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## Effect of daily migraine prevention on health care utilisation in an insured patient population

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**Abstract** The economic benefits of daily migraine prevention have been subject to ongoing debate.

This study was undertaken to determine if the initiation of prevention had an observable effect on ambulatory health care utilisation when compared to acute migraine treatment alone.

Administrative claims data from the Military Health System were used to conduct a retrospective, longitudinal cohort study of 3762 patients with migraine. New users of daily migraine prevention were matched to a reference group of non-users using propensity score methods. This matched sample then was used to evaluate the effect of prevention on ambulatory health care expenditures. The study results showed that exposure to daily migraine prevention led to lower rates of utilisation relative to what new patients would have con-

sumed in the absence of treatment. The results suggest that additional economic benefits could be realised by increasing the appropriate use of daily migraine prevention.

**Keywords** Migraine headache • Prevention • Health care utilisation • Economics

### Introduction

Migraine is a widespread and disabling neurological disorder that presents a formidable challenge to health care providers [1]. The economic consequences of the disease are considerable, placing a significant burden on patients, health plans and employers worldwide [2–6]. Individuals

that receive treatment for migraine generally consume more health care resources than patients without the condition [7]. Moreover, migraine headaches are a significant source of patient disability [2–6, 8, 9]. This disability has in turn been linked to reduced productivity during arguably the most productive years of a person's life [10, 11]. As such, treatments that enhance the management of migraine in a safe and cost-effective manner should be a

priority for health care organisations.

Over the last decade, several advances have enhanced the ability to manage patients who suffer from migraine. One such breakthrough was the expansion of effective choices for daily migraine prevention. While prevention has been shown to reduce the frequency and severity of migraine headaches [12, 13], it is unclear whether or not this treatment has an effect on a patient's use of migraine-related medical services. Cost-effectiveness analysis has suggested that some preventive medications are cost-effective, but for only a subset of patients with frequent headaches or comorbid illness [14, 15]. Because traditional economic evaluations are typically based on efficacy data from clinical trials, the results may not be readily transferable to routine medical practice. As a result, health researchers are more frequently relying on analyses of administrative claims data to compare direct health care expenditures for patients exposed to different treatments in an effort to gauge economic benefits [16].

Two studies of this type recently have examined the relationship between migraine prevention and health care resource utilisation [17, 18]. The results suggest that the addition of a preventive medication to an individual's existing treatment for migraine reduced utilisation of abortive prescription medications, physician visits and emergency room visits which resulted in overall cost-savings to the health plans. However, the results were criticised because of methodological shortcomings in design and implementation of the analysis [19]. In this paper, we build on previous research [17, 18] and attempt to address several threats to validity identified in earlier studies. Our objective is to evaluate if initiation of daily migraine prevention has an observable affect on ambulatory health care utilisation compared to acute migraine treatment alone.

## Materials and methods

### Source of data

We conducted a retrospective longitudinal analysis of pharmacy and medical claims data among beneficiaries suffering from migraine in the US Military Health System (MHS). The data were collected from TRICARE, the health insurance coverage program for the MHS, which covers care provided at military medical facilities and also pays for contracted medical care from the private sector across the USA [20]. Programme beneficiaries include active duty and retired members of the uniformed services in the USA, their family members and survivors. Two years of data were available for the analysis beginning 1 October 2002 and ending 30 September 2004. All research was performed in accordance with appropriate ethical standards and the study protocol was approved by the Institutional Review Board at the University of Minnesota.

### Study population

The initial migraine population was selected based on documentation of headache-related pharmacy and medical encounters that occurred during the study timeline. The initial study population *included* patients who met each of the following criteria: (1) received a prescription for a migraine-specific abortive medication (MSAM) (described below) during the six-month window of 1 April 2003 to 30 September 2003 (the date of the first prescription during this period was labelled as that patient's index date); (2) experienced an ambulatory health care encounter with an ICD-9-CM code 346.XX (migraine) between 1 October 2002 and 30 September 2004; (3) between 17 and 64 years of age on the index date; and (4) eligible for care during the study period. If patients did not meet all four criteria, they were *excluded* from the initial migraine study population.

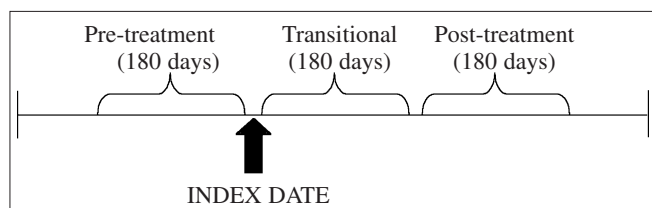
A MSAM mentioned above was defined as a claim for serotonin receptor agonist (e.g., sumatriptan), an ergotamine derivative or an isometheptene-containing product. All MSAMs are indicated primarily for the acute treatment of migraine headache. The abortive medications do not possess any common off-label indications, which minimised the possibility of misclassification bias (i.e., detection of patients who do not suffer from migraine but are receiving treatment with MSAM). Furthermore, identification of patients using the inclusion criteria above was recently reported to be an effective method for claims-based recognition of migraine patients in a managed care population [21].

### Conceptual framework

Several areas of previous research helped develop the conceptual framework for this study. Aspects of the design were based on the Economic, Clinical, and Humanistic Outcomes (ECHO) model [22], originally developed to assist researchers in the examination of causal relationships between pharmaceutical treatments and health outcomes. The Behavioural Model of Health Care Utilisation [23] was incorporated to help identify the determinants of health care utilisation. The model characterises health care utilisation as a function of three categories: (1) predisposing characteristics (e.g., age or gender); (2) enabling characteristics (e.g., insurance status); or (3) need characteristics (e.g., headache frequency or severity). The model was useful because it provided a theoretical framework to identify important explanatory variables in a patient's decision to utilise health resources.

### Dependent variable

The dependent variable measured TRICARE spending for migraine-related outpatient services. Each subject's spending was categorised as prescription, non-emergent ambulatory care or emergency room care, with the sum of all three equal to total outpatient spending for migraine-related care. Prescription spending included the costs of all dispensed medications identified as either *definitely* (e.g., MSAM) or *potentially* (e.g., non-



**Fig. 1** Index date and study defined intervals

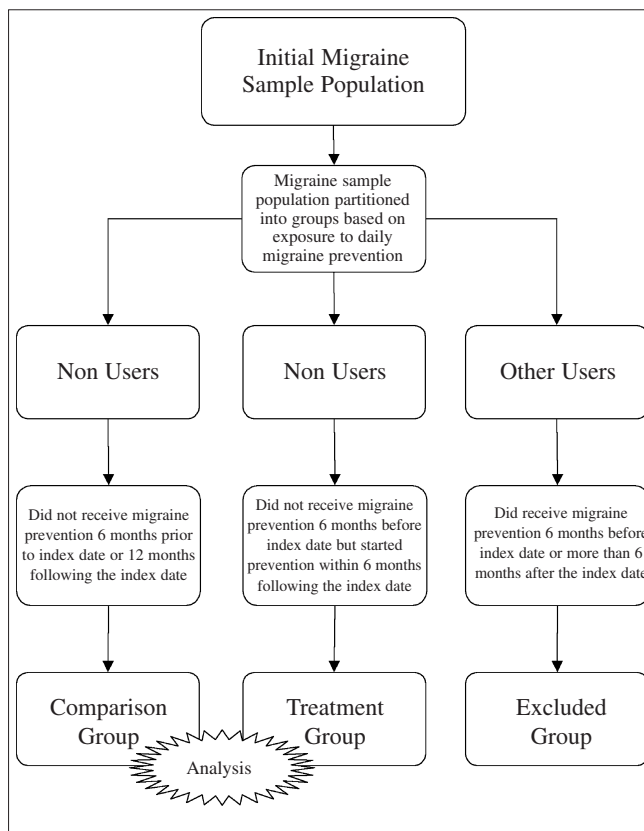
steroidal anti-inflammatories or anti-emetics) related to migraine. This classification has been used previously in migraine research [24] and a complete list of the medications in each category is available from the authors upon request. Spending for migraine-related medical care was derived from claims with a migraine ICD-9-CM diagnosis code (346.XX).

Each subject's spending was measured separately during three 180-day intervals determined from the index date (Fig. 1). The 180-day intervals surrounded the index date with one immediately preceding it and two following the index date. The intervals were referred to as pre-treatment, transitional and post-treatment respectively. Use of 180-day intervals allowed for a standardised comparison of the study outcome measures before and after the index date for each study subject. The primary study endpoints for each category were (1) post-treatment spending and (2) the change in spending from the transitional interval to the post-treatment interval (calculated as the difference between the post-treatment and transitional intervals).

#### Explanatory variables

The independent variable of interest was a dichotomous measure of whether or not an individual was exposed to daily migraine prevention. For the purposes of this study, exposure to prevention was defined as a prescription for either (1) a migraine preventive medication from the American Academy of Neurology's designation of Group One or Group Two [12] or (2) a migraine preventive medication that had an FDA approval for prevention of migraine before 30 September 2004. Exposure status was determined after the initial migraine sample was identified. Subjects were partitioned into one of three mutually exclusive categories based on their use of prevention (Fig. 2). 'Other users' were excluded to minimise potential biases associated with the inclusion of prevalent users of migraine prevention in an observational setting [25].

The remaining explanatory variables were based on the conceptual framework [23]. Predisposing characteristics included gender, age, geographic region and the branch of uniform service. Gender was a dichotomous variable with men as the reference group. Age was modelled as a continuous variable measured in years for each individual at the index date. Geographic region was divided into 11 categories by TRICARE region. The regions included ten areas inside the continental USA and one area for all persons residing overseas. Branch of service corresponded to the Uniform Service of the



**Fig. 2** Flowchart of cohort assignment for initial migraine sample population

United States that the sponsor was assigned to while eligible for care in the MHS. The variable included four categories organised as follows: Army, Navy/Marine Corps, Air Force and a category that included all the remaining branches of the Uniformed Services.

Enabling characteristics included each subject's beneficiary category and preference for non-military pharmacy services. Beneficiary category referred to a TRICARE designation that indicated how a patient was classified in the MHS. The variable distinguished between active duty military personnel and all others categories because subjects on active duty were required to meet certain baseline health requirements and had first dollar health care coverage (i.e., no deductibles, premiums or copayments). The other enabling characteristic was a subject's preference for non-military pharmacy services measured as the percentage of all prescriptions filled outside of a military pharmacy during the study period. It was deemed enabling because prescriptions dispensed from non-military pharmacies required copays (\$3 for generic and \$9 for brand) whereas military pharmacies were free of charge if the product was on the facility's formulary. The reference group included subjects who had all prescriptions filled at military pharmacies. The remaining individuals were split into two groups; one with fewer than 40% and the other with 40% or more of their prescriptions from a non-military pharmacy.

Characteristics of need included pre-treatment measures of comorbidity, migraine frequency, migraine-related health care expenditures and receipt of care from a neurologist. Comorbidity was measured as a continuous variable derived from the number of unique medication classes dispensed during the pre-treatment period. This method has been shown to be a simple and efficient method for measuring comorbidity status and predicting health care expenditures [26–28]. Migraine frequency was assessed by measuring each subject's utilisation of MSAM in defined daily doses (DDD) [29–31]. The formal definition of this variable was the amount of MSAM dispensed in DDDs during the pre-treatment interval. The use of DDDs provided a standardised unit of measurement to account for the various medication classes, drug doses and routes of administration available with MSAM treatment. Furthermore, it provided a proxy for headache frequency because a single DDD was designed to reflect the average amount of abortive medication required to treat a migraine headache [29]. Migraine-related outpatient expenditures were measured as a continuous variable during the pre-treatment period and neurologist care was a dichotomous variable that indicated if an individual had at least one encounter with a neurologist during the pre-treatment period.

#### Data analysis

The statistical analysis included a descriptive investigation of the study population stratified by exposure to daily migraine prevention. Means with standard deviations were calculated for continuous variables. All categorical variables were described as counts and percentages. For comparisons of health plan spending, we created a matched sample based on a propensity score [32]. The propensity score was a measure of the probability that a patient was exposed to prevention determined from the observed explanatory variables. Matching new and non-users of prevention with similar propensity scores removed the bias due to observed characteristics, allowing for a comparison of migraine-related spending between the two groups.

Estimation of the propensity score was accomplished with logistic regression to determine the probability of exposure to prevention during the transitional interval for new and non-users. Explanatory variables were included in the model based on the Behavioural Model for Health Care Utilisation. Once the propensity score had been estimated, a balanced sample was created using caliper matching. The propensity score caliper was defined as 60% of the pooled standard deviation of the estimated propensity score [33]. After randomly ordering observations, the control subject with the closest propensity score in absolute terms that fell within the pre-defined caliper of each treated subject's propensity score was selected. This matching process ensured more homogenous subject pairs than other more commonly used matching strategies such as nearest neighbour matching.

Treated units were designated as unmatched and removed from the sample if the process failed to identify at least one control subject within the caliper above. After running each treated subject through the matching process, the effectiveness of the procedure was assessed by comparing two-sample *t*-statistics and

standardised percent differences ( $d_i$ ) among study covariates for the two groups [34]. Absolute values of  $d_i$  less than 10% and non-significant *t*-tests supported the assumption of balance between the two groups [34]. After confirmation of covariate balance, the association between exposure to daily migraine prevention and resource utilisation was estimated by calculating the difference between matched pairs for each study endpoint. The mean difference between the two study cohorts represented the average treatment effect of daily migraine prevention among the treated subjects. Standard errors and 95% confidence intervals for the matched sample were computed using a bootstrap with 250 replications. The propensity score, the matched sample and the average treatment effects were estimated with the PSMATCH2 module for STATA 9.0 [35].

## Results

The migraine sample population contained 3762 subjects. This included 1144 new users and 2618 non-users of daily migraine prevention. The population characteristics for the full and matched sample are summarised in Table 1. Subjects in the full sample were predominately female, classified as other than active duty, with an average age of 36 years. The majority of the migraine population was located within the continental USA and 10% resided overseas. Subjects received, on average, 4 DDDs per month of MSAM during the pre-treatment interval. Eighteen percent of study subjects in the full sample had at least one encounter with a neurologist during the pre-treatment period. Unadjusted expenditures for migraine-related outpatient care in the full sample were estimated at \$125.35 per member per month, driven primarily by spending on prescription medication (51%) followed closely by non-emergent ambulatory care (40%).

Table 2 summarises the degree of covariate imbalance between the two study cohorts prior to matching for the full sample. Subjects exposed to prevention (i.e., new users) showed evidence of pre-existing differences for several characteristics compared to the reference group of non-users. Caliper matching on the propensity score identified a match for 997 new users (87%) of prevention. The unmatched new users showed evidence of greater dependence on migraine-specific abortive treatment, consumed more outpatient health resources, had higher comorbidity scores and were more likely to receive care from a neurologist than the matched new users of prevention.

After matching, the results confirmed that new and non-users of prevention had balanced distributions of the study explanatory variables. Relative reductions in standardised percent differences ranged from 15% to 96% and no statistical evidence of a difference was detected for

**Table 1** Sample characteristics and unadjusted ambulatory health care spending in the full and matched study cohorts

	Characteristic, <i>N</i> (%)	
	Full	Matched
Number of patients	3762	1,994
Age (in years) <sup>a</sup>	35.8 (11.8)	34.8 (11.5)
Female	3,057 (81)	1,579 (79)
Beneficiary Category		
Active Duty	1,040 (28)	613 (31)
Other	2,722 (72)	1,381 (69)
Branch of Service		
Army	1,264 (34)	675 (34)
Air Force	1,113 (29)	589 (30)
Navy/Marine	1305 (35)	685 (34)
Other	80 (2)	45 (2)
Geographic Region		
Northeast	358 (10)	164 (8)
Mid-Atlantic	652 (17)	363 (18)
Southeast	457 (12)	233 (12)
Gulf South	320 (9)	147 (7)
Heartland	217 (6)	137 (7)
Southwest	358 (10)	192 (10)
Central	569 (15)	296 (15)
Southern California	228 (6)	118 (6)
Golden Gate	87 (2)	61 (3)
Northwest	144 (4)	82 (4)
Overseas	372 (10)	201 (10)
Prescription Service		
MTF Only	1,453 (39)	726 (36)
Low Retail	1,091 (29)	661 (33)
High Retail	1,218 (32)	607 (30)
MSAM Use (in DDDs) <sup>a,b</sup>	3.8 (5.9)	4 (6.3)
Comorbidity (in unique prescriptions) <sup>a,c</sup>	8.7 (6)	9.8 (5.9)
Neurologist Care <sup>c</sup>	660 (18)	441 (22)
Migraine Related Expenditures <sup>a,b,d</sup>		
Definitely Migraine Related Medication	33.84 (68.55)	35.75 (70.77)
Potentially Migraine Related Medication	30.20 (71.80)	36.10 (82.40)
Non Emergent Ambulatory Care	50.63 (92.89)	61.56 (95.94)
Emergency Room Care	10.68 (40.79)	12.44 (41.44)
Total Ambulatory Care	125.35 (175.84)	145.85 (175.20)

MTF, military treatment facility; <sup>a</sup>mean (SD); <sup>b</sup>value reported as per member per month; <sup>c</sup>characteristic determined from pre-treatment interval only; <sup>d</sup>expenditures measured in unadjusted US dollars

study covariates among the matched sample of 1994 patients (Table 2). In addition, the mean predicted probabilities (i.e., the average propensity score) to undergo treatment with daily migraine prevention before matching was reduced to within one percentage point after matching, indicating a high degree of balance among observed characteristics for the two study groups (Table 2).

Table 3 reports utilisation for new and non-users of prevention obtained from the matched sample, with results reported in US dollars. The table compares post-treatment spending (upper half) and the difference between post-treatment and transitional spending (lower half) for each study endpoint. When evaluating post-treatment spending alone, the results showed that new users spent more for migraine-related outpatient care during the post-treatment interval than the matched non-users did (\$534.29, 95% CI \$407.60, \$660.97). The largest differences were observed with non-emergent ambulatory care expenditures followed by spending for potentially and definitely migraine-related prescription medication (Table 3).

Comparing the change in expenditures from the transitional to post-treatment interval suggested that subjects exposed to prevention experienced greater declines in migraine-related outpatient spending than did the reference group of non-users over the same time period (-\$419.28, 95% CI -\$539.39, -\$299.18). This decrease was predominately attributable to a reduction in spending for non-emergent outpatient care (Table 3). Spending on definitely migraine-related prescription medication also decreased at a greater rate among new users of daily migraine prevention compared to the reference group of non-users. The only category of spending that showed evidence of an increase in the treatment group relative to the comparison group was potentially migraine-related prescription medication, but the result was not statistically significant (Table 3).

## Discussion

This study offers additional insight into the association between the initiation of migraine prevention and its effect on ambulatory health care utilisation. The initial assessment of health plan spending suggested that exposure to prevention was associated with higher rates of spending during the post-treatment interval compared to the reference group of migraineurs receiving acute treatment alone. One explanation for this result is that, despite attempts to control for variation in disease severity, undetected differences remained between the two study groups. Current treatment recommendations typically suggest that prevention be reserved for patients with more

debilitating headaches [12, 13]. Use of MSAM provided indirect evidence that this recommendation was being followed during the analysis. New users, on average, received more abortive medication before exposure to prevention than did the reference group of non-users, suggesting that new users also experienced more frequent migraines. Although we matched subjects on baseline use of MSAM, it is unlikely that this variable was able to capture all aspects of migraine disease severity. Thus, residual confounding could explain why subjects exposed to daily migraine prevention experienced higher rates of health care utilisation on average (i.e., new users suffered from greater migraine-related morbidity than did the reference group of non-users).

Based on this conclusion, it seems that exposure to

prevention leads to greater health care utilisation, a counter-intuitive finding if prevention effectively reduces the frequency and severity of migraine headaches. An evaluation of the change in utilisation over time from the transitional to post-treatment period provided more insight into the likelihood of this association [36]. After comparing the change in resource use over time, the results showed that exposure to prevention was associated with greater declines in migraine-related outpatient spending than what might have been expected if the new users had not been exposed to treatment. The biggest changes were observed for non-emergent outpatient care expenditures, followed closely by spending on definitely migraine-related prescription medication. Together, these two categories were responsible for roughly 91% of the

**Table 2** Covariate balance before and after caliper matching on select characteristics

Characteristic	Sample	$X_i$	$X_c$	$d_i$ percent reduction		Sig.
				$d_i$		
Age	Unmatched	34.5	36.4	-16.5		***
	Matched	34.9	34.8	1.0	93.8	ns
Female	Unmatched	0.781	0.827	-11.6		***
	Matched	0.793	0.791	0.5	95.6	ns
Beneficiary Category Active Duty	Unmatched	0.324	0.256	15.2		***
	Matched	0.304	0.311	-1.6	89.8	ns
Prescription Service MTF Only	Unmatched	0.358	0.399	-8.5		**
	Matched	0.368	0.358	2.1	75.7	ns
Low Retail	Unmatched	0.363	0.258	22.7		***
	Matched	0.326	0.339	-2.8	87.5	ns
High Retail	Unmatched	0.280	0.343	-13.7		***
	Matched	0.306	0.303	0.7	95.2	ns
Pre-Treatment Comorbidity	Unmatched	11.069	7.668	55.9		***
	Matched	9.775	9.894	-1.9	96.5	ns
Pre-Treatment Spending (ln)	Unmatched	4.788	4.521	10.2		**
	Matched	4.710	4.767	-2.2	78.6	ns
Pre-Treatment MSAM Use	Unmatched	16.407	15.799	1.4		ns
	Matched	16.323	15.804	1.2	14.6	ns
Neurologist Care	Unmatched	0.288	0.126	40.9		***
	Matched	0.213	0.229	-4	90.1	ns
Propensity Score	Unmatched	0.390	0.267	76.3		***
	Matched	0.341	0.349	-4.6	94	ns

Geographic region and branch of service are not reported in the table but were part of the model specification and balanced after matching.  $d_i$ , standardised percent difference;  $X_i$ , new users covariate mean;  $X_c$ , non-users covariate mean; Sig., statistical significance; ns, not significant. \* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ , determined by a  $t$ -test

**Table 3** Comparison of ambulatory health care spending for matched study cohorts stratified by specification of the dependent variable

Specification of dependent variable	Utilization Estimates			
	New User	Non User	ATT	95% CI <sup>1</sup>
Post-treatment interval spending only				
Definitely migraine related prescription expenditures	266.57	171.82	94.75	54.94, 134.56
Potentially migraine related prescription expenditures	334.74	198.31	136.43	76.56, 196.30
Non-emergent ambulatory care expenditures	447.51	182.99	264.51	191.72, 337.30
Emergency room expenditures	81.08	42.49	38.59	6.69, 70.48
Total migraine related outpatient expenditures	1,129.89	595.61	534.29	407.60, 660.97
Post-treatment and transitional spending difference				
Definitely migraine related prescription expenditures	-87.94	-17.72	-70.22	-110.18, -42.15
Potentially migraine related prescription expenditures	29.03	13.85	15.28	-27.77, 58.33
Non-emergent ambulatory care expenditures	-388.19	-68.71	-319.48	-403.75, -235.23
Emergency room expenditures	-55.74	-16.83	-38.91	-78.51, 0.69
Total migraine related outpatient expenditures	-502.74	-83.46	-419.28	-539.39, -299.18

The measures of effect were calculated from the matched sample ( $N=1994$ ) and measured in unadjusted US dollars. *ATT*, average treatment effect on the treated calculated as the difference between new and non-user utilisation estimates; *Rx*, prescription. <sup>1</sup>95% confidence intervals for the difference were computed using a bootstrap with 250 replications

reduction in health care utilisation.

This conclusion is supported by earlier work arguing that prevention reduces the use of other migraine medications as well as visits to physicians and the emergency room [17]. The results from the current study were able to address some previous criticisms. Incorporating a reference group of non-users matched on all observable characteristics increased the strength of study conclusions to threats against validity [19]. In addition, this study included the costs of daily migraine prevention during the analysis. Despite the differences in methodology, the qualitative conclusions from this and the previous study [17] are very similar.

The seemingly divergent answers reported in this paper can be explained by the treatment of the dependent variable and the type of question addressed. Comparison of post-treatment outcomes only answered the question of whether two identical patients prior to treatment would consume differing amounts of health care after one patient initiated treatment. However, this assumption of equality was unrealistic given the constraints of the observational design. As a result, those exposed to prevention appeared to consume more resources than the reference group. Modelling the change in utilisation over time after the initiation of treatment attempted to adjust for the pre-existing differences. The assumption was that the change in the reference group provided an estimate of the change that would have occurred in the treated group had they not been given treatment. This method can explain why new users were more costly than the reference group but still managed to realise some cost-savings for the health plan

after initiation of daily migraine prevention.

The results from this study should be considered in context of its limitations. First, we were unable to control treatment assignment, which is a common limitation of retrospective claims analyses. As a result, it is possible that the reported treatment effects were due to unobserved characteristics rather than exposure to daily migraine prevention. Another important limitation of the study was the absence of some important explanatory variables known to influence health care utilisation. Where possible, the study employed proxy measures for these unobserved variables. Still, collection of extra data would enhance our understanding of how a patient decides to use health care resources for migraine.

This study excluded indirect costs that are known to be a significant burden in migraine. In addition, generalisability of the study results to populations beyond the Military Health System is another limitation. The descriptive data about subjects with migraine in the military system showed some similarities with previous epidemiological research [37]. However, other unique aspects of military medicine may have influenced the patients' response to migraine prevention. Finally, errors in coding are problematic and difficult to assess in claims data. The assumption was made that military data were accurate because there are penalties for over-reporting care and under-reporting would adversely affect manpower authorisation or revenue in the facilities studied. In addition, several quality checks (i.e., missing or out of range values) were performed during the data analysis to look for any unusual observations. The results suggested that the data were

appropriate for use during the analysis.

In conclusion, the results of this study suggest that exposure to daily migraine prevention did affect ambulatory health care utilisation in the Military Health System compared to a reference group of patients receiving acute migraine treatment alone. Treatment with preventive agents resulted in lower rates of utilisation relative to what new users of prevention would have consumed in the absence of treatment. As a result, the value of prevention appeared to extend beyond just clinical improvement to include economic benefits as well. While the use of prevention remains a patient-specific decision, only a small fraction of migraineurs who could benefit from prevention in the USA are actually receiving it [37]. Increasing the appropriate use of this treat-

ment will require that health care providers take the lead in identification of appropriate candidates for prevention. Furthermore, health plans should encourage candid discussions between health care providers and patients that account for individual preferences and focus on the benefits and risks of preventive treatment. These modest improvements are a first step toward bettering medical care for patients with migraine and increasing appropriate utilisation of daily migraine prevention.

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