Evaluation of a Monthly Coverage Maximum (Drug-Specific Quantity Limit) on the 5-HT₁ Agonists (Triptans) and Dihydroergotamine Nasal Spray

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ABSTRACT

BACKGROUND: Ensuring the appropriate use of migraine therapies is an important consideration for care providers, patients, employers, and managed care organizations (MCOs) because of the high cost of treatment for this fairly prevalent disabling disease. A review of utilization of serotonin 5-HT₁ receptor agonists (triptans) in an MCO determined that about 24% of the patients who received triptan therapy exceeded the manufacturers' recommendations regarding the maximum daily dose and safe treatment guidelines in a 30-day period. An initiative was designed to manage the coverage of migraine abortive therapies with the anticipated outcome of decreasing potential misuse or overuse of the medications.

OBJECTIVE: The objective of this retrospective, observational study was to determine the impact of a monthly drug-specific milligram coverage maximum (quantity limit) on serotonin 5-HT₁ receptor agonists (triptans) and dihydroergotamine (DHE) nasal spray on the utilization and costs of migraine care in an MCO with approximately 600,000 covered members.

METHODS: A longitudinal, retrospective cohort analysis was conducted. All migraine-related services were analyzed, including outpatient medical visits, emergency department utilization, inpatient hospitalizations, and outpatient prescription drug use. The analysis was conducted using medical and pharmacy administrative claims. Analysis of data was performed for the period 12 months prior (October 1999 to September 2000) and 18 months postimplementation of the monthly drug-specific milligram coverage maximum (October 2000 through March 2002).

RESULTS: Imposition of a monthly coverage maximum for migraine-abortive therapies was associated with a 26.1% reduction in overall per-patient-per-month (PPPM) medical costs for migraine care, from \$55.52 PPPM to \$41.02 PPPM ($P<0.01$). Utilization of serotonin 5-HT₁ receptor agonists and DHE nasal spray declined by 16.7%, from 0.18 prescriptions PPPM to 0.15 prescriptions PPPM ($P=0.039$), and direct drug costs declined by 28.8%, from \$29.18 PPPM to \$20.78 PPPM ($P<0.001$). Utilization and costs of outpatient and inpatient migraine-related medical services declined by 40% from \$16.58 PPPM in the preperiod to \$9.94 PPPM in the postperiod ($P<0.001$).

CONCLUSION: A monthly drug-specific milligram coverage maximum was associated with significant reduction in drug costs and utilization of serotonin 5-HT₁ receptor agonists (triptans) and DHE nasal spray. Utilization and costs of migraine-related medical services also declined after implementation of the coverage maximum for triptans and DHE nasal spray. The monthly drug-specific milligram coverage maximum appeared to have been successful in managing utilization of triptans and DHE nasal spray, including reduction of overall costs of migraine-related medical services and direct drug costs.

KEYWORDS: Migraine, Utilization, Costs, Serotonin 5-HT₁ receptor agonists, Quantity limits, Drug therapies, Migraine-related medical services

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Migraine is a fairly prevalent disabling disease resulting in high costs to managed care organizations (MCOs) and employers. The number of migraine patients in the United States in 1999 totaled 27.9 million.¹⁻³ Nearly 75% of all migraine sufferers are women, and it is estimated that 1 out of every 4 households has someone who suffers from migraine headache.¹⁻³ The economic burden of migraine in the United States, including physician visits, tests, pharmacologic therapy, and indirect costs, exceeds \$14 billion annually.⁴ Evaluations of the economic impact have shown the indirect costs of migraine to be considerable.^{4,5}

More than 60% of indirect costs have been attributed to lost work days. In fact, Hu and Markson et al. estimated the annual mean number of missed workdays for men and women with migraine to be 3.8 and 8.3, respectively. The cost of prescription drug therapy has been estimated to comprise 2.1% of the total cost and 30% of the direct treatment cost for migraine.⁴ In 1999, 41% of persons experiencing migraines used prescription drugs as treatment; now, with 7 marketed triptan agents, the percentage has likely increased.⁶

Preventative therapy for migraine is suggested for patients with (1) 2 or more attacks per month producing disability lasting greater than or equal to 3 days, (2) failure of acute therapies, (3) use of abortive therapies more than twice a week, and (4) existence of uncommon migraine conditions.⁷ Historically, only an estimated 3% to 5% of the migraine population is treated with prophylactic therapies.³ Ensuring appropriate management of the patient with a migraine diagnosis and proper use of the chosen drug therapies are important considerations for care providers, patients, employers, and MCOs.

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TABLE 1 Migraine Therapy Quantity-Limit Programs Reported in the Literature

Migraine-related Utilization and Cost Measures	Culley ¹⁵ & Wanovich PPPM*	Lassen et al. ¹⁷ PPPM*	Goldfarb et al. ¹⁶ % change
Triptan Rx's	-0.028	-0.075	-17
Cost of triptans	-\$12.33	-\$21.24	-60.3
Migraineprophylaxis Rx's	+0.768	+0.042	+33.9
Cost of prophylaxis Rx's	-\$0.08	+\$4.62	+49.6
Number of office visits	+3.07	+0.008	+7.8
Cost of office visits	-\$0.16	+\$0.35 per visit	+29.1
Number of ER visits	-0.00095	+0.043	no change†
Cost of ER visits	-\$0.12	+\$21.49 per visit	+56.8†
Other acute pain medication Rx's	-0.610	NA	NA
Other acute pain medication cost	-\$0.32	NA	NA
Migraine-related hospital admissions	+0.0017	NA	+66.7
Cost of migraine-related admissions	+\$1.00	NA	-55
Total change or savings reported	-\$12.25	NA	+1.5

* PPPM=per patient per month.

† Urgent care results listed; emergency department utilization was not reported.

Headache management can be challenging. The complexities of patient care include accurate diagnosis, evaluation of triggers, choice of abortive therapy, and the need for and choice of preventive therapy. Patient education regarding triggers, treatment, prevention, management of rebound headache, and proper medication use is essential. Although numerous educational resources, including specialized Web sites (most sponsored by pharmaceutical manufacturers), are devoted to headache, specialty clinics and managed care-sponsored disease management initiatives specific to headache treatment are few. Overuse of analgesic medications can be a quality concern when managing the patient with a diagnosis of headache and may often be an issue that is overlooked in quantity-limit programs for migraine drugs.

Prevalence data indicate that 85.6% of migraine patients experience 4 or fewer headache occurrences per month.¹ In addition, manufacturers' dosing recommendations for the 5-HT₁ receptor agonists indicate that the safety of treating an average of more than 3 to 4 headaches with these agents in a 30-day period has not been established.⁶⁻¹⁴ MCOs have reported pharmacy cost savings with programs that impose quantity limits on the triptan medications.¹⁵⁻¹⁷ These point-of-service edit programs typically allow for edit overrides after review of clinical information documenting a requirement for doses that exceed program limits.

Pharmacy utilization and cost-outcome measures include

triptan, prophylactic therapies, and acute-pain medications. Medical utilization and cost-outcome measures include primary care physician (PCP) and emergency department or urgent care center visits (Table 1). These quantity-limit programs resulted in cost savings to these health plans. However, other researchers have reported different results. "Lifting of restrictions on triptan usage ..." has been said by one to "produce significant reductions ..." in physician visits and procedures.¹⁸ Another report from the employer perspective found that although triptan restrictions resulted in a total direct medical cost reduction of \$0.38 per patient per month (PPPM), the cost reduction was offset by a loss of 1,830, workday equivalents, which resulted in an additional cost of \$0.47 PPPM.¹⁹

The MCO in the extant study is located in the southeastern United States and is composed of 2 principal lines of business: health maintenance organization (HMO) and preferred provider organization (PPO), covering 600,000 lives (60% HMO and 40% PPO). A preliminary review of triptan medication utilization showed that in the final calendar quarter of 1999, there were 4,714 members (point prevalence=0.78) with a prescription claim for a triptan or dihydroergotamine (DHE) nasal spray; 1,140 (24%) were identified as receiving therapy in a 30-day period that exceeded treatment of 4 headaches per month at the maximum daily dosage. This initial analysis of utilization did not include an evaluation of the use of other analgesics.

In October 2000, based on this preliminary analysis, the health plan MCO designed and implemented a clinical pharmacy initiative to review and analyze, for coverage and payment purposes, the use of migraine medications. The principal intervention that evolved from the initiative placed a monthly drug-specific milligram coverage maximum at community and mail-order pharmacies on triptan medications and DHE nasal spray if prescribed in excess of the manufacturer's recommended specifications for dosages, frequency of use, or duration of administration (Table 2).

Perhaps different from other managed care programs, this MCO coverage maximum initiative and intervention did not allow for medical exceptions or system overrides for additional coverage of medication quantities that exceeded the maximum quantities specified. The initiative was designed to manage the coverage of abortive therapies with the anticipated outcome of decreasing potential misuse or overuse of the medications. At the time of implementation, sumatriptan (Imitrex), rizatriptan (Maxalt), and DHE nasal spray (Migranal) were included on the health plan's preferred medication list (PML, or preferred drug formulary). The triptan medications and DHE nasal spray were not included in a prior-authorization program. No prescription benefit plans included a closed formulary design. All drug benefit plans were based on an open formulary design, and approximately 40% of members were enrolled in a 3-tier copayment structure (lowest copay tier for generic drugs, middle copay tier for brand drugs on the PML, and the third tier for drugs not listed on the PML).

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TABLE 2 Medications Included in the Drug-Specific Milligram Quantity-Limit Intervention

Drug Name and Milligram Strength	Maximum Quantity		Milligram Maximum*	
	Community 30 days	Mail-Order 90 days	Community 30 days	Mail-Order 90 days
Sumatriptan tablets 25 mg	36	108	900 mg	2700 mg
Sumatriptan tablets 50 mg	18	54	900 mg	2700 mg
Sumatriptan tablets 100 mg	9	27	900 mg	2700 mg
Sumatriptan nasal spray 20 mg	9	27	180 mg	540 mg
Sumatriptan nasal spray 5 mg	36	108	180 mg	540 mg
Sumatriptan injectable 6 mg	9	27	54 mg	162 mg
Naratriptan tablets 1 mg	25	75	25 mg	75 mg
Naratriptan tablets 2.5 mg	10	30	25 mg	75 mg
Zolmitriptan tablets 2.5 mg	18	54	45 mg	135 mg
Zolmitriptan tablets 5 mg	9	27	45 mg	135 mg
Rizatriptan tablets 5 mg	24	72	120 mg	360 mg
Rizatriptan tablets 10 mg	12	36	120 mg	360 mg
Almotriptan tablets 6.25 mg	24	72	150 mg	450 mg
Almotriptan tablets 12.5 mg	12	36	150 mg	450 mg
Dihydroergotamine (DHE nasal spray)	1 kit (4 bottles of 4 mg each)	3 kits (12 bottles of 4 mg each)	16 mg	48 mg

* The coverage maximum was milligram-specific for each drug and strength; a maximum was not established for the 5-HT₁ agonist drug category as a whole.

Implementation of the intervention provided the opportunity to study the effects of a drug-specific milligram coverage maximum on the overall utilization and cost of treating migraine patients in this MCO health plan. The goal of the study was to test the hypothesis that the implementation of a monthly drug-specific milligram coverage maximum for selected migraine-abortive drugs would have substantial favorable impact on direct drug cost without an adverse effect on total medical management cost for migraine.

Methods

A longitudinal retrospective cohort analysis of a health care claims database from the MCO was conducted. A total of

30 months of data were observed consisting of 12 months (October 1999 through September 2000) prior to and 18 months (October 2000 through March 2002) postimplementation of the monthly drug-specific milligram coverage maximum. A number of medical utilization and payment measures related to the treatment of migraine were analyzed in this evaluation. All migraine-related services were analyzed, including outpatient medical visits, emergency department (ED) utilization, and inpatient hospitalizations. Assignment to one of these groups was based on place of service, provider type, and ICD-9 coding. ED and inpatient claims were required to have a diagnosis of migraine (ICD-9=346.xx) as the primary diagnosis, located in the first position on the claim to be included in the analysis. Outpatient claims were allowed to have a migraine diagnosis in any diagnosis field on the medical claim. Cost measures for these services were based on the amount of payment to the respective providers from the health plan.

This evaluation included the analysis of outpatient prescription drug utilization and cost. Prescriptions for the following classes of drugs were included: triptans; non-triptans for migraine headache, which were defined as narcotic and non-narcotics analgesics; NSAIDs (including rofecoxib, meloxicam, celecoxib, and valdecoxib); ergotamines (with the nasal spray form of dihydroergotamine analyzed separately); migraine combination products; and prophylactic agents, including beta-blockers, calcium channel blockers, and tricyclic antidepressants. The specific agents included in these analyses are listed in Table 3. Medical and pharmacy claims were adjusted by a general inflation factor of 1.04 per annum.

Patient Inclusion and Exclusion

All members of the commercial HMO and PPO lines of business were included in the initiative, representing a potential eligible population of 600,000 members. Patients were excluded from the intervention if their employer group chose to not participate in the program that imposed the monthly drug-specific milligram coverage maximum for migraine-abortive drugs. Thirteen employer groups made this choice, resulting in an exclusion of 54,000 (9%) members from the intervention and these analyses.

The inclusion criteria for this study were: (1) the patient was a member of an employer group with pharmacy endorsement language that included the drug-specific milligram coverage maximum contract limitation; (2) the patient had at least 1 medical diagnosis of migraine as evidenced by the presence in the medical claims history (outpatient office visits, emergency department visit, or inpatient hospitalization) of ICD-9 of 346.xx or a migraine-related Episode Treatment Group²⁰ of 168 (common migraine), 169 (complicated migraine), or 906.3 (ongoing pharmacy treatment without provider intervention—migraine treatment), in both the preintervention and postintervention periods; and (3) the patient was enrolled at least 6 months prior to and 6 months postimplementation of the

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TABLE 3 Medications Monitored
in the Therapeutic Categories

Triptan Therapy	NSAIDs	Prophylactic Agents
Almotriptan (Axert)	Ibuprofen	Verapamil
Frovatriptan (Frova)	Flurbiprofen	Amitriptyline
Naratriptan (Amerge)	Fenoprofen	Desipramine
Rizatriptan (Maxalt)	Nabumetone	Doxepin
Sumatriptan (Imitrex)	Ketoprofen	Imipramine
Zolmitriptan (Zomig)	Naproxen	Nortriptyline
	Indomethacin	Protriptyline
Ergotamines:	Sulindac	Trimipramine
Dihydroergotamine (DHE)	Tolmetin	Amoxapine
Migranal (nasal DHE)	Meclofenamate	Clomipramine
Ergots, Ergotamine	Etodolac	Carbamazepine
Methysergide	Bromfenac	Divalproex
Ergot combinations	Ketorolac	Felbamate
	Mefenamic acid	Gabapentin
Migraine Combinations	Meloxicam	Lamotrigine
Midrin, etc.	Phenylbutazone	Levetiracetam
	Oxyphenbutazone	Oxycarbazepine
Non-Triptans	Diclofenac	Primidone
Alfentanil	Oxaprozin	Tiagabine
Buprenorphine	Piroxicam	Topiramate
Butalbital	Celecoxib	Valproic Acid
Butorphanol	Rofecoxib	Zonisamide
Codeine		Phenytoin
Dezocine	Prophylactic Agents	Clonazepam
Dihydrocodeine	Acebutolol	Ethosuximide
Fentanyl	Atenolol	Methsuximide
Hydrocodone	Betaxolol	Fosphenytoin
Hydromorphone	Bisoprolol	Trimethadone
Levomethadyl	Carteolol	Phenacemide
Levorphanol	Carvedilol	Mephenytoin
Meperidine	Metoprolol	Diazepam
Methadone	Nadolol	Citalopram
Morphine	Penbutolol	Fluoxetine
Nalbuphine	Pindolol	Fluvoxamine
Oxycodone	Propranolol	Paroxetine
Oxymorphone	Sotalol	Sertraline
Pentazocine	Timolol	Ethotoin
Propoxyphene	Labetalol	
Remifentanil	Amlodipine	
Sufentanil	Bepidil	
Tramadol	Diltiazem	
Salicylates and combinations	Felodipine	
Acetaminophen and combinations	Isradipine	
	Nicardipine	
	Nifedipine	
	Nisoldipine	

required copayment charge.) The final study population of patients, with at least 1 medical claim for migraine and receiving 5-HT₁ receptor agonist or DHE nasal spray therapy, consisted of 6,766 subjects, 1.1% of covered members in this MCO.

Intervention

The drug-specific milligram coverage maximum was implemented as a maximum milligram quantity of medication doses of triptan medications and DHE nasal spray covered for a 1-month time period. The intervention was drug-specific (not drug-class) and milligram-specific. Highlights of the intervention were as follows:

- A per-month maximum milligram quantity coverage limit was placed on specific medications (Table 2).
- The maximum quantity covered was based on FDA and manufacturer dosing recommendations.
- All members, physicians, and pharmacy providers were sent notification via plan newsletters about the pharmacy initiative and maximum quantity-limit intervention (Letters A and B).
- Patients and physicians could receive notification about the drug-specific milligram coverage maximum at the time of prescription dispensing at a dispensing pharmacy. When a prescription was presented at the pharmacy with a quantity that exceeded the maximum coverage, the pharmacist would inform the patient that the prescription quantity exceeded the amount that the health plan would cover and offer the remaining quantity to the patient to be paid by the patient in out-of-pocket costs.
- Patients could (if they desired) purchase the total quantity prescribed by their physician by paying the full cost of the quantity prescribed that exceeded the maximum coverage quantity.
- Claim-system overrides or other medical exceptions were not allowed for medication quantities that exceeded the maximum drug-specific milligram coverage limits per month.

The intervention imposed the drug-specific milligram per month coverage limit across all pharmacy providers, mail-order as well as community pharmacy. Claims for drugs included in the intervention would reject at point-of-service (POS) at the pharmacy. When a pharmacist received a prescription for a triptan or DHE nasal spray and the prescription was entered into the POS system, the claim would pass the eligibility edits and proceed to a Plan File edit (the Plan File contains a description of benefits such as covered drugs, days supply limits, and coverage maximums). Prior claim history was used to trigger the coverage evaluation process.

Drug-specific milligram quantity allowances were determined according to a preset rolling "time period" of 29 days at retail or 67 days at mail-order. The 67-day time period at mail-order was established to allow the member time to mail the prescription, prescription processing by the mail-order pharmacy, and return mail of the drug to the patient. If a prescription

coverage maximum intervention.

After applying the aforementioned exclusion and inclusion criteria, the study population consisted of 21,233 subjects. Patients with total paid amounts of less than \$1 of pharmacy costs in either the preindex or postindex periods were also excluded from the analysis, resulting in an exclusion of 14,467 (68%) patients. (This could occur, for instance, in cases where patients had prescriptions filled that had a cost very close to the

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LETTER A Physician Notification: MCO Physician Newsletter—"Blueline"

Pharmacy Benefit Initiative: Migraine Medications

Medications have a potential to cause harm and result in increased health care costs if used in excess or incorrectly.

Blue Cross and Blue Shield of Florida and Health Options are introducing *Responsible Rx*, a new quality improvement initiative that focuses on the maximum recommended dosage of specific medications. This initiative, which begins September 5, 2000, may help to assist patients by educating them on the use of certain drugs.

Initially, only five medications used in the treatment of migraines will be affected. *Responsible Rx* places a monthly coverage limit on the quantity of these medications. The maximum monthly quantities covered for the specific drugs included in this initiative are based on the manufacturer's recommended dosage and duration of therapy approved by the Food and Drug Administration (FDA) or supported by clinical literature.

It is anticipated that physicians will gain valuable information about the quantity of medications used during a month that may be useful in future patient management decisions for persons afflicted with migraines. Additional drug classes may be added to *Responsible Rx* in the future.

Components of *Responsible Rx*:

- A pre-set maximum quantity for coverage will be placed on some drugs dispensed per month. (Greater quantities can be prescribed and dispensed within one month; however, coverage will not be available.)
- Your Blue Cross and Blue Shield of Florida and Health Options patients will have prescription drug coverage for a pre-set maximum for one copayment per month.
- Members' pharmacists are aware of this initiative and will inform your patients if it applies to their prescriptions.

Drugs with Pre-set Maximum Coverage Quantities

Drug Brand Name	Dose and Pre-set Maximum Coverage Quantity
Imitrex	25 mg=36 tablets; 50 mg=18 tablets; Nasal spray=9 inhalers; Injectable=4 kits (8 syringes)
Amerge	1 mg=25 tablets; 2.5 mg=10 tablets
Zomig	2.5 mg=18 tablets; 5 mg=9 tablets
Maxalt, Maxalt MLT	5 mg=24 tablets; 10 mg=12 tablets
Migranal	1 kit (4 bottles)

claim exceeded the specific milligram maximum quantity for the medication for the rolling time period, the POS system would return a message ("Plan Limits Exceeded") to the pharmacist that required the pharmacist to reverse the original claim and resubmit it for the allowed quantity. For example, if a member attempted to fill 25 mg of naratriptan on April 2, 2003, but had previously filled 25 mg naratriptan on March 5, 2003 (28 days earlier), the claim would be rejected; the patient would need to wait until day 29 (April 3, 2003) or after for the claim to be processed for the new prescription. Similarly, if 75 mg of naratriptan was requested to be filled at mail-order on April 2, 2003, and naratriptan had been filled at mail-order on or after January 26, 2003 (66 days), the claim would be rejected; the patient would have to wait until April 3, 2003 (67 days later) or after, for the claim to be processed and covered.

LETTER B Patient Notification: Member Newsletter—"Florida Blue"

For Your Good Health

Coverage Maximums on Some Drugs Begin

If used in excess or incorrectly, medications are potentially harmful. *Responsible Rx*, a new program launched September 5, 2000, affects the maximum quantity of a medicine that will be covered in a 30-day period.

Responsible Rx currently includes five medicines prescribed for migraine headaches. Under this program, your plan will cover quantities of medication based on dosing guidelines established by the manufacturer of the medication and approved by the Food and Drug Administration. The quantities cover a typical course of treatment or therapy. You may fill or refill a prescription up to the quantity covered by one copayment each month. Amounts prescribed over the maximum may be filled but will not be covered under plan benefits.

The drugs currently covered under the *Responsible Rx* program are: Imitrex, Amerge, Zomig, Maxalt or Maxalt MLT, and Migranal. Other drugs for various conditions may be added in the future.

Your doctors and pharmacists have been informed of the program. We believe *Responsible Rx* may offer health care providers and patients valuable information about the quantity of medications used during a month. If you have any questions about the program, please feel free to speak to your doctor or pharmacist, or call the customer service number on your ID card.

Outcome Measures

A number of cost and utilization measures were used to observe outcomes in the study population over the entire study period and in comparing preintervention to postintervention periods. The following *utilization* measures PPPM were employed: (1) number of prescriptions, (2) quantity [units] dispensed, (3) days supply, (4) medical office visits, (5) emergency room visits, and (6) inpatient hospitalizations. The *financial* measures PPPM included payments for (7) prescription drugs, (8) total migraine-related prescription care, (9) medical visits, (10) emergency room visits, (11) inpatient hospitalization, (12) total migraine-related medical services, and (13) total migraine-related care. Total migraine-related prescription care was the calculated cost PPPM based on the sum of all prescription drugs used to treat migraine (Table 3).

The drug cost was based on the "amount paid" field on the prescription claim record and was defined as the total amount paid to the pharmacy (average wholesale price [AWP] per metric unit x quantity [metric units] dispensed less the contractual discount [with the pharmacy] + dispensing fee - patient copay = amount paid). All financial measures (such as those analyzed related to medical utilization) were based on plan-paid amounts, defined as the amount paid by the health plan to the respective providers, after subtraction of the patient copayment or other applicable cost share.

Statistical Analysis

The goal of the study was to test the null hypotheses that the implementation of a monthly drug-specific milligram coverage maximum for selected migraine-abortive drugs would have no

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TABLE 4 Characteristics of Migraine Patients

Age	N	%
0-18 years	286	4.2
19-34 years	1,322	19.5
35-44 years	1,949	28.8
45-54 years	1,712	25.3
55-64 years	632	9.3
65+years	865	12.8
Total	6,766	
Gender		
Female	5,484	81.1
Male	1,282	18.9

FIGURE 1 Number of Triptan Prescriptions Per Patient Per Month

FIGURE 2 Number of Prescriptions Per Patient Per Month

impact on direct drug costs for migraine therapy or total medical care costs. The alternative hypothesis was that the intervention would have a significant effect on direct drug cost and total medical care costs for members with migraine. Because claims data were used to obtain cost information, total costs did not include patient copayments, coinsurance, deductibles, or negotiated discounts with providers. Therefore, the total (health plan) paid amount from claims data served as a proxy for the actual total cost of migraine care.

Due to the skewed nature of the data (i.e., having variance that increases with the mean), the treatment differences in paid amounts and utilization counts were estimated using a generalized linear model (GLM) with a log-link function and gamma and negative-binomial distributions, respectively.²¹ Because patients may not be observed for equal amounts of time, the length of follow-up for each patient in each period was included in the models as an offset variable. Since total paid amounts for the preintervention and postintervention periods for each patient tend to be correlated, Generalized Estimating Equations (GEE) with compound symmetry of variance-covariance matrix was applied to account for these correlations.²² GEE was developed as an extension of the GLM to accommodate correlated data and is widely used by researchers in a number of fields.

A dummy variable (1=postperiod, 0=preperiod) was introduced to the models to estimate the effect of implementation of the quantity-limit intervention. All models were adjusted for age and sex. Due to the strong nonlinear relationship between age and total paid amount, the age variable was transformed into 5 dummy variables corresponding, respectively, to the following 5 age groups: ≤30, 31 to 40, 41 to 50, 51 to 60, and >60 years. In addition, the impact of disease severity, captured in terms of comorbidity, was assessed by adding the Charlson Comorbidity Index (CCI) as an independent predictor to the models.²³ The CCI assigns weights for a number of major conditions present among secondary diagnoses. The index score is the total of assigned weights and represents a measure of the burden of comorbid diseases. CCI was used to ensure that the population carried the same illness burden in the preperiod and postperiod.

The analyses of costs and utilization of specific migraine-related medical services such as management (professional [physician] component of claims including physician office visits), facility, surgical, office visits, and pharmacy were complicated by the fact that a significant number of patients incurred no costs for particular services within the period. For this reason, 2-part models were employed to estimate the total paid amount for each service group. First, logistic regression was used to estimate the probability of incurring some costs or utilization within a specific time period (preperiod and postperiod), given the aforementioned independent predictors.²⁴ Second, a generalized linear model with log-link function and gamma distribution (costs) or negative binomial distribution (utilization) was used to estimate the treatment differences, conditional on incurring any costs or utilization for migraine and

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pharmacy services and prescriptions. The expected values were then calculated by multiplying these 2 estimates together.²⁴ Due to the correlation of the data in the preperiod and postperiod for each patient, the GEE method was used in both stages of the 2-part model.

In all models, interactions between covariates (age, gender, CCI) were evaluated and found to be nonsignificant. A 2-sided *P* value of <0.05 was considered to indicate statistical significance. All analyses were performed using the UNIX-based SAS v.8.2 software system.²⁵

Results

A total of 6,766 patients (1.1% of eligible health plan members) met the criteria for inclusion in the study. All migraine-related health care claims for these patients, preintervention and postintervention, were reviewed and analyzed. Patient characteristics are shown in Table 4. During the study period, total enrollment in the MCO remained stable, with a mean of 602,892 members (SD=38,563). The number of patients eligible for inclusion in the study who utilized services each month remained fairly constant at 4,863 (SD=293). The majority (81%, n=5,484) of patients were female, which is perhaps slightly higher than national estimates (75%).² In the study population, 54% (n=3,661) were between the ages of 35 and 54 years; 4% (n=286) were under age 18 years, and nearly 13% (n=865) were 65 years or older.

The number of prescriptions PPPM for triptans and all non-triptans (narcotic and nonnarcotic analgesics) was steadily increasing in this MCO between October 1999 and September 2000, the preintervention period (Figures 1 and 2). From October 2000 through March 2002, the postintervention period, utilization of these 2 groups of medications began to steadily decline. As of March 2002, the rate of prescription utilization PPPM for these groups of medications was below the lowest levels seen at any time during the preintervention period.

Similar findings were evident when analyzing utilization by means of quantity, or units, PPPM (Figure 3). Utilization of the drugs included in the quantity-limit intervention, as measured by days of drug therapy supplied, indicated a consistent rise in the 12 months prior to implementation. Postimplementation, this days supply utilization measure decreased in retail prescriptions and increased in the mail-order pharmacy component. Overall, postimplementation, the days of therapy supplied of triptans and DHE nasal spray remained stable (Figure 4).

Table 5 depicts the aggregate utilization and cost measures preimplementation (12 months) and postimplementation (18 months) of the monthly drug-specific milligram coverage maximum for the 6,766 patients identified. The intervention resulted in a reduction in utilization of the agents included in the monthly coverage maximum (triptans and dihydroergotamine nasal spray) from 0.18 prescriptions PPPM in the preperiod to 0.15 prescriptions PPPM in the postperiod (*P*=0.039). During the postintervention evaluation period, there were also

FIGURE 3 Quantity (Units) Dispensed Per Patient Per Month

FIGURE 4 Days Supplied Per Patient Per Month

fewer prescriptions dispensed for migraine combination products, ergotamines, and non-triptan agents (Table 5).

The analysis of payments PPPM for the prescription drug measures showed a significant decline in the postintervention period for the triptan agents and DHE nasal spray (\$29.18 versus \$20.78, *P*<0.001). The decline began in September 2000 at the time of member notification about the initiative (Figure 5). The decline in payments for the medications included in the drug-specific milligram coverage maximum initiative resulted in a decrease in the total migraine-related prescription care PPPM (\$38.95 versus \$31.08, *P*<0.001).

The utilization of migraine-related outpatient office visits fell steadily after the implementation of the drug-specific milligram coverage maximum initiative (Figure 6). Outpatient office visit PPPM utilization fell postimplementation (0.08 PPPM versus 0.05 PPPM, *P*<0.001). Migraine-related ED visits also declined (0.012 PPPM versus 0.009 PPPM, *P*=0.013) as did inpatient hospitalizations (0.0014 PPPM versus 0.0007 PPPM, *P*<0.001).

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TABLE 5 Utilization and Cost Measures for Preimplementation and Postimplementation of the Monthly Drug-Specific Milligram Quantity Limit

Measures	Drug Payments PPPM*			# of Rxs PPPM*		
	Pre	Post	P value	Pre	Post	P value
Triptans + DHE nasal spray†	\$29.18	\$20.78	<0.001	0.18	0.15	0.039
Migraine combos	\$ 0.24	\$ 0.18	0.085	0.04	0.03	<0.001
Ergotamines	\$ 0.34	\$ 0.25	0.480	0.01	0.00	0.006
Non-Triptans	\$ 5.61	\$ 6.07	<0.001	0.34	0.28	<0.001
NSAIDs	\$ 0.45	\$ 0.48	0.739	0.02	0.02	0.632
Prophylactic agents	\$ 3.13	\$ 3.33	0.221	0.10	0.09	0.617
Migraine-related Rx care	\$38.95	\$31.08	<0.001			
Measures	Medical Payments PPPM*			Visits PPPM*		
	Pre	Post	P value	Pre	Post	P value
Outpatient office visit	\$15.41	\$ 9.32	<0.001	0.08	0.05	<0.001
Emergency room visit	\$ 0.02	\$ 0.01	0.269	0.012	0.009	0.013
Inpatient hospitalization	\$ 1.15	\$ 0.62	<0.001	0.0014	0.0007	<0.001
Migraine-related medical care	\$16.58	\$ 9.94	<0.001			
Total migraine-related care	\$55.52	\$41.02	<0.001			

* PPPM = per patient per month.

† dihydroergotamine nasal spray (DHE nasal spray).

Note: Payments were obtained for preperiods and postperiods from claims for the drugs and services listed. Total costs in each period were calculated per patient per month (PPPM). Total patient months preimplementation=12; postimplementation=18. The same patients were followed pre and post; N=6,766.

The analysis of medical service payments showed a significant decrease in office visit payments (\$15.41 PPPM versus \$9.32 PPPM, $P<0.001$) and inpatient visit payments (\$1.15 PPPM versus \$0.62 PPPM, $P<0.001$) (Figure 7). A slight decrease was noted in emergency department payments. Total migraine-related medical service payments PPPM declined over the 18-month postintervention period (\$16.58 versus \$9.94, $P<0.001$) (Table 5). Finally, the decreases in payments PPPM for migraine medications coupled with the decreases in medical management payments over the 18-month period (Figure 8), contributed to significant reduction in total migraine-related care payments PPPM (\$55.52 versus \$41.02, $P<0.001$).

Discussion

This 660,000-member MCO located in the southeastern United States implemented a monthly drug-specific milligram coverage maximum (quantity limit) for triptan agents and DHE nasal spray in an effort to encourage patients and prescribers to review therapeutic goals and management strategies for migraine. The utilization of the triptan agents and other pain therapies in the migraine population was increasing prior to implementation of the quantity-limit intervention, and potential misuse of the triptan medications, in particular, was presumed as the quantity of units dispensed per month increased.

The MCO health plan desired to measure the impact of imposition of the drug-specific milligram coverage maximum on the cost and utilization of migraine-abortive therapies, alter-

nate medication use, physician visits, or ED visits. All medication categories related to migraine therapy decreased in the number of prescriptions PPPM after imposition of the quantity limit. Only the measures of triptan prescriptions PPPM and days supplied obtained at mail order increased (Figures 1 and 4). These findings were likely the result of an increase in the number of contracts containing a mail-order pharmacy option and the realization by some health plan members of the ability to obtain a greater quantity of migraine medication in 1 prescription fill (i.e., 3-month quantity; 90-day supply). The rise in the total days supplied for triptan medications overall was fueled by the increase in days supplied in the mail-order environment. Although days supply was evaluated, it was felt to be a poor measure of utilization for this drug category due to the variability in the value entered at POS in the days supply field on the prescription claim for drugs that are acute therapies and often prescribed to be used "as needed."

Utilization of serotonin 5-HT₁ receptor agonists and DHE nasal spray declined by 16.7%, and the costs for these agents declined by 28.8%. The relative cost of the drugs included in the quantity-limit intervention during the preimplementation period (triptans and DHE nasal spray) among total migraine-related drug costs was 74.9%; that percentage declined in the postimplementation period to a share of 66.8%. Importantly, the decline in utilization of the abortive agents included in the quantity-limit intervention was not associated with an increase in the number of prescriptions PPPM for migraine prophylaxis

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agents or migraine combination therapies. In fact, utilization decreased in all drug categories, and there were no increases in any other medication category. This evaluation did not measure the utilization of alternative therapies such as over-the-counter (OTC) analgesics that could have increased during the postimplementation period. Changes in utilization of OTC therapies could not be measured using available prescription claims data.

The decrease in prescription utilization was accompanied by reductions in payments for triptans and DHE nasal spray that resulted in a reduction in total payments for prescription drugs. In the 18 months following implementation of the quantity-limit intervention, the only other significant change in medication-related payments was found in an increase in payments PPPM for the "non-triptan" agents, which included largely the narcotic analgesic medications. This finding may have been due to a change in utilization favoring some popular and costly therapies in the narcotic medication category such as long-acting oxycodone products. There was no increase in either the payments for nonsteroidal anti-inflammatory agents (\$0.45 PPPM versus \$0.48 PPPM, $P=0.739$) or payments for drugs for migraine prophylaxis (\$3.13 PPPM versus \$3.33 PPPM, $P=0.221$).

These findings contrast with other studies that reported increases in migraine prophylaxis prescriptions PPPM after implementation of a quantity-limit program.¹⁶⁻¹⁸ The previously reported programs included medical exception opportunities through prior-authorization procedures. A prior-authorization process offers the opportunity for interactions between clinicians that could have an impact (potential increase) on the prescribing of migraine prophylaxis therapy. Our quantity-limit intervention did not allow for overrides of quantity maximums, and no clinical interaction with prescribers took place to encourage the prescribing of migraine-prophylaxis therapy. Changes in prescription drug copayments and expansion of 3-tier prescription benefits in response to the rising cost and utilization of prescription drugs were common in the MCO health plan at the end of 2000 and in 2001. These changes could have impacted the utilization of medications monitored in this analysis; however, overall, utilization as measured by prescriptions PPPM for this health plan during the 30-month evaluation period increased by 11.8%, from 0.657 prescriptions PPPM to 0.734 prescriptions PPPM (data not presented here).

The reductions in prescription utilization and costs for these migraine patients subject to the drug-specific milligram quantity limit were not associated with an increase in utilization or costs in medical claims. Outpatient office visit utilization was the largest component of all medical service utilization measures (Figure 8), and in October 1999, the rate of outpatient office visit utilization for migraine was 0.41 PPPM. By September 2000, outpatient office visits for migraine had risen to 0.81 visits PPPM. Just after implementation of the quantity-limit intervention, the outpatient office visit utilization rate fell to 0.44 by December 2000, a rate similar to that observed in

FIGURE 5 Average Triptan Payments Per Patient Per Month

FIGURE 6 Medical Service Utilization Per Patient Per Month

FIGURE 7 Average Medical Payments Per Patient Per Month

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FIGURE 8 Total Migraine Payments Per Patient Per Month

October 1999, in the preimplementation period. By the end of the postimplementation period, the utilization rate appeared to stabilize at approximately 0.3 outpatient medical office visits PPPM. ED utilization also declined in the 18 months postimplementation. There were no significant medical service utilization management programs implemented by this MCO health plan during this time period that had the potential to mask an increase in utilization of services by the patient population. However, the implementation of this quantity-limit intervention occurred coincident to a change in physician reimbursement, from capitation to fee-for-service, that was expected to result in a measurable increase in physician office visits. The decrease in medical utilization is therefore difficult to explain and would appear to be fairly robust given the coincident change in physician reimbursement. Overall, migraine-related medical service utilization declined by 37% and payments to medical providers declined by 40% during the postintervention period. There was a significant reduction (26.1%) in overall payments associated with migraine care PPPM.

The impact of quantity-limit interventions for migraine abortive drugs on prescription and medical service utilization have been previously reported to be associated with overall cost reductions due to decreases in utilization and direct drug cost of triptans. These cost reductions in triptans observed by others were often associated with increases in physician office visits and, in some cases, inpatient hospitalizations or ED visits. Our analysis found significant decreases in all medical service utilization, all categories of drug utilization, total migraine-related services (either medical or pharmacy), and in payments for triptans and DHE nasal spray during the 18-month measurement period following implementation of the quantity-limit intervention for triptans and DHE nasal spray.

Limitations

This study had several limitations. The monthly drug-specific milligram coverage maximum was not inclusive of all abortive therapies for the treatment of migraine. For example, butorphanol spray is sometimes used for the treatment of acute migraine. It is indicated for the treatment of pain syndromes other than migraine, and the dosage maximum is unclear, making it difficult to assign a 1-month drug-specific milligram coverage limit. In addition, since this intervention did not include prior-authorization criteria, indications for the use of an agent like butorphanol could not be considered. Finally, establishment of the quantity-limit intervention as a drug-specific milligram amount, and not drug class-specific, could have permitted patients to obtain multiple triptan therapies to circumvent the coverage maximums. This analysis was not constructed to determine use of duplicative therapies within the triptan or other therapeutic classes.

Another limitation was the inclusion of only administrative claims data to determine diagnoses and to serve as principal measures of utilization and cost. Therefore, prescription quantities for triptans and DHE nasal spray that exceeded the monthly drug-specific milligram coverage maximums (i.e., paid for in cash by health plan members) were not measured. This data source does not include analgesics and other medications purchased OTC. In addition, the clinical severity of the patient's migraine, level of disability, and other variables such as weight, smoking habits, and race are not recorded in medical and pharmacy claims data and thus were unavailable for analysis. The exclusive use of claims data also did not permit an evaluation of clinical outcomes such as work performance, absenteeism, quality of life, and other migraine-related, disease-related measures that could have been impacted by the monthly drug-specific milligram coverage maximums in this intervention.

This study included analysis of the payments for migraine-related care and did not examine other factors that may have had an impact on the total cost of health care in this population of patients identified by medical claims with diagnostic codes for migraine. For example, there could have been an association between use of larger quantities of abortive therapies and adverse effects prior to the implementation of the monthly coverage maximum, which could have contributed to higher preinitiative medical visits. The cost impact of the quantity-limit intervention on patient use of OTC analgesic or other alternate therapies also was not measured. In addition, during the 30-month study period, there were changes made in payment structures and reimbursement agreements with providers (for example, the payment structure for primary care physicians was changed from a capitation to fee-for-service reimbursement) that may have had an impact (upward or downward) on the health care costs of managing these specific patients. This analysis was not expressly designed to explore these possibilities, and analysis of the impact of payment structure changes was not finalized at the time of preparation of this manuscript.

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This was a longitudinal preanalysis and postanalysis that included no control group. Use of the same patient population in the preperiods and postperiods allowed the patients to serve as their own controls, decreasing prevariability and postvariability. Culley and Wanovich reported the impact of a quantity-limit program using a preintervention and postintervention evaluation, but no statistical analysis was reported; that study did not involve a single cohort, and the groups in the preperiods and postperiods were not comparable.¹⁶ Goldfarb et al. analyzed the effect of a triptan quantity-limit program in a retrospective claims evaluation, but these authors did not report statistical significance for the impact of the intervention.¹⁷ Our evaluation found significant predifferences and postdifferences in many of the outcome measures reported.

Lastly, the total clinical and economic significance of the decrease in utilization of the migraine medications in the absence of an increase in medical utilization is not known. This evaluation did not include an examination of cost-effectiveness or the cost of changes in work performance, productivity, or absenteeism.

Conclusion

A monthly, drug-specific milligram coverage maximum (quantity limit) on the triptan medications and DHE nasal spray was associated with a significant reduction in costs and utilization of abortive agents for migraine. The relative cost of the drugs included in the quantity-limit intervention (triptans and DHE nasal spray) declined from 74.9% of all migraine-related drug therapy to 66.9% after implementation of the quantity limits. Migraine-related medical services in the outpatient and inpatient service areas decreased when compared to the 12-month period prior to implementation of the quantity-limit intervention. Overall, the quantity-limit intervention appeared to have been successful in managing apparent overutilization of triptans and DHE nasal spray.

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