J Headache Pain (2002) 3:63–69

REVIEW

Stewart J. Tepper
Alan M. Rapoport
Fred Sheftell

Strategies of care for acute treatment of migraine

Received: 5 February 2002
Accepted: 28 March 2002

S.J. Tepper (✉) • A.M. Rapoport • F. Sheftell
The New England Center For Headache,
778 Long Ridge Road, Stamford, CT 06902-1251, USA
e-mail: sjtepper@aol.com
Tel.: +1-203-968-1799
Fax: +1-203-968-8303

S.J. Tepper • A.M. Rapoport
Department of Neurology,
Yale University School of Medicine,
New Haven, CT, USA

F. Sheftell
Department of Psychiatry,
New York Medical College,
New York City, NY, USA

Abstract The clinical questions posed by the advent of acute migraine-specific treatment (triptans) are on which patient to use specific treatment for migraine, and when in the attack to treat patients. Three strategies have been proposed for selecting treatment for acute migraine, and these strategies were studied in The Disability in Strategies of Care (DISC) study: step care across attacks, step care within attacks, and stratified care. Stratified care, which matches treatment to level of disability is superior to the other two strategies. A recent prospective study suggests that triptans should be used during the mild phase of pain for optimal benefit. Thus, patients with time loss from episodic migraine are optimal candidates for triptan therapy from the beginning, and treating early in attacks, without delay, optimizes the likelihood of pain relief and reducing that time loss and disability.

Key words Migraine • Disability • Stratified care • Step care • Triptans

Introduction

Initially, the acute treatment of migraine involved alleviation of pain with non-specific treatment, such as aspirin, mixed analgesics and opiates. Aspirin was unhelpful for severe, disabling headache. Opiates reduced pain, but often with the burden of sedation and nausea, both of which compromised return to normal functioning.

Wolff's pathophysiological model of migraine envisaged migraine pain as caused by extracranial vasodilation, and aura by cerebral vasoconstriction [1]. The acute treatment of migraine would thus involve use of a vasoconstrictive agent, such as an ergot, to reverse the vascular cause of the headache [1]. Other vasoconstrictive agents include isometheptene mucate, caffeine, triptans, and serotonin itself. Intravenously administered serotonin (5-HT) relieves migraine, but causes significant adverse effects, including blood pressure change, nausea, and diaphoresis [2]. Ergots and triptans are 5-$HT_{1B/1D}$ agonists, and their action in migraine may be due to both their serotonergic activity and vasoconstriction. The serotonin agonist effect may inhibit neurogenic inflammation peripherally around extracerebral intracranial vessels in the meninges, and probably also inhibits nociceptive afferent input centrally. The vasoconstriction reverses peripheral meningeal vasodilation. It is by no means certain which mechanism is most important in acute migraine pain and its treatment, but it is clear that triptans are migraine specific.

The clinical questions which have evolved and are critical in the acute treatment of migraine are on which patient to use specific treatment for migraine, and when in the attack to treat patients?

Goals of acute treatment

The US Headache Consortium published a list of goals for migraine treatment in *Neurology* [3]. The goals are: "to treat attacks rapidly and consistently, restore the patient's ability to function, minimize the use of back-up and rescue medications, optimize self-care and reduce subsequent use of resources, be cost effective for overall management, and have minimal or no adverse events." These goals are clearly what physicians set out to accomplish in the acute treatment of migraine. But are they what the patients want from acute treatment?

Over the last 15 years, a number of clinical endpoints have been used in the evaluation of acute migraine medications. The International Headache Society (IHS) has utilized a 4-point scale from 0-3, where 1 is mild pain, 2 is moderate pain, and 3 is severe pain. The endpoint developed by Glaxo scientists in conjunction with headache specialists was "headache response", meaning a patient moving from moderate or severe pain to mild pain or no pain at a particular point in time after treatment, often set at 2 hours.

The IHS had previously suggested a more rigorous endpoint, "pain free," meaning a score of 0 after treatment. The advantage of this endpoint is a lower placebo rate and clear cut maximal improvement, but the disadvantage is that it raises the bar for treatment, and may discourage patients and doctors alike when they find that treatment of a moderate to severe headache results in only a 30%–40% or lower likelihood of a pain-free response at 2 hours.

All of the studies published on triptans through the year 2000 used what many clinicians viewed as an artificial model in which patients were told to wait until they had at least moderate to severe pain before treating. This was to ensure that they really had a migraine, which by one of the IHS criteria requires moderate to severe pain for diagnosis. However, this was not meant to be the correct clinical technique to maximize benefit from an acute medication. In fact by allowing the migraine pain to reach a moderate to severe intensity, although the diagnosis becomes clearer, the treatment may have become less effective.

Several studies have asked patients what characteristics of an acute migraine medication is most important to them. While this is not the same as asking what goals a physician should set in acute treatment, it is close enough to provide the patient's perspective.

Lipton and Stuart found that the three attributes most important to patients in an acute migraine medication are, in order: (1) complete pain relief (pain free), (2) no recurrence of headache, and (3) rapid onset of pain relief [4]. Recently, the IHS has suggested incorporation of these three features in an even more rigorous single clinical endpoint with which to evaluate acute migraine medications. This clinical endpoint is called "sustained pain free," and consists of a patient with a migraine reaching a pain-free state within 2 hours after taking acute medication and then having no recurrent migraine or use of rescue medication for the next 24 hours. Thus, to optimize acute treatment, we should correctly select our patients for specific acute migraine treatment, and then use these specific medications in such a way as to reach the sustained pain-free state, the patient's desired goal and the new standard of the IHS.

Strategies for selecting acute migraine medication

Richard Lipton [5], after surveying various approaches to acute migraine treatment, described three strategies for treating acute migraine, which he called "step care across attacks," "step care within attacks" (also called "staged care"), and "stratified care." The most critical decision for the clinician is deciding which approach will result in the best outcome for patients. Prior to 2000, this decision was based on common sense, but not randomized prospective evidence. However, a study published by Lipton and colleagues in *JAMA* in 2000 gave strong evidence that a stratified approach yields optimal clinical outcome [5].

Step care across attacks

This approach is an old traditional style of practicing by medication cost. After a diagnosis of migraine, the least expensive non-specific medication is selected by the physician for the patient to use first. It may be recommended that the patient use this medicine for several attacks. If the medication fails to treat the headache satisfactorily, and the patient returns to see the same physician after this treatment failure, the physician will then "step up" to the next stronger drug, usually another non-specific drug, and so forth. This may go on until a medication works, or the patient lapses from care, or the doctor finally steps up to a specific, more effective medication. An example of this would be starting with naproxen sodium, then a mixture of aspirin, acetaminophen, and caffeine, then to a prescription-strength mixed analgesic, then to an opiate and finally to a triptan.

One problem with this approach is that patients have usually tried low level treatments by the time they reach the neurologist. The patient may become incensed at being told to try again with non-specific medication, especially an over the counter (OTC) medication. The patient may lapse from care, with economic and social consequences to the patient and employer as migraine attacks continue to produce disability.

Step care across attacks is acute treatment by medication cost. The equivalent would be treating all patients with asthma first with a non-prescription inhaler, then if the asthma worsens or doesn't respond the patient would step up to the next least expensive treatment, such as an oral steroid. If that didn't work, generic prescription inhalers would be next. However, this pre-ordained order pays no attention to the characteristics of the patient or the patient's individual disease at the point of treatment. It is treatment entirely dictated by cost of medication, paying no attention to other costs, such as going to the emergency room or not being able to work or take care of the house.

The argument in favor of this approach is: why use an expensive specific medication when a less expensive might work? How would you know if the less expensive drug would have worked unless you tried it first? It might be cost effective to use this approach, the argument goes, and a prospective study was needed to determine its truth.

Step care within attacks (staged care)

This approach involves starting with a non-specific, less expensive medication first, and then if it fails, having the patient next take a stronger medication and ultimately a more expensive migraine-specific medication. The patient would only use the migraine-specific drug if she clearly had a severe migraine and the lower level medicine had failed. The lower level, migraine-specific medication would in fact be used as a rescue medication, not as the first and most appropriate treatment for the headache. Many neurologists recommended this approach in the days when only injectable sumatriptan and ergots were available. The idea was to start with a medication such as naproxen sodium, then step up to injectable treatment if necessary, since the injectable drug was more invasive and expensive.

Patients often take the staged care approach themselves. They will start with non-steroidal anti-inflammatory drugs (NSAIDs) and OTC medications or prescribed non-specific medication, and step up to the triptan during the attack only if the lower level medication fails. They hoard their more expensive, migraine-specific medication. The argument is that if triptans work "at any time" during an attack, why not save them for later?

Stratified care

The third strategy is stratified care, defined as matching treatment to a patient's individual needs or the characteristics of the disease. There have been two types of stratified care described.

The first type evaluates the characteristics of the attack itself. This involves establishing:

1. The severity of the peak intensity of the attack
2. The time to peak intensity, i.e. the rate at which the attacks escalates. How much time do you have to give adequate treatment before the patient is disabled?
3. The presence of associated symptoms, e.g. nausea, vomiting and photo- or phonophobia.
4. The time to associated symptoms.

If Patient A has peak intensity which is severe with vomiting, and time to peak intensity and vomiting is short, injectable sumatriptan is the treatment of choice [6]. If Patient B has peak intensity which is also severe, and time to peak intensity is short, but the patient never vomits, then an oral triptan might be the drug of choice.

The US Headache Consortium guidelines have suggested that NSAIDs or aspirin/acetaminophen/caffeine can be effective for moderate level migraine [3]. However, studies on ibuprofen and aspirin/acetaminophen/caffeine OTC medications for acute migraine treatment are not as strong methodologically as those suggesting effectiveness for triptans, because in the OTC studies, patients were selected who had reduced frequency of vomiting and did not require bedrest more than 20% of the time with their migraine attacks. Therefore, these were less severe attacks, while in the triptan studies, all comers with episodic migraine of any intensity were included [7, 8]. Thus, the evidence for effectiveness in the acute treatment of migraine is not equivalent for the non-specific medications and the triptans.

The question as to which oral triptan to select for rapid onset is bedeviled by the methodologic flaw previously mentioned. In all of the studies on triptans through 2001, participants in the studies from which we derive our data were instructed to wait until headache intensity was moderate to severe before treating.

Oral triptans can be divided into two clinical groups. Group I consists of those triptans with fast onset and relatively high headache response and pain-free rates at 2 hours; they are clearly suitable for Patient B. Group I includes sumatriptan (Imitrex, Imigran), zolmitriptan (Zomig, Zomigon, Ascotop), rizatriptan (Maxalt), almotriptan (Axert, Almogran), and eletriptan (Relpax).

Group II triptans have slower onset and lower efficacy rates. The Group II triptans are naratriptan (Amerge, Naramig) and frovatriptan (Frova).

The question is which oral triptan from Group I has the greatest likelihood of achieving a sustained pain-free response. Adelman et al. [9] suggested a greater likelihood of sustained pain-free response with rizatriptan than with the currently available Group I triptans. Two studies suggested time to headache relief is shorter with rizatriptan than with oral sumatriptan, although there have been questions raised on the statistical techniques in the articles [10-13]. Finally,

all of the studies as noted have been done by instructing patients to wait to treat moderate to severe pain.

The similarities between the Group I triptans are greater than the differences, and the population differences are smaller than individual patient preferences. Many physicians continue to begin with sumatriptan because of the flexibility of form, with oral, nasal and subcutaneous forms available in the US, and suppository available in Europe as well. It is hard to go wrong with any Group I triptan for Patient B. The question is how best to use it.

The second type of stratified care is that which is based on disability or impact of migraine on the patient over time, rather than evaluation of the character of multiple attacks. In this form of stratified care, a disability or impact assessment tool is used.

The most studied tool is the migraine disability assessment scale (MIDAS), developed by Lipton and colleagues [14]. This scale uses five questions to assess disability:

1. On how many days in the last 3 months did you miss work or school because of your headaches?
2. On 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.)
3. On how many days in the last 3 months did you not do household work because of your headaches?
4. On 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.)
5. On how many days in the last 3 months did you miss family, social or leisure activities because of your headaches?

Each day of at least 50% disability is given one point, and a score of greater than 10 suggests moderate to severe level of disability. The entire MIDAS set of five questions can be condensed into a single question: "On how many days in the last 3 months have you been at least 50% disabled from work, home, school, and/or recreational activity?"

The second impact tool currently in use is the headache impact test (HIT-6). The six questions are:

1. When you have headaches, how often is the pain severe?
2. How often do headaches limit your ability to do your usual daily activities including household work, work, school, or social activities?
3. When you have a headache, how often do you wish you could lie down?
4. In the past 4 weeks, how often have you felt too tired to do work or do daily activities because of your headaches?
5. In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?
6. In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?

Possible answers are: never (0 points), almost never (5 points), sometimes (10 points), very often (15 points) or always (20 points). The total score is interpreted as follows: ≤50 points, little or no impact; 50–55 points, some impact; 55–60 points, moderate impact; >60 points severe impact; and >50 points, seeing a doctor is recommended [15]

The Disability in Strategies of Care (DISC) study was published in *JAMA* in November 2000, and is the first randomized prospective comparison of step care across attacks, step care within attacks (staged care), and stratified care [5]. Patients with episodic migraine were treated with either 900 mg aspirin and 10 mg metoclopramide as non-specific medication or zolmitriptan as the specific triptan. The patients were randomized by the strategy with which to treat them. The first group received step care across six attacks. Patients received aspirin and metoclopramide to use to abort migraine for 3 attacks, and if this was not successful, the patients were allowed to "step up" to zolmitriptan for the fourth through sixth attacks. Group II received step care within attacks. The patients were given aspirin and metoclopramide for each of 6 attacks and if it didn't work, they were given zolmitriptan to step up to at 2 hours. This is the strategy that most patients currently use, with triptans used for rescue when non-specific medication fails.

Group III was the stratified care group. The patients were stratified by MIDAS score to a low treatment need group (if their MIDAS scores were less than 11, or less than 11 days of at least 50% disability in the previous 3 months), to receive aspirin and metoclopramide, or to a moderate to high treatment need group (if their MIDAS scores were 10) to receive zolmitriptan first for each attack. If after six attacks, the patients receiving aspirin and metoclopramide wished to switch to zolmitriptan, they were then allowed to do so.

The primary endpoints were the 2-hour headache response rate over 6 attacks, and the disability time per attack. Note that the study was not meant to see which worked better, low level, non-specific treatment or specific treatment with triptans. Rather this was a study to determine which strategy for care would work better for patients. The idea was to find out when to use which treatment strategy in which patient type.

All primary endpoints were superior with stratified care as the strategy for treatment, as opposed to the step care strategies. Stratified care was superior to step care across attacks and step care within attacks for headache response at 1 and 2 hours. Stratified care was significantly superior for headache response over step care across attacks at 4 hours as well. One would not expect to see a difference between stratified care and step care within attacks if you observed out to the 4-hour time point, because if the aspirin/metoclopramide didn't work by 2 hours, the patient was allowed to use zolmitriptan at 2

hours, and there was no difference for the 2 strategies at 4 hours. It is worth noting that even in the patients who were stratified to aspirin/metoclopramide in the stratified care group, 56% chose to step up to zolmitriptan after 6 attacks treated with aspirin/metoclopramide. This suggests that even in the low treatment need group, patients felt a need for stronger or specific medication more often than not.

Disability time was also less for stratified care consistently, 185 minutes for stratified care, 200 minutes for step care within attacks and 210 minutes for step care across attacks (all comparisons are statistically significant). This suggested pharmacoeconomic benefit for choosing a stratified care strategy in patient care. Therefore, two post-hoc analyses have been undertaken since the primary endpoints were calculated.

In the first of these analyses, impairment of normal activities (paid work, non-paid work, leisure time) per attack was significantly reduced ($p<0.001$) with stratified care (6.7 h) compared to step care across attacks (8.7 h). Stratified care patients who suffered a migraine during work time had lower mean lost work hour equivalents (LWHE) than step care across attack patents (3.4 h vs. 4.4 h). Calculations based on LWHE, average weekly earnings ($13.37/h) and drug costs ($14.17/tablet) showed a cost to society of $369 for stratified care patients and $408 for step care across attacks patients, a difference of $39 over 6 attacks. Assuming that leisure time and non-paid work are valued by the patient as much as work time, the cost to society of impaired normal activities was $606 for stratified care patients and $717 for step care across attacks patients, a difference of $112 over 6 attacks. Savings from impaired work and lost work productivity were $18.80 per attack for stratified care over step care across attacks. Unexpectedly, drug costs were also less for stratified care savings ($8.80) than with step care across attacks [16].

Rapoport and colleagues [17] estimated annual costs to be $534 for step care across attacks and $546 for stratified care, but the cost per attack was $80 for step care and $45 for stratified care. In this analysis, the costs were felt to be essentially equivalent over the long term, and the care was superior for stratified care per attack. Thus, at a minimum, there was no additional cost for using the stratified approach, and there were better patient outcomes and reduced disability documented in the DISC trial [17].

The DISC study has yielded prospective evidence for a beneficial effect of matching treatment to disability. It is clear that patients with more than 10 days of at least 50% disability in the last 3 months according to the MIDAS score should be given triptan therapy at the outset as their first medication for acute treatment, not a lower level medication which will need to be stepped up across attacks or in the same attack. So now we know which patients should receive triptans from the beginning.

Having decided which patients will benefit from triptans given to them at their first medical encounter about the headache, the next question is how to use the triptans to best achieve a sustained pain-free response. Patients currently are using the step care within attacks approach to determine *when* to take their triptans. They wait after treatment with low-level medication until the non-specific drugs fail, and then take the triptans when the migraine pain is at a moderate to severe level.

Some patients even skip the low level medication and simply wait until the migraine is “bad enough to be worth using a triptan,” i.e. at a moderate to severe level. They believe that by waiting they can hoard the triptans for appropriate use, since, as noted earlier, there is frequently a limitation on number of tablets per month reimbursed by insurance companies in the US.

It is also important to remember that every double-blind placebo-controlled study on the use of triptans published through the year 2001 used the methodology of having patients wait until they reached a moderate to severe level pain before using the triptan. So all data we have on headache response, pain-free response, adverse events, and recurrence are for how well triptans treat moderate to severe level pain - exactly what patients are currently doing.

Roger Cady and others have long believed that treating early in a migraine attack when the pain is mild will improve the effectiveness of acute therapy. Cady [18] made reference to Nat Blau’s phases of migraine [19] from prodrome to aura to mild phase, moderate-severe phase, resolution, and postdrome, and recommended treatment in the mild phase of the attack, rather than waiting for a moderate to severe level of pain.

Using post-hoc analysis, Cady and colleagues [20] studied both the Spectrum study [21, 23] and the M09 study authored by Pfaffenrath et al. [22] to examine the results for patients who violated the clinical protocol and treated acute attacks with either sumatriptan or placebo at mild level pain, rather than waiting for moderate to severe level pain. Both studies offered placebo-controlled, albeit non-randomized groups of patients to compare the outcomes of treating mild versus moderate to severe level pain for sustained pain-free response [20-23].

In the protocol violators of the Spectrum study, patients who treated moderate to severe pain had a 2-hour pain-free response of 27%. When they treated mild pain the 2-hour pain-free response was 50%. Furthermore for those patients who treated moderate pain, the 4-hour pain-free response was 48%, while the 4-hour pain-free response for patients treating mild pain was 85%. Furthermore, the recurrence rate was also reduced when patients treated mild pain, to 13% vs. 18% when they treated moderate to severe pain. Thus, sustained 2-hour and 4-hour pain-free responses were higher when patients used sumatriptan to treat mild pain.

To address the need for prospective data, two prospective, placebo-controlled, parallel-group, single-attack stud-

ies were presented by Roger Cady at the International Headache Congress (IHC) which was held in New York City in June 2001 [24]. Patients were treated with placebo or sumatriptan (50 mg or 100 mg) at the mild phase of pain; 50% of patients who took 50 mg and 57% who took 100 mg were pain free at 2 hours, while 61% with 50 mg and 68% with 100 mg were pain free at 4 hours. Of the patients who treated with 50 mg sumatriptan, 43% had no migraine symptoms, a more rigorous endpoint, while 49% of patients who treated with 100 mg sumatriptan had no migraine symptoms at 2 hours.

Another interesting result in the protocol violators of the Spectrum study was a reduction in adverse events from 5.2% in patients treating moderate to severe pain to 0 in those treating mild pain. The explanation for this reduction in side effects from the 50 mg sumatriptan may be the termination of the migraine attack before recruitment of second-order (brainstem) and third-order (thalamus) neurons, i.e. central sensitization or allodynia [23].

Rami Burstein and colleagues [25] published evidence that as migraine progresses, cutaneous allodynia is manifested; they suggested that earlier treatment might avoid this process by preventing central sensitization or windup [25]. If migraine is allowed to proceed, multiple non-painful stimuli are perceived as painful, e.g. light, noise, smell, movement, and sensitivity to effect of medication. Treating early would prevent this.

In the protocol violators of the M09 study [22], patients who treated with 50 mg sumatriptan at the moderate level of pain achieved a 2-hour pain-free response of 31%, while those who treated at mild pain had a 2-hour pain-free response of 51%. At 4 hours, the numbers were 56% pain free for the moderate to severe level treatment and 75% for the mild level treatment. For 100 mg sumatriptan, there was a dramatic difference in effectiveness for treating early compared to 50 mg. The 2-hour pain-free response for 100 mg sumatriptan for treating moderate level pain was 36% (61% at 4 hours). When mild pain was treated, 67% were pain free at 2 hours and 91% were pain free at 4 hours.

There was also evidence for reduced recurrence, as measured by sustained pain-free response at 2 hours (19% for the 50-mg treatment at moderate to severe pain, and 34% for the treatment of mild pain). With 100 mg sumatriptan, 24% achieved a sustained pain-free response when treating moderate pain, 53% when treating mild level pain.

There is post-hoc evidence for early intervention with other triptans as well. Sheftell et al. [26] reviewed the naratriptan database for evidence that early treatment would be associated with lower recurrence. They found that patients who treated in the first 90 minutes of an attack were less likely to experience recurrence than those who treated after 2 hours. They speculated that achieving a pain-free response might be tied to reduced recurrence rate [26].

In the MAXIMM study, an open label extension study on the use of zolmitriptan for up to one year, the patients who treated milder levels pain had better outcome than those who treated severe headache [27]. The same finding has been reported for almotriptan, where in the open label extension study, there were better results in those patients who treated lower level pain than severe pain [28].

It thus is likely that the benefit of early intervention, which results in a greater likelihood of a sustained pain-free effect, is a triptan class effect. In the meantime, however, the preponderance of evidence suggests that early intervention is the best way to use triptans to achieve optimal results in terms of both patient outcome and pharmacoeconomics. A sustained pain-free result means fewer tablets per attack since there is no recurrence: this results in more effective and less expensive treatment.

Conclusions

Selection of patients for specific migraine treatment involves stratifying the patient according to disability or characteristics of the migraine attack. If the patient has had more than 10 days of at least 50% disability in any domain in the past three months, initial acute treatment should be with a triptan (although more than half of the patients stratified to non-specific treatment in the DISC study [5] required a triptan later). If the patient has been stratified to use a triptan, he or she should be instructed to not step up in an attack or delay treatment, but rather to treat with the triptan at the mild level of pain to avoid incomplete response, recurrence, and disability.

References

1. Wolff HG (1963) Headache and other head pain. Oxford University, New York
2. Kimball RW, Friedman AP, Vallejo E (1960) Effect of serotonin in migraine patients. Neurology 10:107–111
3. Silberstein SD, for the US Headache Consortium (2000) Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 55:754–763
4. Lipton RB, Stewart WF (1999) Acute migraine therapy: Do doctors understand what patients with migraine want from therapy? Headache 39 [Suppl 2]:S20–S26

5. Lipton RB, Stewart WF, Stone AM et al (2000) Stratified care vs. step care strategies for migraine. The Disability in Strategies of Care (DISC) Study. JAMA 284:2599–2605
6. Sheftell FD, Weeks RE, Rapoport AM, Siegel S, Baskin S, Arrowsmith F (1994) Subcutaneous sumatriptan in a clinical setting: the first 100 consecutive patients with acute migraine in a tertiary care center. Headache 34:67–72
7. Lipton RB, Stewart WF, Ryan RE Jr, Saper J, Silberstein S, Sheftell F (1998) Efficacy and safety of the nonprescription combination of acetaminophen, aspirin and caffeine in alleviating headache pain of an acute migraine attack. Three double-blind, placebo-controlled trials. Arch Neurol 55:210–217
8. Kellstein DE, Lipton RB, Geetha R, Koronkiewicz K, Evans FT, Stewart WF, Wilkes K, Furey SA, Subramanian T, Cooper SA (2000) Evaluation of a novel solubilized formulation of ibuprofen in the treatment of migraine headache: a randomized, double-blind, placebo-controlled, dose ranging study. Cephalalgia 20:233–243
9. Adelman JU, Lipton RB, Ferrari MD, Diener H-C, McCarroll KA, Vandormael D, Lines CR (2001) Comparison of rizatripan and other triptans on stringent measures of efficacy. Neurology 57:1377–1383
10. Tfelt-Hansen, P, Teall J, Rodriguez F, Giacovazzo M, Paz J, Malbecq W, Block GA, Reines SA, Visser WH, on behalf of the Rizatriptan 030 Study Group (1998) Oral rizatriptan versus oral sumatriptan: a direct comparative study in the acute treatment of migraine. Headache 38:748–755
11. Goldstein J, Ryan R, Jiang K, Getson A, Norman B, Block GA, Lines C, and the Rizatriptan 046 Study Group (1998) Crossover comparison of rizatriptan 10 mg versus sumatriptan 25 mg and 50 mg in migraine. Headache 38:737–747
12. Tepper SJ (1999) Rizatriptan – A new agent for the treatment of migraine. Today Ther Trends 17:147-157
13. Tepper SJ, Rapoport AM (1999) The triptans: a summary. CNS Drugs 12:403–441
14. Lipton RB, Goadsby PJ, Sawyer JPC, Blakeborough P, Stewart WF (2000) Migraine: diagnosis and assessment of disability. Rev Contemp Pharmacother 11:63–73
15. Ware JE, Bayliss MB, Dahloff C, Kosinski M, Diamond M, Batenhorst AS (2000) Developing short static assessments from the Headache Impact Test (HIT Item Pool). Cephalalgia 20:308 (abstract)
16. Tepper SJ, Meddis D (2000) Reducing the cost of impairment of normal activities due to migraine: a stratified-care approach. Headache 40:434–435 (abstract)
17. Rapoport A, Williams P, Sawyer J (2000) Stratified care: cost-efficient in the management of migraine. Headache 40:426 (abstract)
18. Cady RK (2000) Primary Care Network Patient. Centered strategies for effective management of migraine. PCN Publishing, Springfield, MO
19. Blau JN (1987) Migraine. Chapman Hall, London
20. Cady RK, Sheftell F, Lipton RB, O'Quinn S, Jones M, Putnam DG, Crisp A, Metz A, McNeal S (2000) Effect of early intervention with sumatriptan on migraine pain: retrospective analyses of data from three clinical trials. Clin Ther 22:1035–1047
21. Lipton RB, Stewart WF, Cady R, Hall C, O'Quinn S, Kuhn T, Gutterman D (2000) Sumatriptan for the range of headaches in migraine sufferers: Results of the Spectrum study. Headache 40:783-791
22. Pffaffenrath V, Cunin G, Sjonell G, Prendergast S (1998) Efficacy and safety of sumatriptan tablets (25 mg, 50 mg, and 100 mg) in the acute treatment of migraine: Defining the optimum doses of oral sumatriptan. Headache 38:184–190
23. Lipton RB, Stewart WF, Cady R, Hall C, O'Quinn S, Kuhn T, Gutterman D (2000) Treatment of mild headache in disabled migraine sufferers: results of the Spectrum Study. Headache 40:792–797
24. Cady R (2001) Early Intervention Symposium, International Headache Congress, 30 June 2001, New York
25. Burstein R, Yarnitsky D, Goor-Aryeh I, Ransil BJ, Bajwa Z (2000) An association between migraine and cutaneous allodynia. Ann Neurol 47(5):614–624
26. Sheftell F, O'Quinn S, Watson C, Pait D, Winter P (2000) Low migraine headache recurrence with naratriptan: clinical parameters related to recurrence. Headache 40:103–110
27. Tepper SJ, Donnan GA, Dowson AJ, Bomhof MAM, Elkind A, Meloche J, Fletcher PE, Millson DS (1999) A long-term study to maximise migraine relief with zolmitriptan. Curr Med Res Opin 15:254–271
28. Mathew NT (2000) Long term efficacy and tolerability of almotriptan: Results of a 1-year open study on almotriptan. In: Almotriptan: complete migraine therapy, Headache World 2000. London, 6 September 2000, pp 11–12