

Research Submission

Predictors of Adherence to Triptans: Factors of Sustained vs Lapsed Users

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Objective.—The present study was conducted to identify factors that predict adherence to triptans by migraine patients.

Background.—Triptans have demonstrated efficacy for acute migraine yet many migraine sufferers discontinue their use.

Design and Methods.—A survey study was conducted using 785 subjects (390 health maintenance organizations [HMO] and 395 non-HMO). Of those, 586 were sustained users of triptans (defined by at least 1 refill within the past year), and 199 were classified as lapsed users (ie, individuals who had 0 refills in the past year). Groups were compared on a variety of measures including a comprehensive Migraine Survey that included items related to efficacy and adverse events associated with the patient's current medication, as well as the Headache Impact Test (HIT)-6 and Migraine Disability Assessment Score (MIDAS) questionnaires. Data were analyzed with multivariate analysis of variance and stepwise multiple regression.

Results.—Sustained users of triptans were significantly more satisfied with their medication, confident in the medication's ability to control headache, and reported control of migraine with fewer doses of medication. Sustained users also switched triptans products significantly less often than lapsed users, and reported greater benefit from triptan intervention in restoring normal daily functions, including improved cognitive ability, compared with lapsed users' ratings of their nontriptan medication. More lapsed users than sustained users reported adverse events associated with past triptan use. Results from multiple and logistic regression analyses correctly classified 95% of sustained users and identified the most significant predictors for sustained use as: satisfaction and belief in medication, reliability of response, effectiveness in rapidly restoring normal levels of productivity, and fewer doses of medication for resolving an attack. The HIT-6 and MIDAS distinguished between sustained and lapsed triptan users on days unable to do household work and missed family and social events.

Conclusions.—Predictors of adherence to triptans included satisfaction and confidence in triptans' ability to stop the migraine and associated symptoms and to return the individual to normal functioning. The findings suggest that lapsed users may not be receiving optimal treatment, and that if their past response to triptans was a consequence of inadequate education, they may benefit from additional education on proper use of triptans.

Key words: migraine, triptans, MIDAS, HIT-6, questionnaire, pain-free

Abbreviations: HIT, Headache Impact Test; HMO, health maintenance organization; IHS, International Headache Society; MANOVA, multivariate analysis of variance; MIDAS, Migraine Disability Assessment Score

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Migraine is a chronic neurological disease with disabling episodic manifestations typically recurring over decades of an individual's life. During a migraine sufferer's lifetime migraine can progress from an episodic to chronic disease.¹⁻³ There is an age-related bias in the occurrence of migraine attacks toward younger adults, often during productive years of their career and family. Additionally, there exists a gender bias in the adult US population toward women, estimated to be 3 to 1.⁴ These factors compound the overall disability and pervasive nature of migraine and account for the significant impact of migraine on individual sufferers, their families, the workplace, and the healthcare system.⁵⁻⁷ Effective treatment of migraine has the potential to markedly reduce the impact of this disease.

In 1993, subcutaneous sumatriptan was heralded as a breakthrough for the treatment of migraine. Supporting the introduction of sumatriptan were clinical trials demonstrating that 70% of migraine sufferers were able to experience relief of headache within 1 hour and that nearly 50% became pain-free.^{8,9} Perhaps more importantly, the "era of the triptans" ushered in legitimate scientific research that ultimately changed the classification of migraine from a syndrome of vascular hyperreactivity to a complex neurological disease.¹⁰

Since the introduction of subcutaneous sumatriptan, 7 oral formulations, 2 oral dissolving formulations, and 2 intranasal formulations have been introduced into the world markets. These medications have demonstrated significant therapeutic efficacy over placebo and nonspecific headache therapies in large clinical trials.^{11,12} Throughout the last 2 decades considerable effort and educational resources have been directed toward helping physicians improve their diagnostic and therapeutic acumen for migraine.

Conflict of Interest: J.K. Evans was an employee of Merck & Co., at the time this article was written and may potentially own stock and/or hold stock options in the company. R.K. Cady serves as a consultant for GlaxoSmithKline and Merck and Co., Inc., is on the advisory boards of GlaxoSmithKline and Merck and Co., Inc., and has received research grants from GlaxoSmithKline, Merck and Co., Inc., and Pfizer. M. Maizels has served as a paid lecturer and scientific advisor and has received research support from Merck and Co., Inc. D.L. Reeves and D.M. Levinson have no interests to disclose.

In addition, newer research has shown that initiating triptan therapy earlier in the course of a migraine than was utilized in clinical trials provides significant improvement in therapeutic outcome, a paradigm called early intervention.¹³⁻¹⁷ However, despite these scientific and pharmaceutical advancements, migraine continues to be a frequently misdiagnosed and undertreated disease entity.¹⁸ It has been stated by pharmaceutical companies that the number of patients using triptans for acute migraine has remained essentially the same (approximately 4 million) over the last 5 years. If true, this implies that with each new patient diagnosed and prescribed a triptan, there is a triptan user who lapses from continued use of triptans.

Even though there have been studies about what patients want or expect from medication,¹⁹ there is a scarcity of data clarifying factors associated with patients who continue triptan use compared with those who do not. The present study represents a survey of 785 diagnosed migraineurs who had been prescribed a triptan medication and who subsequently continued or discontinued triptan therapy. Surveys about headache impact, functional disability, and satisfaction with current migraine treatment were used to characterize differences in the present-day experience of sustained triptan users vs users who switched to nontriptan therapies.

METHODS

Study Design.—This study provided information on 785 migraineurs with at least a 1-year history of the disease, who had been diagnosed by a clinician and prescribed a triptan medication for acute therapy. Data were collected from 2 sources, Clinvest Research Network and a health maintenance organization (HMO) pharmacy database, from June to October, 2006.

Patients and Procedures.—*Source 1.*—Ten primary care practice sites within the Clinvest Research Network that were not affiliated with an HMO were used to recruit 395 patients (~40/site) with a diagnosis of migraine and current or past use of a triptan for migraine therapy. This was accomplished through the use of questionnaire cards placed in the waiting room that queried study inclusion criteria such as age, number of migraines per month, number of years

with migraine, and triptan use. Questionnaires were reviewed to confirm a diagnosis of migraine with or without aura as defined by the International Headache Society (IHS 1.1 and/or 1.2) and eligibility. Individuals who met inclusion criteria were offered the opportunity to participate and asked to complete a detailed Migraine Survey regarding their migraine history and their current or past use of triptan medication(s). The Migraine Survey consisted of 22 pages of questions answered using a 5-point Likert scale, regarding understanding of migraine and medication use, as well as demographic information (age, gender, and year of migraine diagnosis) and use of other nontriptan medications taken for migraine. Subjects also completed the Headache Impact Test (HIT)-6 (accessible online at http://www.qualitymetric.com/products/surveys/pdf/HIT-6_Sample.pdf, or at <http://www.neurohealth.info/pdf/hit6.pdf>) and Migraine Disability Assessment Score (MIDAS) questionnaires (Appendix 1). A total of 400 completed Migraine Surveys were collected.

Patients and Procedures.—*Source 2.*—A large HMO pharmacy database was searched and data collected to identify patients who obtained at least 1 prescription for a triptan in 2004. Migraine Surveys were then mailed to eligible patients. Collection of Migraine Surveys continued until there was a total of 390 completed surveys. The HMO cohort also completed the HIT-6 and MIDAS questionnaires.

Statistical Methods.—Data were assessed using a multivariate analysis of variance (MANOVA), to characterize and compare the groups in terms of answers to individual questions on the HIT-6, MIDAS, and Migraine Survey.

Secondarily, data from the Migraine Survey which measured triptan efficacy were analyzed by stepwise multiple regression.

RESULTS

Demographics.—There were 785 participants in the study: 680 women (mean age = 48.96) and 105 men (mean age = 42.57). Of those, 586 were sustained users of triptans, while 199 had lapsed from use of the prescribed triptan. Both groups reported a diagnosis of migraine of >30 years, with 1979 the mean year of

diagnosis for both groups. Of the 785 participants, 395 used non-HMO healthcare providers, while 390 were enrolled in an HMO program (Kaiser Permanente). The respective mean ages of these 2 groups were 41.17 and 53.72 years; this difference was statistically significant, and therefore comparisons of these groups were performed adjusting for age as a covariate.

Analysis of HIT-6 and MIDAS.—Both groups were compared on the basis of HIT-6 and MIDAS. Complete data sets were obtained on 775 participants. No significant differences were observed on any specific questions included in the HIT-6.

For the MIDAS, no differences were observed either on severity of headache pain, or frequency of headache. However, MANOVA revealed for the lapsed group significantly higher numbers of days on which they did not do household work or they missed family, social, or leisure activities because of headache. In short, both groups experienced severe pain and moderate impact but the lapsed group missed significantly more days of normal activity.

For analysis of measures which constitute efficacy attributable to triptans, including satisfaction, effectiveness, confidence in the medication, time to being pain-free, and perceived adverse events of the medication, questions were derived from the subsection of the Migraine Survey specifically dealing with current or noncurrent use of triptans. The answers to these questions for the 2 groups were analyzed by MANOVA, and showed that between-group differences were significant on all the measures with sustained users recording higher scores on satisfaction, dose, and confidence. The sustained users switched triptans significantly less often during the past year than did the lapsed users (means = 1.86 and 1.96; $F = 4.50$, $P < .05$). Other measures on which the sustained users had significantly higher scores than the lapsed users were belief in their control over their migraines (means = 3.00 and 2.60; $F = 20.06$, $P < .001$), and belief in their medications as important for treatment outcome (means = 2.95 and 1.85; $F = 119.17$, $P < .001$).

Other items yielding nominal data dealt with the use of opioids and with following the instructions of the health care professional. Chi-square tests

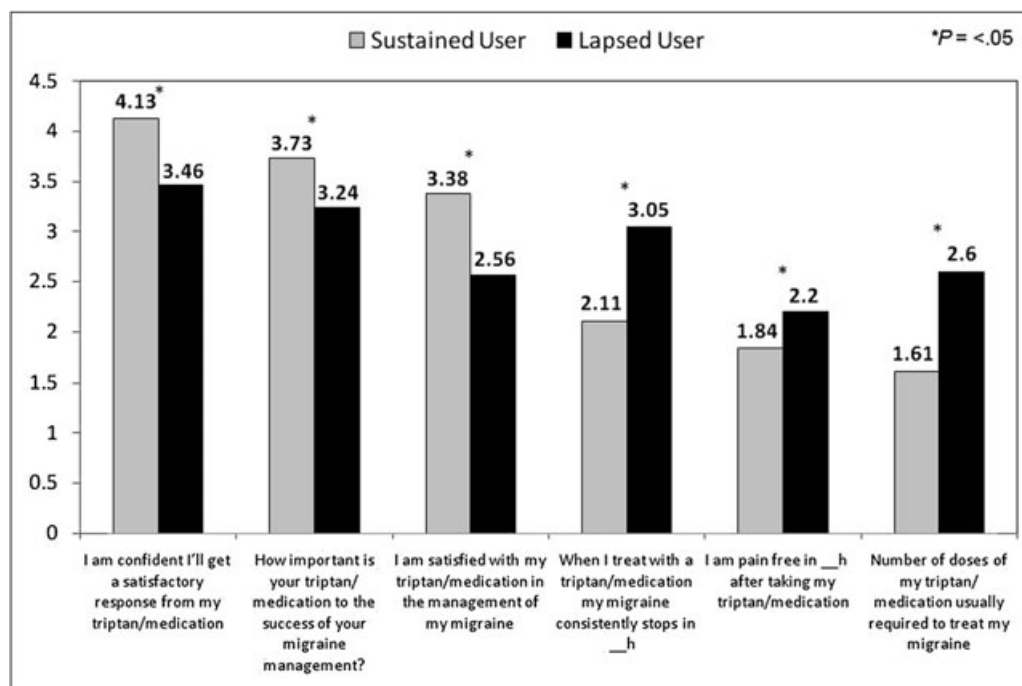


Figure.—Predictors of adherence to triptans.

revealed significant differences on both items. A greater percentage of lapsed users indicated that they were using opioid analgesics, but nearly half of the sustained users also reported using opioids within the last year. Similarly, the percentage of patients who reported following their health care professional's instructions was significantly higher for sustained users, although most patients in both groups followed their provider's instructions.

Prediction of Satisfaction With Triptans.—Because of the large number ($n = 586$) of sustained users who participated in the study, a stepwise multiple regression was performed using the triptan efficacy measures as predictors of satisfaction. The results indicate that the most important predictor of satisfaction was confidence in the medication. This was followed by the importance of the medication, satisfaction in the response from the medication, how quickly the medication stops the migraine, and how quickly the patient returns to a pain-free condition. Subjects who sustained use of triptans had a significantly higher level of satisfaction with them than lapsed users had with their current medication (Fig.).

DISCUSSION

Predictors of Subjects Who Sustained or Who Lapsed in Use of Triptans.—Severity and impact of migraine as measured by the HIT-6 did not distinguish between patients who continued or discontinued their use of triptans. Likewise, headache severity scores were not statistically different for these 2 populations on the MIDAS questionnaire either. This suggests that the severity and frequency of attacks are quite similar between the 2 groups of study subjects. However, the MIDAS did differentiate the 2 populations in terms of time lost from work and leisure activities. This suggests that limiting functional incapacitation may be the more salient advantage triptans provide for sustained users.

The evaluation of specific treatment attributes was more favorable for sustained users of triptans than for lapsed users who were taking nontriptans, across all attributes surveyed. Specifically, sustained users were far more satisfied with, and confident in, triptans as an abortive agent for migraine than were the lapsed users with their current treatment medications. This may reflect generally less successful treatment with acute pharmacological therapy among

lapsed users; alternatively, lapsed users may be more likely to be using medication in a suboptimal manner or employ less effective treatment strategies such as using medications in a sequential fashion or waiting until a migraine attack is well developed before initiating treatment. However, 57% of sustained users of triptans also used concomitant nontriptan therapy. Further suggestion of confidence in medication is reflected in the fewer doses of medication needed to treat an attack of migraine for sustained users. Together these 3 factors may provide positive feedback to the patient, resulting in more favorable ratings of satisfaction, confidence, and time to pain-free status.

Of particular interest were the results regarding the concept of having confidence in acute treatment. Whereas early surveys suggested that patients using acute therapy desired rapid relief,¹ the present study suggests that in order for a patient to continue the use of triptans, it is more important that these interventions provide that relief consistently over time.¹⁹ If acute interventions are inconsistent in successfully treating migraine or in preventing recurrence over a period of several attacks, it is possible that confidence in a return to normal activity and function might remain impaired even when a specific attack is successfully treated.

The mean differences in scores for some of the other efficacy-related Migraine Survey items were not very large but were nonetheless statistically significant. This may be due to high levels of power resulting from the large number of subjects associated with the error terms in the analyses (in some cases as large as 767). Thus, in the context of the large sample size ($N = 785$), appropriate caution should be used in the interpretation of small differences which emerged as significant.

In the analysis of ways in which patients felt triptans allowed them to function, the various attributes proffered as reasons for improved functional ability appeared to be important aspects of treatment among sustained triptan users compared with lapsed users. An interesting attribute of triptans in the population of sustained triptan users was that triptans allowed them to “think clearly.” Small pilot studies have suggested that successful treatment with triptans is asso-

ciated with rapid return to normal cognitive function²⁰ although it is not clear whether triptans improve resumption of normal cognition primarily, or whether this effect is secondary to resolution of the migraine itself. An alternative explanation may be that some nontriptan therapies such as opioids may cause cognitive impairment. Regardless, the present findings emphasize the importance of cognitive impairment as an aspect of migraine which warrants further study.

Interestingly, the only negative feature of triptans that separated sustained users from lapsed users was the occurrence of adverse events, which were reported more frequently by lapsed users. This disparity may reflect biological differences in the subpopulation or a tendency to intervene with triptans late in the evolution of migraine, resulting in more adverse events. With regard to the number of doses required to treat a migraine, the difference between sustained and lapsed users was statistically significant. Cost did not differentiate sustained users from lapsed users in either the HMO or the non-HMO populations.

It is known that patients often treat their migraines with more than 1 medication at a time. Between-group differences in use of opioid analgesics were therefore assessed, as it has been suggested that use of opioids may reduce the therapeutic response to triptan therapy.²¹ In this study, opioid use was relatively common to both groups and did not appear to be a factor differentiating sustained from lapsed use of triptans. In addition, 57% of the sustained users also used nonsteroidal antiinflammatory drugs, suggesting that even among sustained users, triptans are often one of several treatment options patients are utilizing. Specific attributes of these nontriptans were not evaluated for the sustained users in this study.

Prediction of Satisfaction With Triptans.—Given the large number of sustained users who provided data for the study, it was feasible to perform a stepwise multiple regression using the efficacy measures on the Migraine Survey as predictors of satisfaction. Patients who sustained use of triptans had a significantly higher level of satisfaction than lapsed users had with their current nontriptan medication. The most important predictor of satisfaction was found to be confidence in the medication, followed by (2) the

importance of the medication, (3) satisfaction in the response from the medication, (4) how quickly it stops the migraine, and (5) how fast the patient returns to a pain-free condition. Collectively, these measures accounted for nearly 60% of the variance in satisfaction, which underscores their significance relative to the other 16 factors in the assessment. It may be important for health care professionals to query patients about these 5 parameters when deciding if a specific therapy, particularly a triptan, is efficacious for a given patient.

The signal importance of confidence in medication as a predictor of sustained use of triptans strongly emphasizes the need to properly educate patients, as the optimal use of acute migraine medications includes setting appropriate expectations about therapeutic outcomes. Sustained users of triptans also reported less frequent switching of medication, which may suggest earlier success in discovering an efficacious treatment but could also reflect better education by health care professionals, and consequently less of a tendency to switch medications prematurely. Further study would help to clarify this aspect of triptan use and its relationship to overall treatment satisfaction.

Demographic Considerations.—The prevalence of migraine in the general population of the US has been defined in 3 large, well-constructed epidemiological studies.^{5,6,22} Most recently and consistent with the previous 2 studies, Lipton et al found that approximately 12% of adults in the US suffer with migraine. That study also concluded that 17.1% of females and 5.6% of males have migraine as defined by IHS criteria.²³ The gender bias in the general population is approximately 3 : 1 (female to male). These studies suggest that the symptomatology, frequency, and impact of migraine are essentially the same for men and women in the general US population and that the prevalence of migraine increases from 12 to 40 years of age and declines thereafter.

A large, comprehensive epidemiological study of the population of patients receiving care for migraine has not been reported in the literature to date. Data from clinical trials may more closely reflect the epidemiology of clinical populations, but clinical trials are generally not exclusive to patients who have spon-

taneously engaged the medical system for headache care. Characteristically clinical trial populations have a gender bias of women to men of approximately 6-8 : 1, which is considerably higher than that observed in epidemiological studies of the general population.^{24,25} Moreover, the average age of subjects in migraine clinical trial populations is in the range of 30s to early 40s, which is somewhat older than in the general migraine population. Thus, clinical trial populations appear to be somewhat unique compared with patients characterizing the general population. In the present study, all patients had sought treatment for headaches, obtained a medical diagnosis of migraine, and were prescribed a triptan. Patients in this study population were considerably older than one would predict from population-based studies and even clinical trials. In this population the mean age of patients was 49 years for women and 43 years for men. This age distinction was more pronounced when the population was segregated by whether or not they participated in an HMO, and indeed the average age of the patients in the HMO population was >47.5. Furthermore, in this highly selected subpopulation, the gender bias of migraine for females to males was 6.6 : 1 and the average duration for which they reportedly had been diagnosed with migraine was 38 years. These data suggest a different and important distinction in demographics between a medical population of migraine sufferers and the general population.

The disability in the study population was severe with the average HIT-6 score being 63 and moderate with the average MIDAS total score of 18.93. Further, based on MIDAS, there were 16.23 days of lost productivity for sustained users vs 21.63 lost days for lapsed users. Interestingly, the impact of migraine was not shared equally by both genders. Women in this study population experienced 18.54 days of missed activity in the previous 3 months, compared with men, who missed 11.79 days. This gender difference in disability associated with migraine is not reflected in population-based epidemiological studies.^{5,26} These data may indicate that the population seeking medical management for migraine and deemed worthy of triptan therapy consists of older patients with long-established histories of disabling migraine, and that women are more likely to be included in this

subgroup than population-based studies would suggest. Although this study was not designed to ascertain the epidemiology of subpopulations of migraineurs and caution must be taken in the extrapolation of the data, it is feasible to speculate that future well designed studies of the epidemiology of migraine sufferers seeking medical care for headaches is warranted, especially given the larger percentage of the general migraine population for whom migraine is a self-diagnosed and self-managed medical condition.

Summary and Conclusions.—This study provides some of the first insights into the dynamics of migraineurs who sustain use of triptans compared with those who lapse from triptan use, and the findings may help clinicians to plan better care for patients who may be missing out on the advantages of triptans. The study showed that sustained users are continuing to use triptans because of their perceived value, and that patients' confidence in the medication is perhaps the critical factor in their decision to continue using triptans. Lapsed users are less satisfied with current therapy, and presumably also with triptans as they discontinued their use. Some of these patients may simply not respond as well to available migraine medications in general, but there may be others who abandoned triptan therapy perhaps too soon because of incorrect use or inaccurate expectations. This situation may be rectifiable with enhanced education about triptans. In addition, these data provide a perspective on the demographic characteristics of migraine sufferers who seek headache care, are given a diagnosis of migraine, and are prescribed a triptan as an acute treatment medication. The findings of this study also suggest that there may be greater disability for women with migraine who are prescribed a triptan than for men.

Defining optimal outcome for patients using triptans for acute migraine therapy has been an elusive target since their introduction in the early 1990s. Critical issues have emerged that include finding the optimal dosage, formulation, and timing of triptan medications. Early clinical trials defined success as headache relief and improvement rather than resolution of migraine associated symptoms and functional capacity. With the advent of early intervention the

primary end point has shifted to pain-free status at 2 hours postdose, and sustained pain freedom over 24 hours.²⁷ The present study appears to support this higher level of efficacy as a more accurate reflection of patients' desires. However, a significant number of patients appear unable to successfully utilize triptans in early intervention strategies.²⁸ This underscores the need for health care professionals to understand the therapeutic needs of their patients and be able to communicate effectively strategies that will allow them to obtain successful outcomes over time. Clearly, further study is warranted on the demographics of the clinical population of migraine sufferers and factors that constitute long-term successful management of migraine.

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APPENDIX 1

Migraine Disability Assessment Score (MIDAS)

MIDAS Questionnaire

Date Completed ____/____/____

Instructions: Please answer the following questions about ALL your headaches you have had over the last 3 months. Write your answer on the line. 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?_____
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.)_____
3. On how many days in the last 3 months did you not do household work because of your headaches?_____
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.)_____
5. On how many days in the last 3 months did you miss family, social, or leisure activities because of your headaches?_____

Your rating – Total 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.)_____
- 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.)_____

Grade	Definition	MIDAS Score
I	Little or no disability	0-5
II	Mild disability	6-10
III	Moderate disability	11-20
IV	Severe disability	21+