doi: 10.1111/j.1742-1241.2006.01208.x

Improved migraine management in primary care: results of a patient treatment experience study using zolmitriptan orally disintegrating tablet

G. SHAPERO,[1] A. DOWSON,[2] J.-P. LACOSTE,[3] P. ALMQVIST[4]
[1]Markham Headache and Pain Treatment Centre, Markham, ON, Canada, [2]The King's Headache Service, King's College Hospital, London, UK, [3]Department of Internal Medicine, Hôpitaux de Paris, Paris, France, [4]AstraZeneca R&D, Södertälje, Sweden

SUMMARY

The 'Zomig Appropriate for Primary care' programme was developed to address the needs of primary care physicians (PCPs) to improve migraine management. As part of the programme, an international, open-label, 6-month clinical study was performed. The study included new and tangible outcome variables relevant to PCPs and recruited patients presenting in primary care with an established migraine diagnosis. Patients treated up to three migraine attacks per month with zolmitriptan orally disintegrating tablet (ODT) 2.5 mg. All other migraine attacks occurring during the study period were treated with the patient's usual migraine medication (including other triptans). Questionnaires were used to record patient treatment experiences at the study end. The primary end-point was the proportion of patients wanting to continue using zolmitriptan ODT. Some 595 patients treated 7171 migraine attacks with zolmitriptan ODT. Of the 504 patients who completed the 6-month questionnaire, 380 (75.4%) wished to continue using zolmitriptan ODT. The results of the study indicate that patient-orientated end-points are more motivational and meaningful to physicians than traditional end-points used in controlled clinical trials, allowing them to make informed decisions regarding migraine management.

Keywords: Migraine; primary care; zolmitriptan orally disintegrating tablet; Zomig Appropriate for Primary care

INTRODUCTION

Primary care physicians (PCPs) are the only point of contact for the majority of patients suffering from migraine attacks, as only a small proportion of these patients are referred to a neurologist or headache specialist. However, PCPs receive little formal education regarding migraine, and management guidelines are generally impractical for use in routine clinical practice. Consequently, migraine- and headache-related knowledge tends to be variable among PCPs (1,2), and many migraine sufferers who consult PCPs for migraine do not receive a correct diagnosis. A study from the USA showed that more than half of patients with migraine, as defined by the International Headache Society (IHS) criteria (3), were incorrectly diagnosed by a physician (4).

Of those patients correctly diagnosed as suffering from migraine, many are inadequately treated. Indeed, a high proportion of PCPs prescribe simple analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) for migraine (even for severe attacks), rather than migraine-specific treatments (2,5). Follow up is frequently poor, and many patients lapse from care (6). This is reflected in the high proportion of patients taking over-the-counter pain medication, resulting in a high incidence of dissatisfaction among patients (7). For the majority of patients, however, migraine is generally treatable.

The 5-$HT_{1B/1D}$ receptor agonists, known as the triptans, are migraine-specific agents that have revolutionised the treatment of migraine. Although triptans are proven to be effective and well tolerated in the acute treatment of migraine attacks (8), research indicates that there is an under-utilisation of these agents in primary care (9). To better understand the patient benefits of prescribing triptans, therefore, PCPs require information on more patient-relevant end-points than those typically used in most clinical

Correspondence to:
Gary Shapero, MD, Markham Headache and Pain Treatment Centre, 10 Unionville Gate, Suite #301 and #302, Unionville, Markham, ON L3R 0W7, Canada
Tel.: + 1 905 475 9700
Fax: + 1 905 475 4270
Email: gshapero1@on.aibn.com

trials (10,11). Established regulatory end-points used in controlled clinical studies (e.g. 2-h headache response, typically defined as an improvement in pain intensity from moderate to severe at baseline to mild or none at 2 h postdose) are not always relevant in primary care, where patient experiences and preferences are of greater importance for the evaluation of treatment satisfaction and success. Indeed, the IHS guidelines for migraine treatment trials state that patients' evaluation of migraine medications is a clinically relevant measure (12). In contrast to the majority of clinical trials performed to date, an open-label study design in a real-life primary care setting, without a dictated dosing regimen (although still following the prescribing information), is more relevant to PCPs as the results are more likely to reflect the situation in clinical practice.

The 'Zomig Appropriate for Primary care' (ZAP) programme was designed to address the needs of PCPs with the aim of improving the diagnosis and management of migraine patients in primary care (13). As part of this initiative, a clinical programme was developed in which zolmitriptan was used as a first-line treatment to give participating PCPs hands-on experience of using triptan therapy to manage patients with migraine. In turn, treatment outcomes were generated that were meaningful to both patients and physicians. This programme encompassed three clinical studies that were performed in the primary care setting: an international core study (Canada, France and the UK) and two local studies (USA and Spain). The present manuscript reports the results of the international core study that utilised zolmitriptan orally disintegrating tablet (ODT) 2.5 mg, which has been shown to be an effective and well-tolerated acute treatment for migraine in controlled clinical trials (14–16). The objectives of the core study were to: (i) create a real-life primary care situation by giving patients options in the management of individual migraine attacks; i.e. patient-centred stratified care; and (ii) generate patient-reported outcomes relevant to PCPs by focussing on patients' experiences regarding the efficacy and tolerability of zolmitriptan ODT. Patient preferences and treatment satisfaction were also assessed.

STUDY METHODS

Study Population

To reflect a real-life situation, the inclusion/exclusion criteria for the study were as stated in the prescribing information for zolmitriptan ODT. Patients (aged: 18–65 years) presenting in primary care with an established diagnosis of migraine with or without aura, who had experienced at least one migraine attack per month in the previous 3 months, were eligible for inclusion. Exclusion criteria included: a history of basilar, ophthalmoplegic or hemiplegic migraine or any potentially serious neurological condition that is associated with headache; a history of, or significant risk factors for, cardiovascular disease; uncontrolled hypertension; and use of monoamine oxidase-A inhibitors, methysergide or methylergonovine in the 2 weeks before entering the study.

Study Design

This multinational, multicentre, 6-month, open-label study was conducted at 79 study centres between October 2003 and December 2004. The study was conducted in accordance with the Declaration of Helsinki and all investigators complied with Good Clinical Practice. Written informed consent was obtained from each patient prior to participation in the study, the protocol having received independent institutional review board or ethical committee approval from the respective participating centres.

Patients' eligibility for inclusion in the study was determined at an initial screening visit. Migraine headache history and usual migraine treatments (if any) were recorded. Patients were instructed to treat up to three migraine attacks per month with zolmitriptan ODT 2.5 mg. All other migraine attacks occurring during the study period were treated with the patients' usual migraine medication (including other triptans). Patients could treat at any time after the onset of headache pain and for any symptom severity (again reflecting a real-life situation). After taking zolmitriptan ODT, patients could not use a second dose of zolmitriptan or other escape medication for at least 2 h.

Investigator-led questionnaires were used to record patient treatment experiences and preferences at 2 and 6 months after the start of the study. Information regarding adverse events was recorded. At the end of the study, the PCP also completed a short questionnaire, indicating whether or not the prescription of zolmitriptan ODT should be continued for each patient in the future.

Assessments

The primary outcome variable was the proportion of patients who wanted to continue to use zolmitriptan ODT after 6 months' treatment. Secondary outcome variables from the patient questionnaire included:

- the reasons why patients wanted/did not want to continue using zolmitriptan ODT;
- the proportion of patients who reported zolmitriptan ODT to be convenient to use (agree/disagree);
- the proportion of patients who reported that zolmitriptan ODT allows early treatment of a migraine attack (agree/disagree);
- patient's assessment of:
  - efficacy [how long before zolmitriptan ODT starts to work; the time to headache disappearing; the propor-

tion of patients who reported zolmitriptan ODT to be rapidly effective and highly effective (agree/disagree)];
- reliability [the proportion of patients who reported zolmitriptan ODT to be a reliable treatment (agree/disagree)];
- value [the time to return to usual activities; satisfaction with zolmitriptan ODT (rated on a four-point scale: very satisfied, satisfied, unsatisfied and very unsatisfied); the proportion of patients who prefer zolmitriptan ODT to usual therapy (agree/disagree)];
- control [the proportion of patients reporting to be confident in quick control of migraine with zolmitriptan ODT; the proportion of patients who reported being back in control of life with zolmitriptan ODT (agree/disagree)];
- tolerability [the proportion of patients who reported that side effects were of little/no concern (agree/disagree/had no side effects); the proportion of patients who reported that side effects would stop use of zolmitriptan ODT again].

Secondary outcome variables from the PCP questionnaire were the proportion of patients for whom PCPs wanted to continue prescribing zolmitriptan ODT and the reasons why PCPs wanted/did not want to continue prescribing such therapy.

Statistical Analysis

The primary outcome variable was the proportion of patients wanting to continue using zolmitriptan ODT. A sample size of 600 patients was estimated based on the least favourable scenario, where an equal number of patients wanted to continue/discontinue the use of zolmitriptan ODT. It was considered that the sample size, even in the least favourable scenario, would be large enough to produce clinically relevant findings representative of the general migraine population. All outcome variables were summarised descriptively and no hypothesis test was performed.

All patients treating at least one migraine attack with study medication were included in the safety population. The intention-to-treat (ITT) population comprised all patients who treated at least one migraine attack with study medication and who returned to the clinic to provide post-treatment assessment data.

STUDY RESULTS

Study Population

A total of 621 patients were enrolled in the study, of whom 597 patients treated at least one migraine attack with study medication and were included in the safety population. The ITT population comprised 595 patients (Canada: 190; France: 204; and UK: 201), who treated a total of 7171 migraine attacks with zolmitriptan ODT and provided post-treatment efficacy data. Demographic and baseline clinical characteristics of the ITT population are shown in Table 1. The ITT population was predominantly female (508; 85.4%), with a mean age of 41.8 years. The mean age at migraine onset was 22.8 years, and the mean number of migraine attacks experienced in the 3 months before the study was 8.5. Migraine attacks were generally associated with photophobia (87.4% of patients) and nausea (83.7%). The most frequently used migraine treatments were analgesics (84.6% of patients), triptans (71.1%) and NSAIDs (64.7%). Level of satisfaction with usual migraine therapy (satisfied or very satisfied) ranged from 20.6% for ergots to 85.7% for triptans (Table 1).

Table 1 Demographic and baseline clinical characteristics of the intention-to-treat population ($n = 595$)

Characteristic	
Mean age (years)	41.8
Gender; *n* (%)	
Male	87 (14.6)
Female	508 (85.4)
Mean age at onset of migraine attacks (years)	22.8
Mean number of migraine attacks in the last 3 months	8.5
Migraine-associated symptoms; *n* (%)	
Photophobia	520 (87.4)
Nausea	498 (83.7)
Phonophobia	438 (73.6)
Vomiting	196 (32.9)
Usual migraine medication; *n* (%)	
Analgesics (other than NSAIDs)	501 (84.6)
Triptans	421 (71.1)
NSAIDs	383 (64.7)
Antiemetics	181 (30.6)
Ergots	102 (17.2)
Patient satisfaction* with usual migraine medication; *n* (%)	
Triptans	361/421 (85.7)
Antiemetics	75/181 (41.4)
NSAIDs	135/383 (35.2)
Analgesics (other than NSAIDs)	167/501 (33.3)
Ergots	21/102 (20.6)

*Satisfied or very satisfied. NSAIDs, non-steroidal anti-inflammatory drugs.

A total of 97 out of 621 enrolled patients (15.6%) did not complete the 6-month study period, most commonly because of the lack of efficacy (24; 3.9%), adverse events (21; 3.4%) and the loss to follow up (19; 3.1%). In accordance with the study design, these patients were expected to continue with their usual antimigraine therapy.

Assessments

Of the 504 patients who completed the 6-month questionnaire, three quarters (380; 75.4%) wished to continue using

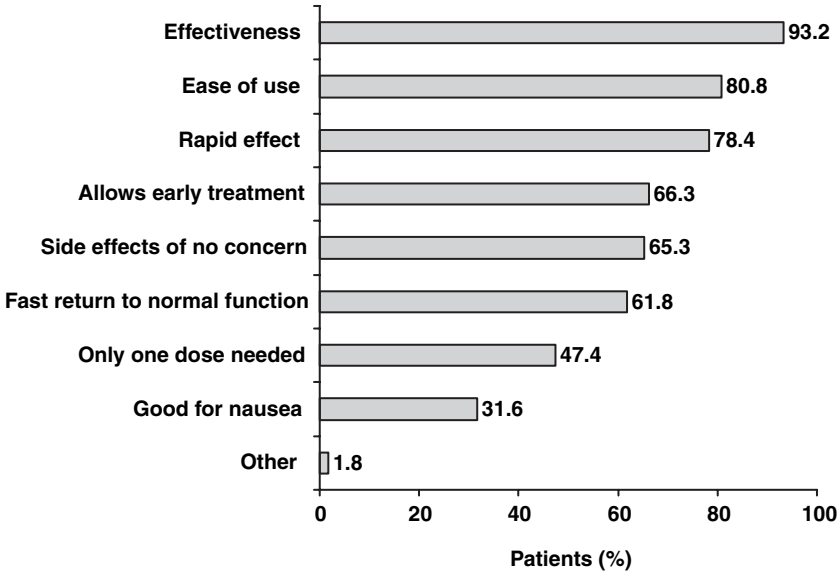

Figure 1 Reasons stated by migraineurs for wanting to continue using zolmitriptan orally disintegrating tablet after 6 months' treatment (patients could give more than one reason; $n = 380$)

zolmitriptan ODT. The main reasons why patients wanted to continue using zolmitriptan ODT included effectiveness [93.2% (of 380)], ease of use (80.8%) and rapid effect (78.4%) (Figure 1). Of the 124 (24.6%) patients who did not want to continue using zolmitriptan ODT, reasons why included preferred usual treatment [66.9% (of 124)], poor effect (53.2%) and adverse events (22.6%). Almost all (95.4%) of the patients completing the 6-month questionnaire agreed that zolmitriptan ODT was convenient to use and 84.3% of patients reported that zolmitriptan ODT allowed early treatment.

Over half (56.6%) of the patients reported that zolmitriptan ODT typically starts to work within 30 min of administration (Figure 2). Furthermore, the cumulative percentage of patients reporting that zolmitriptan ODT starts to work within 2 h postdose was 90.8%. When asked how long it takes for headache pain to disappear after taking zolmitriptan ODT, approaching two-thirds (60.9%) of patients stated within 60 min and 80.4% stated within 2 h (Figure 3).

Zolmitriptan ODT was considered to be rapidly and highly effective by 79.3% and 76.3% of patients, respectively. In addition, 58.5% would choose zolmitriptan ODT to treat migraine attacks of any intensity and 83.7% stated that zolmitriptan ODT was a reliable treatment.

When asked about the value of zolmitriptan ODT, 74.3% of patients were able to resume usual activities within 2 h of treatment (Figure 4). Most patients (84.1%) were satisfied/very satisfied with zolmitriptan ODT; only 5.0% of patients were very unsatisfied with treatment (Figure 5). Over two-thirds of patients (70.9%) preferred zolmitriptan ODT to their usual migraine therapies. In the subgroup of 358 patients who had been using other triptans, the results

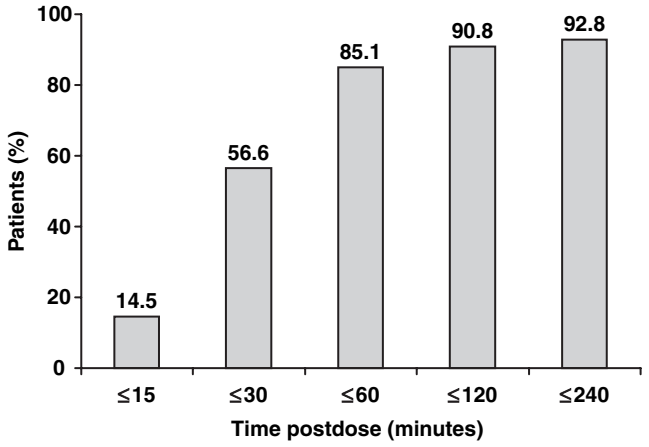

Figure 2 Cumulative percentage of migraineurs who reported that zolmitriptan orally disintegrating tablet starts to work within 15, 30, 60, 120 and 240 min of administration [$n = 595$ (missing data: $n = 93$)]

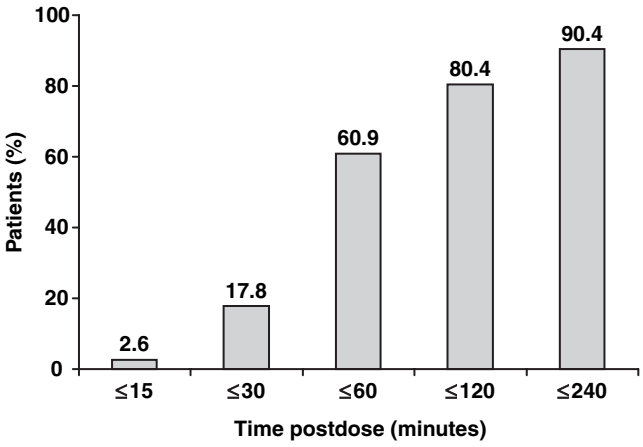

Figure 3 Cumulative percentage of migraineurs who reported that headache pain had disappeared within 15, 30, 60, 120 and 240 min of administration of zolmitriptan orally disintegrating tablet [$n = 595$ (missing data: $n = 94$)]

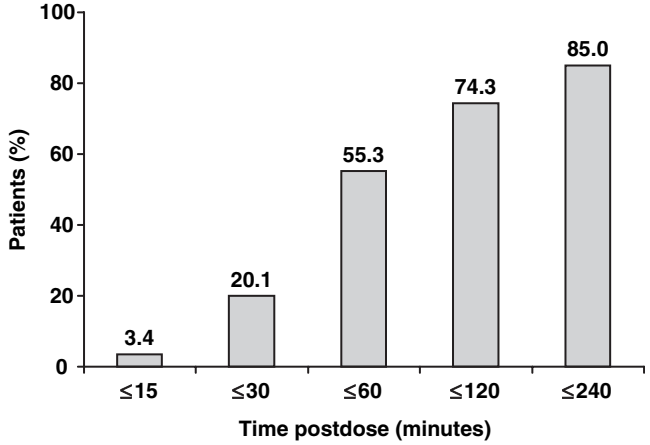

Figure 4 Cumulative percentage of migraineurs who reported the ability to resume usual activities within 15, 30, 60, 120 and 240 min of administration of zolmitriptan orally disintegrating tablet [$n = 595$ (missing data: $n = 94$)]

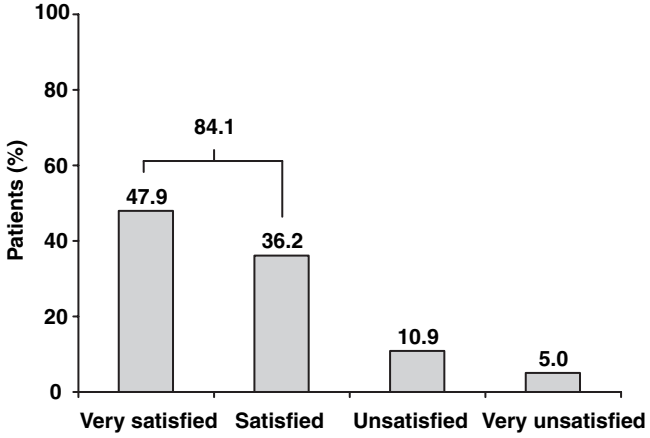

Figure 5 The percentage of migraineurs who were very satisfied, satisfied, unsatisfied or very unsatisfied with zolmitriptan orally disintegrating tablet after 6 months' treatment [$n = 595$ (missing data: $n = 92$)]

were similar: 69.0% preferred zolmitriptan ODT to usual treatment. The majority of patients (77.7%) felt confident that migraine could be quickly controlled using zolmitriptan ODT, with 56.4% agreeing that treatment with zolmitriptan ODT resulted in being back in control of life.

After 6 months' treatment experience, 90.4% of patients reported either no zolmitriptan ODT-related adverse events (50.6%) or stated that adverse events were of little or no concern (39.8%). Only 6.4% of patients stated that adverse events would prevent future use of zolmitriptan ODT.

Primary care physicians wished to continue prescribing zolmitriptan ODT for over two-thirds of 585 evaluable patients (396; 67.7%). Reasons why included effectiveness [94.7% (of 396)], rapid effect (74.0%) and ease of use (73.7%). Of the PCPs who did not wish to continue prescribing zolmitriptan ODT for 189 (32.3%) patients, reasons why included poor effect [52.4% (of 189)] and preferred usual treatment (48.7%).

DISCUSSION

Migraine is highly prevalent in primary care. However, there is little support for PCPs to manage this condition, resulting in under-diagnosis and under-treatment of patients. Consequently, when asked about what additional information would influence the wider use of migraine-specific medications in primary care, many PCPs stated efficacy, tolerability and cost-effectiveness information (data on file, AstraZeneca). All of these issues are addressed in the present study, which was conducted as part of the wider ZAP programme.

Efficacy is generally seen as the most important factor in determining migraine treatment selection. However, traditional measures of efficacy are not relevant to most PCPs, for whom patient-related efficacy end-points are more meaningful. The current study was therefore designed to allow physicians to receive feedback from patients and to make their own assessment on treatment in terms that are more meaningful to them.

The efficacy of zolmitriptan ODT was highly acceptable to patients for the acute treatment of migraine, as indicated by the high proportion of patients who wished to continue to use it. Most patients were satisfied or very satisfied with zolmitriptan ODT and preferred it to their usual therapy (including other triptans). The fact that many patients preferred zolmitriptan ODT to their usual triptan therapy is notable, as the level of satisfaction with such treatment was particularly high (85.7%). Furthermore, PCPs wished to continue prescribing zolmitriptan ODT for over two-thirds of patients. This provides a good indication that the combination of hands-on experience of using zolmitriptan ODT, the more patient-orientated end-points and patient feedback on treatment experience and preferences, were motivating and relevant to PCPs. Furthermore, the positive responses from patients and physicians to the efficacy variables used in this study, and the fact that they were highly consistent across countries (data not shown), makes these variables useful for future studies.

Primary care physicians frequently cite concerns about safety and tolerability of the triptans as a barrier to use. The ZAP core study results indicate very strongly that this perception is misplaced, as nine out of 10 patients reported no adverse events or events that were of little or no concern. These results supplement the regulatory clinical trial data which demonstrate that zolmitriptan ODT is a well-tolerated treatment for migraine (14,15). The withdrawal rate because of adverse events in this study was very low (3.4%) and similar to that seen in controlled studies of zolmitriptan ODT (14,16).

Although cost effectiveness *per se* was not measured in the current study (it was not a health economics study), the value of triptan therapy to patients was clearly expressed in terms of both having a rapid return to usual daily activities and being back in control of life quickly, thus reducing the negative impact of a migraine attack.

A limitation of the present study is that it utilised an open-label, non-comparative design. Consequently, the results may have been confounded by the psychological impact of patients' willingness to please their physician, although the results parallel the efficacy and favourable tolerability of zolmitriptan ODT in controlled clinical trials (14–16). The lack of a comparative arm also means that patient preference for zolmitriptan ODT may reflect a preference for the drug itself, rather than this specific formulation. These limitations, however, need to be set against the fact that the study was conducted under conditions that mirrored real life as closely as possible, and thereby provided treatment experience data that was meaningful to both patients and physicians.

CONCLUSIONS

Hands-on clinical experience with zolmitriptan ODT, as part of the wider ZAP programme that encompasses physician education, simplified guidelines and diagnostic and treatment tools, was associated with high rates of patient and physician satisfaction in the management of migraine in primary care.

DISCLOSURES

Dr Shapero has received research funding and/or has acted as an advisor to AstraZeneca, GlaxoSmithKline, Merck Frosst, Pfizer, Allergan, Proctor and Gamble, Janssen and Ortho-McNeil during the last 5 years. Dr Dowson is an advisor to, or has received research funding from, Allergan, Almirall, Ariston, AstraZeneca, GlaxoSmithKline, Janssen, Menarini, Merck, NMT, Organon, Ortho-McNeil and Pfizer. Dr Lacoste has received research funding and/or has acted as an advisor to AstraZeneca, GlaxoSmithKline, Pfizer, Janssen, UPSA Laboratories, Schwarz Pharma, Sanofi Aventis and Almirall during the last 5 years. Dr Almqvist was an employee of AstraZeneca (study sponsor) at the time the study was conducted.

ACKNOWLEDGEMENTS

This study was supported by AstraZeneca. We thank Steve Winter, from Wolters Kluwer Health, who provided medical writing support funded by AstraZeneca.

REFERENCES

1 Dowson AJ, Shapero G, Baos V et al. Primary care needs assessment for guidance on headache management. *Headache Care* 2005; **2**: 43–6.
2 Kern R, Shapero G, Boudreau G et al. There is a strong unmet need for improved headache education among primary care physicians: results from a primary care needs assessment. *Headache Care* 2005; **2**: 47–9.
3 International Headache Society. Headache classification subcommittee. *Cephalalgia* 1988; **8** (Suppl. 7): S1–96.
4 Lipton RB, Diamond S, Reed M et al. Migraine diagnosis and treatment: results from the American Migraine Study II. *Headache* 2001; **41**: 638–45.
5 MacGregor EA, Brandes J, Eikermann A. Migraine prevalence and treatment patterns: the global Migraine and Zolmitriptan Evaluation survey. *Headache* 2003; **43**: 19–26.
6 Edmeads J, Lainez JM, Brandes JL et al. Potential of the Migraine Disability Assessment (MIDAS) Questionnaire as a public health initiative and in clinical practice. *Neurology* 2001; **56** (6 Suppl. 1): S29–34.
7 MacGregor EA, Brandes J, Gendolla A, Giammarco R. Migraine treatment strategies: the global Migraine And Zolmitriptan Evaluation (MAZE) survey – phase IV. *Curr Med Res Opin* 2004; **20**: 1777–83.
8 Gawel MJ, Worthington I, Maggisano A. Systematic review of the use of triptans in acute migraine. *Can J Neurol Sci* 2001; **28**: 30–41.
9 Gibbs TS, Fleischer AB Jr, Feldman SR et al. Health care utilization in patients with migraine: demographics and patterns of care in the ambulatory setting. *Headache* 2003; **43**: 330–5.
10 MacGregor EA. The doctor and the migraine patient: improving compliance. *Neurology* 1997; **48** (Suppl. 3): S16–20.
11 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.
12 Tfelt-Hansen P, Block G, Dahlöf C et al. International Headache Society clinical trials subcommittee. Guidelines for controlled trials of drugs in migraine: second edition. *Cephalalgia* 2000; **20**: 765–86.
13 Almqvist P, Brandreth T. ZAP primary care programme: headache education through clinical experience. *Headache Care* 2005; **2**: 239–42.
14 Dowson AJ, MacGregor EA, Purdy RA et al. Zolmitriptan orally disintegrating tablet is effective in the acute treatment of migraine. *Cephalalgia* 2002; **22**: 101–6.
15 Spierings ELH, Rapoport AM, Dodick DW, Charlesworth B. Acute treatment of migraine with zolmitriptan 5 mg orally disintegrating tablet. *CNS Drugs* 2004; **18**: 1133–41.
16 Loder EW, Dowson AJ, Spierings EL. Part II: clinical efficacy and tolerability of zolmitriptan orally disintegrating tablet in the acute treatment of migraine. *Curr Med Res Opin* 2005; **21** (Suppl. 3): S8–12.

Paper received April 2006, accepted August 2006

