designed from the outset to be brief, and simple to complete and score by yes/no answers. The use of clinically-relevant domains provides prior evidence of face validity.

The individual 27 Migraine-ACT questions all exhibited good-to-excellent test-retest reliability in the total population and within the five countries taking part in the study. Assessment of construct validity demonstrated that many of the 27 Migraine-ACT items correlated with the SF-36 QOL questionnaire,[11] the MIDAS questionnaire[10] and the MTAQ disease management questionnaire[66] and allowed selection of the best four items in the final questionnaire. The four-item Migraine-ACT questionnaire was highly reliable and valid. In assessing the impact items, the ability to function normally after treatment (a measure of headache-related disability) was markedly more discriminating than other measures. Numerous studies have previously indicated that the disruption of patients' everyday activities is the key measure of illness severity in migraine patients.[23,54,55,67,68] In addition, the resolution of headache at 2 hours provided a more discriminating assessment of global response than other items tested, agreeing with data from other studies.[5,64,69]

The total Migraine-ACT score is achieved by summing the answers to the four items without weighting ('yes' = 1 and 'no' = 0). A score of 4 corresponds to the physician not needing to re-evaluate the patient while 0 corresponds to a very high need for re-evaluation. Scores of 2, 1 and 0 correlated with lower than average quality of life,[11] MIDAS scores equivalent to severe disability[10] and MTAQ scores above the threshold for when follow up is deemed warranted.[66] From these data, it was deduced that a Migraine-ACT score of 2, 1 and 0 identifies patients for whom a change in acute treatment may be warranted. These patients have reduced quality of life, severe headache-related disability and a considerable number of outstanding management issues. It was suggested that a score of ≤ 2 may indicate that a change in the patient's acute medication is warranted and a score of ≤ 1 may indicate that the change is mandated.[43]

The 4-item Migraine-ACT questionnaire is therefore a rapid, reliable, brief, simple to complete and score assessment tool, which can be recommended for everyday clinical use by the clinician to identify patients who require a change in their current acute migraine treatment. Table 1 summarises the key features of the questionnaire.

Table 1. Features of the Migraine-ACT questionnaire.

Property	Feature of Migraine-ACT questionnaire
Objective	Assess the need to change a migraine patient's acute medication
Questions	Four yes/no questions on headache-related disability, global response, consistency of response and emotional impact
Scoring	5-point scale (0–4), with a score ≤ 2 indicating that a change in acute medication is warranted
Reliability, validity and potential clinical utility	Good
Who conducts the questionnaire	Physician (primary care or specialist)

5.2 Implications: methodological, research and clinical

The importance of assessing headache-related disability was first identified by Lipton, Stewart and colleagues several years ago. This research led to the understanding that disability is the key driver of headache severity,[23] and to the development of the MIDAS questionnaire.[10] The literature searches and studies outlined in this thesis have extended the knowledge of disability assessments and expanded their potential use in research and in the clinic in several areas:

Methodological

1. The type of naturalistic, longitudinal clinical studies used in this thesis are suitable for use in primary care and produce clinically-meaningful results, as described above. The potential advantages of this type of study over the conventional controlled or open-label clinical study are:
    a. Real-life patients are more representative of the general patient population than the selected groups of patients seen in conventional clinical studies, where children, women pregnant or wishing to become pregnant, patients with some co-morbidities and older people are usually excluded.
    b. Fewer patients may be required in order to achieve the clinical effect.
    c. Commercially-available drugs, doses and formulations are used according to everyday clinical practices, allowing real-life comparisons.
    d. The long-term effectiveness of treatment is investigated, rather than the efficacy at a point in time.

Research

1. Conventional clinical study endpoints for headache may be relatively insensitive.[3] MIDAS is now frequently used as an endpoint and we now have the Migraine-ACT questionnaire, based on disability and symptom relief, which shows promise as a new study endpoint.
2. There is an emotional component associated with headache-related disability, encompassing sedation, poor social interaction, sadness, anger and anxiety. The pattern of the emotional disturbances varies in different headache subtypes.
3. All disability and impact measures are not the same. HIT is more a diagnostic tool than a severity tool. MIDAS and SPI are tools that assess headache severity and not diagnosis.

Clinical

1. The pattern of disability related to headaches can differ at different time periods in the patient's life and also with respect to the different headache subtypes experienced by the

patient. This emphasises the importance of the physician's correct diagnosis (or diagnoses) and their prospective monitoring of patients over time.

2. Physicians should assess headache-related disability when they evaluate their headache patients. One of the available questionnaires (MIDAS, HIT or SPI) can be used, or just a simple question about the disturbance to daily activities may help to start discussions and reveal clinical information.
3. Assessments of disability play key roles in the management of headache:
    a. Improving communication between the healthcare professional and the patient.
    b. As part of the diagnostic procedure. Perhaps few physicians will use HIT alone for diagnosis, but HIT, or a general question on disability can provide valuable diagnostic information and is useful for case finding.
    c. As part of the assessment of headache severity, helping to tailor treatment to each patient's individual needs.
    e. As an integral part of primary care guidelines for headache, so guiding treatment choice.
    f. Assessing disability is a suitable job for the practice nurse, and forms a key part of their role in headache management.
4. The DSQ is a sensitive inclusive tool for the screening of headache sufferers when they first present for care. It contains one question on disability, together with other questions on different headache features. It has considerable potential clinical utility in the management of headache in primary care. Patients should be able to obtain a copy at their first point of care, whether a GP surgery, pharmacist, optician, dentist or other provider. They can complete the DSQ, either at home by themselves or with the help of the practitioner. The practitioner then reviews the DSQ and provides appropriate advice. Using the questionnaire, there is the potential for earlier and better headache diagnoses. The DSQ may be particularly useful to pharmacists. Following pharmacist intervention, patients can either be treated immediately or, if appropriate, be empowered to obtain help from the GP sooner rather than later.
5. The MIDAS questionnaire is also suitable for first-line use in the clinic. Patients identified with a marked level of disability can have improvements in their headaches simply by receiving appropriate information from a nurse or other healthcare professional.
6. The Migraine-ACT questionnaire has been developed as a rapid, reliable and accurate screener to identify patients whose current acute treatment regimen needs to be changed. It contains four questions on headache-related disability, emotional impact, and response to treatment. It is intended for use by the primary care physician in everyday clinical practice. A score of 2, 1 or 0 is suggested as being indicative of the need to change medications.

5.3 Methodological issues and suggestions for future research

As well as advantages, the naturalistic studies conducted for this thesis have several potential disadvantages that need to be taken into account when evaluating the results:

1. The studies were relatively small in terms of numbers of patients and sometimes in duration.
2. The open design means that results could not be unequivocally assigned to the intervention used. Other factors, e.g. a placebo response, could bias the results.
3. The studies may not have been powered appropriately.
4. Asymmetries of design may have occurred.
5. Some of the questionnaires used were not validated.

Each study is now considered in turn for its methodological robustness and the potential for future research.

Chapter 3.3: Disability associated with headaches occurring inside and outside the menstrual period

This study investigated the prevalence of headache, depression and bodily pain in women attending a UK general practice. The disability associated with migraine and other headache attacks occurring during and outside the menstrual period was assessed in those women with migraine. Results showed that the patients reported a high prevalence of headache, depression and bodily pain**.** For migraine sufferers, migraine attacks that took place during the menstrual period tended to be more disabling than those taking place outside the menstrual period, but the opposite was true for non-migraine headache.

The questionnaires (headache, depression and bodily pain) used in the first part of this study were not validated tools, but were devised by the investigators to be simple to use and potentially applicable to primary care clinical practice. They were not tested for reliability or validity, and additional studies would be required for this. Despite this, headache subtype and the severity of depression and bodily pain were identified for each patient. The prevalence of the headache subtypes was close to expected values, although depression was probably over-estimated. Future work on this topic should probably use validated diagnostic questionnaires for headache (e.g. the DSQ)[40] and depression (e.g. the Beck Depression Inventory).[70]

The design of this prevalence study was also not optimal. Additional items that should have been taken into account included defining the sample in relationship to the population under study, random sampling, defining an acceptable response rate (> 50%), and conducting a non-response analysis. There was the possibility of the responders being a self-selecting population with significant problems, although the similarities in age range between the responders and the total population argues against this.

Part 2

The menstrual headache questionnaire used in Part 2 of the study was also not validated. However, it was based on the IHS diagnostic criteria pertaining at the time[71] and contained items now used in the MIDAS questionnaire.[10] It therefore contained items with proven reliability and validity. However, the questionnaire should be tested for reliability if it is used again. This in fact seems unlikely to happen, as the MIDAS questionnaire could be used in its place.

Some methodological issues were raised by the study analyses that have implications for the design of future studies. The data were confounded by the fact that some of the events were repeatedly measured in individual patients, and that some patients only had one type of headache. A much larger sample of patients would be necessary to allow both within and between patient group comparisons. The results should be taken with caution as data were analysed between the groups for only 30 patients experiencing 203 headache attacks. However, non-parametric testing with the Mann-Whitney U Test showed one significant and one marginally significant result from only four analyses, which indicates that the results were unlikely to have arisen by chance. Analysis of means or medians was not a useful measure in the present study because the data were not normally distributed. Many headache attacks scored zero on the two analyses, leading to floor effects being observed. Such floor effects have been reported with use of the MIDAS Questionnaire, on which the analyses were based.[72] Future studies may benefit from using assessments of headache impact which provide a normal distribution of results, such as the Headache Impact Test[45,46] or the Short Pain Inventory.[32]

This study is best considered a pilot investigation of questionnaires to assess headache, depression, bodily pain and the disability associated with headache. While the methodology

used has been superseded by more recent developments, it served to investigate new ways to measure headache-related disability at a time when validated questionnaires were not available for headache. Such studies are necessary in the development of new tools and their publication serves scientific accountability.

Chapter 3.4: the emotional impact of different headache subtypes over time
In this prospective, within-group, comparative study, the SPI was used to assess how the mood disturbances and coping abilities change over time in patients with episodic TTH, migraine and CDH attending a primary care headache centre. The healthcare resource utilisation of these patients was also assessed retrospectively. The results showed that patients with headache had significant emotional symptoms associated with their headaches. These symptoms resolved within 1–2 days for patients with episodic TTH and migraine. However, patients with CDH were profoundly affected, and did not improve physically or emotionally from their headache over a 7-day period. Headache patients generally experienced higher levels of sedation than did patients with other pain conditions.

The limitations to this study are discussed below in the text on Chapter 4.3

Chapter 4.3: comparison of HIT and SPI
This sub-analysis of study 3.4 above compared the psychometric properties of the Headache Impact Test (HIT-DYNA®) with the 17-item Short Pain Inventory (SPI©) and the abilities of the SPI and HIT in terms of discriminating headache severity and diagnosis. The results showed the HIT to be poorly related to the severity of the pain but very closely related to the diagnostic label. In contrast to this, the SPI was very closely related to severity but not related to diagnosis.

In the two chapters based on this study (3.4 and 4.3), relatively small numbers of patients took part, and a high proportion of patients did not experience a headache (especially those with TTH) and hence did not complete a SPI questionnaire in the 6 weeks allowed. A longer study duration could have led to a reduction in the drop out rate. The healthcare utilisation analysis was performed with retrospective collected data, for practical reasons. Of course, a prospective design would have been more powerful. Patients from a primary care headache centre were recruited so that, as far as possible, criteria for a naturalistic study were met.

SPI is now a well-established questionnaire that can be used to assess any pain state.[32,38,50] It is available to interested healthcare professionals at www.headachetest.co.uk and can be completed on-line. Future studies should include SPI as an endpoint in controlled studies of headache treatments, in comparison to more conventional endpoints (including other disability questionnaires).

Chapter 4.2: the clinical utility of the MIDAS questionnaire when used by nurses at patient screening
This audit assessed the outcome of a nurse intervention strategy in patients presenting with headache to a primary care surgery. The results showed that advice on headache management given by a nurse led to significant improvements in the patients' outcomes. MIDAS appeared to be a sensitive outcome measure for reduction in disability in headache sufferers.

The main shortcoming of this study was that it was uncontrolled. As no control group was included, the reductions in MIDAS and other items could have been due to a placebo effect. Nevertheless, there was good evidence of significant improvements in MIDAS items and significant reductions in headache consultations, as parametric and non-parametric analyses exhibited the same patterns of results.

A further shortcoming was that the numbers of patients reduced as the visits proceeded due to drop outs. This could have caused some bias, leading to an improvement in the patients' condition. This is because, psychologically, patients are more likely to continue with an investigation if they are generally feeling well or better than if they are deteriorating or have no change in their condition. However, the results were promising enough to pave the way for future randomised, controlled studies investigating the role of nurses in headache management.

Chapter 4.4: utility of disability questions in headache diagnosis

This prospective, open investigation was set up to validate the 8-item Headache Diagnostic Screening Questionnaire (DSQ), containing questions screening for possible sinister symptoms, and evaluating headache impact, frequency and duration, the use of symptomatic medications and the presence of migraine aura symptoms. The results showed that the Headache DSQ is a brief, rapid to use and accurate diagnostic screening questionnaire for headache, and is especially sensitive for migraine and MOH. It can be recommended for screening new headache patients at and below the primary care level.

Some weaknesses were observed in this study. The study was not properly randomised, with alternate patients being openly assigned to seeing the pharmacist or GP first. The study was not large enough to determine whether the order of seeing these healthcare professionals had any effect on the results. However, the pharmacists and GPs were blind to each other's assessments. The entry criteria for numbers of patients with episodic TTH and cluster headache were not met by the patients recruited into the study. For this reason the specificity of the DSQ could not be assessed.

The accuracy of the DSQ for CDH without MOH was poor, and patients tended to underestimate the duration and/or the frequency of their headaches. Additionally, migraine patients sometimes confused aura symptoms with prodromes when answering question 8 *(Do changes in your senses (sight, taste, smell or touch) occur before the headache starts?).* Small changes were made to the questionnaire to rectify these points, as part of its ongoing development. A follow-up randomised study with the modified DSQ is warranted to assess its sensitivity and specificity. Further studies with the DSQ could also be conducted in specialist headache clinics (where cluster headache patients are more common and could be assessed) and in pharmacies (where episodic TTH sufferers may be encountered frequently and could be assessed). In addition, it would be interesting to see if GPs' diagnostic accuracy could improve to the specialist level if they had access to the DSQ.

However, the value of this study is that the Headache DSQ as developed is a brief, rapid to use and accurate diagnostic screening questionnaire for headache, and is especially sensitive for migraine and MOH. The DSQ, and other questionnaires, demonstrate the utility of incorporating assessments of disability into diagnostic questionnaires. It is recommended for screening new headache patients at and below the primary care level, although future studies will more fully define its place in the clinic.

Chapters 4.5 and 4.6: development and testing of the Migraine-ACT questionnaire

This study designed and tested a new 4-item assessment tool, the Migraine Assessment of Current Therapy (Migraine-ACT) questionnaire for use by clinicians, to quickly evaluate how a recently prescribed acute medication is working, and to identify patients who require a change of their current acute treatment. The results showed that Migraine-ACT, containing four questions on headache impact (measured as headache-related disability), global response and consistency of response to therapy and emotional impact, was reliable, valid, easy to use and

score, and exhibited considerable potential clinical utility. Migraine-ACT can be recommended for everyday clinical use by clinicians.

The Migraine-ACT study used rigorous methodology to confirm the reliability and validity of the questionnaire. The result is a robust questionnaire that is suitable for use in research and in the clinic. However, additional studies are required to further examine the clinical utility of Migraine-ACT, to define the score that indicates a change in treatment is needed, and to investigate its sensitivity to change for use as an outcome tool in comparison to other endpoints. The study was conducted in secondary care referral centres. Studies in primary care practice are particularly needed to demonstrate the utility of Migraine-ACT in the everyday management of migraine. The main use of Migraine-ACT is likely to be in primary care, and naturalistic studies conducted in this domain will determine the true utility of the questionnaire. Pharmacists and nurses may also find the questionnaire useful and studies with these professionals would also be valuable.

5.4 Final remarks

The research and studies contained in this thesis have confirmed the clinical importance of assessing disability when managing headache patients. Disability assessments play key roles in the screening, diagnosis and treatment of these patients. While there is no definitive method to measure disability, several tools are available and have utility in diagnosis (HIT), assessing headache severity and monitoring treatments (MIDAS) and in assessing emotional disability (SPI). Disability assessments also play key roles in the development of other questionnaires. The DSQ sensitively screens for diagnosis using questions on disability and other headache features, features consistent with those of other diagnostic questionnaires. Migraine-ACT assesses the need to change acute medications using questions on headache-related disability, emotional impact, and overall response and consistency of response. While these questionnaires require further development, physicians are now closer to the goals of having definitive diagnostic and outcome measures in their armamentarium.

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6

Summary

Introduction

The main aim of this thesis is to investigate the clinical significance of headache-related disability; the clinical importance of assessing disability, the means of recognising the patients with severe disability and the development of new ways to assess headache-related disability and their utility in clinical practice. The main methodology used in the thesis was critical reviews of the literature and open, naturalistic studies designed to mimic the situation in everyday primary care clinical practice.

Clinical significance of headache-related disability

In **Chapter 3.1**, the factors involved in the understanding of clinical study evidence are reviewed, and new study endpoints discussed that may be relevant to headache clinical practice. Large, randomised, double-blind, controlled clinical trials form the gold standard of clinical evidence for evaluating new medications. Meta-analyses and *post hoc* analyses of existing trials are increasingly used to compare therapies, but should not be used on their own to evaluate therapies. Controlled clinical trials evaluating triptans in the acute treatment of migraine demonstrate clear superiority of the drugs over placebo, but only small differences are reported in studies comparing individual triptans and triptans with non-triptan medications. In contrast, patients can clearly distinguish between triptans and non-triptans and between different triptans in clinical practice. This incongruity may be due to the relative insensitivity of the standard clinical trial endpoint, relief of headache. New and more sensitive clinical trial endpoints are required for use in clinical studies that reflect everyday general practice (naturalistic studies). Among the potential endpoints are assessments of patient preference, impact on the patient's daily life and quality of life. However, novel endpoints should be developed, in collaboration with patients, which can summarise the whole migraine experience.

Chapter 3.2 reviews the evidence that patient preference may be a clinical study endpoint that is useful in headache clinical practice. Patient preference assesses a global measure of efficacy and tolerability, and may be a valid and sensitive means of distinguishing between the triptans. In a series of studies, patients consistently expressed a clear preference for triptans over their usual non-triptan acute medications, e.g. analgesics and ergotamine. Direct comparator studies of patient preference with oral triptans showed that patients could distinguish between different triptans, and between different formulations of the same triptan. Patients could even distinguish between the three oral doses of sumatriptan. The most frequently provided reasons for preference were speed of response and overall effectiveness. Patient preference may therefore be a sensitive and valid clinical trial endpoint and physicians should consider using it when reviewing the efficacy of acute migraine medications.

Chapter 3.3 describes a study that investigated the prevalence of headache, depression and bodily pain in women attending a UK general practice. The disability associated with migraine and other headache attacks occurring during and outside the menstrual period was also assessed in those women with migraine. Women aged 14–50 years completed two questionnaires. The first questionnaire assessed the point prevalence of headache and bodily

pain, and the 5-year prevalence of depression in the total population. The second questionnaire assessed the disability of all headaches over a 2-month period (to capture a complete menstrual cycle) for patients reporting migraine who were still menstruating. Disability was assessed as the time lost and time spent at less than 50% productivity in normal activities due to headache, and analysed as rank sums using the Mann-Whitney U Test. The first part of the study showed that the prevalence of headache (66.1%), depression (55.4%) and bodily pain (40.6%) were high in this population of women. In the second part of the study, for migraine, the rank order of time at less than 50% productivity was significantly greater for attacks taking place inside the menstrual period than for those occurring outside the menstrual period (p=0.01). For non-migraine headaches, the time lost appeared to be numerically greater for attacks taking place outside the menstrual period than for those occurring inside the menstrual period, and the comparison approached significance (p=0.06). In conclusion, the patients reported a high prevalence of headache, depression and bodily pain**.** For migraine sufferers, migraine attacks that took place during the menstrual period tended to be more disabling than those taking place outside the menstrual period, but the opposite was true for non-migraine headache.

Chapter 3.4 describes a prospective, within-group, comparative study, in which the Short Pain Inventory (SPI©) was used to assess how the mood disturbances and coping abilities changed over time in patients with episodic tension-type headache (TTH), migraine and chronic daily headache (CDH) attending a primary care headache centre. The healthcare resource utilisation of these patients was also assessed retrospectively.
Patients completed the SPI 10 times over a 7-day period, starting 1 hour after the onset of their next headache. The SPI data were analysed statistically as Z scores and coping Z scores for the Total Pain Disturbance, Total Mood Disturbance, and individual sub-scores for sedation, social interaction, sadness, anxiety and anger. Data from the healthcare resource utilisation questionnaire were analysed as descriptive statistics. Seventy five patients completed the healthcare utilisation questionnaire and 42 (56.0%) completed the SPI for the 7-day period. All headache patients showed considerable mood disturbances during a headache. In general the disturbances were severe in intensity and of the order CDH>migraine>TTH. The pattern of mood disturbance was different for each type of headache, as was the patients' ability to cope with the mood changes. Patients with CDH experienced pain and emotional symptoms, particularly sedation, throughout the 7-day monitoring period. For TTH and migraine, the pain and emotional symptoms resolved within 1–2 days after the headache. The level of healthcare resource utilisation was also in the order CDH>migraine>TTH, similar to the data reported for the SPI. In conclusion, patients with headache had significant emotional symptoms associated with their headaches. These symptoms resolved within 1–2 days for patients with episodic TTH and migraine. However, patients with CDH were profoundly affected, and did not improve physically or emotionally from their headache over a 7-day period. Headache patients generally experienced higher levels of sedation than did patients with other pain conditions.

Assessing headache-related disability

Chapter 4.1 reviews the disability caused by migraine and other headache disorders. Migraine is a remarkably disabling condition, although unpredictable and heterogeneous in frequency, duration and severity. It can be difficult to manage in primary care, where it is under-recognised, under-diagnosed and under-treated. Proposals have been made that migraine care could be improved by incorporating assessments of disability into management strategies. Research has shown that measuring headache-related disability, together with assessments of pain intensity, headache frequency, tiredness, mood alterations and cognition can be used to assess the impact of migraine on sufferers' lives and society. From this research two simple and brief impact tools were developed; the Migraine Disability Assessment (MIDAS) Questionnaire and the Headache Impact Test (HIT). Both tools are scientifically valid measures of headache

severity and have the potential to improve communication between patients and their physicians, assess headache severity and act as outcome measures to monitor treatment efficacy. Disability-based tools are also being increasingly recommended as part of generalised headache management guidelines to produce an individualised treatment plan for each patient in concert with other clinical assessments. It is not possible as yet to unequivocally recommend the optimal impact tool for use in primary care, but it should be usable by GPs, pharmacists, nurses and patients, and for research purposes.

Chapter 4.2 describes an audit that assessed the outcome of a nurse intervention strategy in patients presenting with headache to a primary care surgery. Patients aged 18–65 years attending the surgery who reported headache in the previous 3 months were assessed by a nurse and completed a MIDAS Questionnaire and a questionnaire investigating headache features and physician consultations. All patients were given oral and written advice on headache management by the nurse. Patients were reviewed after 3 and 6 months with the same questionnaires. A total of 195 patients took part in the study. At baseline, 136 (69.7%) were MIDAS Grade I/II and 59 (30.3%) were Grade III/IV. Compared with baseline, patients reported significant mean reductions at 6 months in: total MIDAS scores (5.9 *versus* 9.6; p = 0.014); headache frequency (MIDAS A score: 7.0 *versus* 12.6; p = 0.009); headache severity (MIDAS B score: 5.0 *versus* 6.0; p = 0.003); and physician consultations for headache (3-month period: 0.05 *versus* 0.30; p = 0.05). In conclusion, advice on headache management given by a nurse can potentially lead to significantly improved patient outcomes. MIDAS appeared to be a sensitive outcome measure for reduction in disability in headache sufferers. These results warrant further investigation in randomised, controlled clinical studies.

Chapter 4.3 describes a sub-analysis of Study 3.4 investigating the psychometric properties of Internet HIT (HIT-DYNA®) compared with the SPI©. Also compared were the abilities of the SPI and HIT in terms of discriminating headache severity and diagnosis. Result showed that the HIT score correlated 0.28 with the severity of the headaches whereas the SPI correlated 0.76 on its Total Mood Disturbance score. The correlations of the HIT items with pain severity never rose above 0.26 whereas the correlations of the SPI items were all typically about 0.7. The SPI significantly discriminated with headache severity levels (none, mild, moderate, severe, extreme), with t values of 2–20. The HIT scores were far less powerful at discriminating severity, with t test values from 2–5. HIT scores at screening significantly discriminated with diagnosis, with the resolution between TTH and CDH reaching 1/100 million. The SPI summary scores and subscales did not discriminate with diagnosis. These differences between HIT and SPI were confirmed by factor analysis. In conclusion, the results showed the HIT to be poorly related to the severity of the pain but very closely related to the diagnostic label. In contrast to this, the SPI was very closely related to severity but not related to diagnosis.

Chapter 4.4 describes a prospective, open investigation designed to validate a new inclusive diagnostic questionnaire for headache, the 8-item Headache Diagnostic Screening Questionnaire (DSQ), containing questions screening for possible sinister symptoms, and evaluating headache-related disability, frequency and duration, the use of symptomatic medications and the presence of migraine aura symptoms. Patients completed the DSQ on their own and with a pharmacist's help. The same pharmacist, a GP and a headache specialist conducted a differential headache diagnosis according to their usual practices. Diagnoses were deduced from the DSQ using an algorithm by a healthcare professional, who was blind to the other diagnoses. The primary endpoint was the sensitivity of the DSQ, measured as the proportion of correct diagnoses assessed from the patient, pharmacist and GP responses, compared with the gold standard of specialist diagnosis, for each headache subtype. Eighty seven patients (80.5% women, mean age 52.9 years) completed the study, all completing the

questionnaire without help within a few minutes. Most patients were diagnosed by the specialist with migraine (with or without aura) or CDH (with or without medication overuse headache [MOH]). The overall sensitivity of the patient-completed DSQ was good (59.3%) and similar to the pharmacist-completed DSQ (66.6%) and GP diagnosis (59.4%). The accuracy of the DSQ-derived diagnoses was greatest for total migraine, migraine with aura, MOH and migraine without aura. The accuracy of the pharmacists' headache diagnosis was improved markedly when they used the DSQ, particularly with regard to diagnosing migraine with and without aura and MOH. In conclusion, the Headache DSQ is a brief, rapid to use and accurate diagnostic screening questionnaire for headache, and is especially sensitive for migraine and MOH. It can be recommended for screening new headache patients at and below the primary care level.

Chapters 4.5 and 4.6 describe the design and testing of a new 4-item assessment tool, the Migraine Assessment of Current Therapy (Migraine-ACT) questionnaire for use by clinicians, to quickly evaluate how a recently prescribed acute medication is working, and to identify patients who require a change of their current acute treatment. A 27-item Migraine-ACT questionnaire was developed by an international advisory board of headache specialists. Questions were formulated in four domains: headache impact, global assessment of relief, consistency of response and emotional response, all with yes (score = 1) or no (score = 0) answers. Migraine patients (*n* = 185) attending secondary care headache clinics entered a multinational, prospective, observational study to investigate the test-retest reliability and construct validity of the 27-item Migraine-ACT. Patients completed the Migraine-ACT on two occasions, separated by a 1-week interval, and test-retest reliability was assessed by Pearson product moment and Spearman rank measures. Construct validity was assessed by correlating patients' answers to the 27-item Migraine-ACT with those to other questionnaires (individual domains and total scores) conceptually related to it; the Short-Form 36 quality of life questionnaire (SF-36), the Migraine Disability Assessment (MIDAS) questionnaire and the Migraine Therapy Assessment Questionnaire (MTAQ). Discriminatory t-tests were used to identify the four Migraine-ACT questions (one in each domain) which discriminated best between the domains of the SF-36, MIDAS, and MTAQ. These four items constituted the final 4-item Migraine-ACT. The test-retest reliability of the 27 Migraine-ACT questions ranged from good to excellent, and correlation coefficients were highly significant for all items. The consistency of reporting the yes and no answers was also excellent. Correlations of Migraine-ACT items with SF-36 and MIDAS items and SF-36, MIDAS and MTAQ total scores indicated that the following were the most discriminating items, in the respective four domains, and constitute the final Migraine-ACT questionnaire:

- Consistency of response - **Does your migraine medication work consistently, in the majority of your attacks?**
- Global assessment of relief - **Does the headache pain disappear within 2 hours?**
- Impact - **Are you able to function normally within 2 hours?**
- Emotional response - **Are you comfortable enough with your medication to be able to plan your daily activities**

The 4-item Migraine-ACT was shown to be highly reliable (Spearman / Pearson measure r = 0.82). The individual questions, and the total 4-item Migraine-ACT score, showed good correlation with items of the SF-36, MIDAS and MTAQ questionnaires, particularly with the total MTAQ and SF-36 scores. Additional testing confirmed the good reliability, validity and potential clinical utility of the 4-item questionnaire. In conclusion, the 4-item Migraine-ACT questionnaire is brief and simple to complete and score, and has demonstrated reliability, accuracy and simplicity. A score of ≤ 2 indicates that a change in medication may be warranted. Migraine-ACT can therefore be recommended for everyday clinical use by clinicians.

Chapter 5 describes the main discussion points arising from this research. The searches and studies contained in this thesis have confirmed the clinical importance of assessing disability when managing headache patients. Disability-based assessments play key roles in the screening, diagnosis and treatment of these patients. While there is no definitive method to measure disability, several tools are available and have utility in diagnosis (HIT), assessing headache severity and monitoring treatments (MIDAS) and in assessing emotional disability (SPI). Disability assessments also play key roles in the development of other questionnaires. The DSQ sensitively screens for diagnosis using questions on disability and other headache features, features consistent with those of other diagnostic questionnaires. Migraine-ACT assesses the need to change acute medications using questions on headache-related disability, emotional impact, and overall response and consistency of response.

The main limitations of the naturalistic studies were that they were open-label, small in terms of numbers of patients and sometimes duration, resulting in lack of power and possible design asymmetries. Larger, controlled studies are now required to take this research forward. However, the type of naturalistic, prospective, open, longitudinal study described here is eminently suited for research in primary care.

In conclusion, the main clinical applications of this work are:

- The validation of naturalistic studies for use in primary care.
- The use of disability-based measures for assessing headache patients in screening, diagnosis, to assess severity, and as part of guidelines for treatment.
- The development of a disability-based tool (DSQ) for diagnosing headaches.
- The development of a disability-based tool (Migraine-ACT) for assessing the need to change a migraine patient's acute medication.