Adherence to Oral Migraine Prophylaxis Medications in Patients with Chronic Migraine

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BACKGROUND

Migraine is an episodic neurological disorder that affects 12% of Americans and millions worldwide.[1] Prevalence peaks between the ages of 25 and 55 and is approximately three times more common in women.[2] Frequency and severity of headaches are used to classify two main subtypes of migraine: episodic and chronic. Although there is some disagreement among experts as to the exact definition of chronic migraine, the revised 2nd Edition of the International Classification of Headache Disorders (ICHD-2R) is the most often cited.[3,4,5] ICHD-2R defines chronic migraine (CM) as ≥15 headache days per month with ≥8 days per month that meet criteria for migraine, for more than three months, with each episode lasting greater than four hours. Episodic migraine has been generally characterized by the presence of migraine headaches on 0 to 14 days per month. Estimates of CM range from 1.4% to 2.2% among adults worldwide and approximately one out of 100 adults in the US.[6] CM is a disabling disorder that has been shown to significantly reduce quality of life and leaves many patients unable to perform daily activities.[7,8] It has also been associated with significant resource utilization including increased healthcare provider visits, emergency department visits, and diagnostic testing.[9,10]

Patients with frequent headaches, such as those suffering from CM, may benefit from prophylactic treatment. Guidelines drafted by the United States Headache Consortium recommend first line prophylaxis with propranolol, timolol, amitriptyline, or divalproex.[11] In the US only onabotulinumtoxinA is indicated for the treatment of CM.[12,13] Oral prophylactic agents require adherence to various dosing regimens in order to adequately reduce the burden of migraine. Adherence has been identified as a significant health problem in the US and it is estimated that non-adherence is associated with over $290 billion in additional health care costs per year.[14] The lack of adherence has been well established in a variety of chronic conditions.[15] Non-adherence has been linked with poor health outcomes in

hypercholesterolemia, hypertension, intestinal disease, and sleep disorders.[16] It is a significant public health problem that affects the health of Americans and significantly burdens the US healthcare system.

Although adherence has been well studied among migraine patients, only one study has investigated adherence using claims databases in this population.[17,18,19,20] Using data from 2003-2005, Berger et al investigated adherence to migraine prophylaxis medications in a large claims database that included over 1.6 million privately insured individuals.[20] At the time of that study claims data did not distinguish between chronic and episodic migraine diagnoses. This database, known today as the Truven Health MarketScan® Databases, has been updated and expanded yearly to now include more specific claims data on over 40 million covered lives per year. To date, no study has examined adherence to prophylactic therapy among the chronic migraine population using real world data from large claims databases such as MarketScan.

OBJECTIVE

The aim of this study is to describe the chronic migraine population through a large US insurance claims database from 2008 to 2011 and to assess adherence, switching, and resource use among patients taking oral migraine prophylactics.

METHODS

Data Source

Data were obtained from MarketScan® Research Databases, which contain inpatient, outpatient, and pharmacy claims for patients covered by commercial, Medicare, and Medicaid insurance plans in the US. The inpatient and outpatient claims database includes details from medical claims such as International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes, Current Procedural Terminology (CPT) codes, dates of service, and various financial billing information. The pharmacy claims

database provides the National Drug Code (NDC) and generic identifier (ID) of the drug dispensed, date dispensed, quantity and days' supply, channel of dispensing (mail order vs. retail), and copayment information for each claim. A separate eligibility file provides additional information about each subject such as age, gender, plan type, employment status, comorbidities, geographic location, and dates of enrollment.

All patient-level data are encrypted to protect patient privacy, and compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) is ensured by the data administrator - Truven Health Analytics.[21] Because of these protections, and the fact that the dataset was created by an analyst who did not serve as an investigator on the project, the University of Washington Human Subjects Division Institutional Review Board (IRB) determined that the study protocol did not meet the federal definition of "human subjects research" and thus did not require IRB review and approval.

Sample Selection

Inclusion criteria: To create the analytic dataset, both commercial and Medicare supplemental claims databases were queried for patients 18 years and older who were diagnosed with CM and who initiated an oral migraine prophylactic agent between January 1, 2008 and December 31, 2011. The beginning of the look back period was chosen because, in 2008, a separate ICD-9-CM diagnosis code was established and added for chronic migraine (346.7) as part of a sub classification within the migraine diagnosis.[22] The index date was established by the appearance of the first pharmacy claim for an oral prophylactic medication filled after the diagnosis of CM. Drugs included in the analysis were those representative of the three main classes of medications used in migraine prophylaxis: antidepressants (amitriptyline, nortriptyline, citalopram, escitalopram, sertraline, fluoxetine, paroxetine), beta blockers (propranolol, metoprolol, nadolol, atenolol), and anti-seizure (gabapentin, topiramate, divalproex) medications.

Exclusion criteria: Patients taking more than one prophylactic agent on the index date or patients who did not have continuous enrollment for six months prior to the index date, and 6 or 12 months post index date, were excluded from the analysis. The medications of interest in this analysis may also be used to treat chronic conditions other than migraine. In an effort to limit the analysis to only those patients taking the prophylactic medication for migraine prophylaxis, we excluded patients whose first pharmacy claim for a beta blocker was within 6 or 12 months after a diagnosis of congestive heart failure (ICD-9-CM 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.10, and 404.XX) or hypertension (ICD-9-CM 401.XX, and 405.XX), whose first pharmacy claim for an antidepressant was within 6 or 12 months after a diagnosis of depression (ICD-9-CM 290.21, 292.84, 296.XX, 298.0, 300.4, 309.0, 309.1, 311.0); or whose first pharmacy claim for an anti-seizure medication was within 90 days of a seizure diagnosis (ICD-9-CM 345.XX).

Adherence

Adherence is defined as the extent to which a patient follows prescribed directions with respect to timing, dose, and frequency of a medication.[23,24] There are a variety of ways to measure adherence including biological assays, pill counts, electronic monitoring, claims data analysis, or patient-reports using surveys or interviews.[25] Claims database analyses are one of the most commonly used methods, due to the capability of conducting large studies quickly, and at relatively low cost.[26] There has been some debate about the most appropriate method for calculating adherence from claims databases. The most commonly cited method uses a metric called the medication possession ratio (MPR), which is calculated from the sum of the number of days' supply dispensed divided by the total number of days in the follow-up period.[27] This method tends to over-estimate adherence because it does not correct for double counting of overlapping days that occurs when medications are refilled early.[28] An alternative to MPR is to calculate the proportion of days covered (PDC), which uses the total number of days that a

drug is available to the patient, rather than the day's supply.[29] PDC is perhaps a more accurate method for calculating adherence because it does not allow for the double counting that occurs with MPR calculations. Cut-points for adherence using MPR and PDC are arbitrary; however, current evidence points to 80% as an optimal cut-point for either of these methods.[30]

Adherence to migraine prophylactic agents among the CM patient population were calculated with both MPR and PDC. Using the formula for each method in turn, follow-up time periods of 6 and 12 months (183 and 365 days respectively) were used in the denominator of two separate analyses:

$$\text{MPR} = (\text{total \# of days' supply}) / (\text{follow-up period})$$

$$\text{PDC} = (\text{total \# of days drug is available}) / (\text{follow-up period})$$

Claims with days' supply of zero were excluded. The last fill's days' supply was adjusted to include only the days up to the end of the follow-up. Due to overlapping days' supplies, MPR calculations may generate values higher than 1. For cases where MPR was greater than 1, we truncated the values at 1. Adherence rates were reported as the proportion of patients who have at least 80% MPR or PDC at 6 and 12 months, stratified by each medication. Adherence rates were compared among the prophylactic medications and demographics were evaluated among both adherent and non-adherent groups.

Switching

The date of discontinuation was identified as the day the patient was to run out of their medication based on the days' supply of the last pharmacy claim for that medication. Discontinuation was defined by a minimum of 60-day gap between two consecutive pharmacy claims for the initial prophylactic agent. Switching was defined to occur when a patient discontinued one prophylactic and, within a pre-specified time frame, started another medication for the same indication. Switch rate was reported as the proportion of patients for whom was recorded a pharmacy claim for one of the 13 medications of

interest within 30 days prior to or 60 days post discontinuation of the initial prophylactic. Results are presented for both 6 and 12 months of follow-up and stratified by the initial prophylactic medication.

Resource Utilization

Emergency room (ER) visits are readily available from medical claims data and were thus used as the measure of resource utilization. ER visits with a primary diagnosis of migraine (ICD-9-CM code 346.XX) were summed for each patient during the 6 and 12 month follow-up periods. Results were reported as the proportion of patients with one or more ER visits for migraine stratified by prophylactic medication and adherence rates (both MPR and PDC). ER utilization was compared among adherent and non-adherent patients for each prophylactic medication using logistic regression.

Statistical Analysis

This is an exploratory analysis and thus no hypothesis testing was conducted. Descriptive statistics were used to characterize each variable of interest; means and standard deviations for continuous variables and proportions for categorical variables.

Bivariate analyses were conducted to compare patient demographics among patients taking each medication; and separately between patients who were and were not adherent. T-tests and chi-2 tests were used to estimate means and standard deviations for continuous data and or proportions for categorical variables, respectively. Unadjusted and adjusted comparisons were made using logistic regression models for adherence and ER visits. The dependent variable was adherence (MPR or PDC ≥80%) or ER visits (≥1 visit during follow-up). The primary independent variable was the type of prophylactic medication specified in the claims data. Decisions about which covariates to include were made using clinical, epidemiological, and statistical methods. Each covariate was evaluated for its potential as a confounder, effect modifier or precision variable. Bivariate comparisons between each

potential covariate and each medication of interest were made; a p-value of 0.1 was used to determine which of these were included in the regression models. Due to repeat testing during regression modeling, a Bonferroni correction was used to calculate a suitable alpha level. The correction indicated a significance level of 0.004 and thus an alpha level of 0.01 (99% confidence intervals) was chosen for each of the analyses. Analyses were conducted using STATA 12 (College Station, TX).[31]

Rates of switching were characterized using descriptive statistics. The proportion of patients who switched from the first prophylactic medication to a second prophylactic during the study period were reported and the results were stratified by the initial prophylactic. Although there was no time-to-discontinuation data available we were able to use the index date of the first prophylactic and the date of initiation of the second prophylactic to calculate a time-to-switch variable. This new variable was used to generate Kaplan-Meier (KM) curves and Cox Proportional Hazards (PH) models, which were used to analyze time-to-switching among those who had a switch during the 6 or 12 month follow-up. KM curves estimate time to switching using a log-rank test, and Cox PH models generate estimates of the hazard ratio associated with switching. In the Cox model the primary dependent variable was the number of days to switching from the first prophylactic agent. The primary independent variable was the type of prophylactic medication that appeared in the claims data. The proportional hazard assumption was tested for each covariate and related chi^2 p-value was reported in the table (values greater than 0.05 were considered to have met the assumption test).

ER visits were counted for each patient and reported for each study drug as a proportion of patients with one or more ER visit during the follow-up period. The results were tabulated by drug and adherence status. Logistic regression models were used to test the association between adherence and ER visits. The primary dependent variable was ER visits and the primary independent variable was

adherence (using both mpr and pdc methods separately). Aside from the covariates decided upon a-priory, this model also included the type of prophylactic medication that appeared in the claims data.

RESULTS

In the MarketScan Databases, we identified 47,555 patients who had a diagnosis of chronic migraine between 2008 and 2011. After applying inclusion/exclusion criteria there were 1,640 patients included in the analysis of the 6-month follow-up cohort and 861 patients in the 12-month follow-up cohort. The most commonly prescribed prophylactics in both cohorts were topiramate, amitriptyline and gabapentin.

Demographics

Tables 1 and 2 show the demographics for both 6-Month and 12-Month cohorts compared among the different prophylactic medications. The majority of patients were female with a mean age approximately 40 years old. Preferred provider organization (PPO) health insurance was the most common plan type and a large portion of patients were working full time. Both cohorts had significant co-morbidities, of which the most common were headache disorders other than CM, cancer, hypertension, depression, sleep disorder, and gastro esophageal reflux disorder (GERD). Our sample included patients from all regions of the United States with slightly disproportionate numbers from the South and Northeast. Close to 90% of both cohorts lived in a metropolitan area. Only about half of the demographic variables differed significantly among the various prophylactics. Appendix 1 highlights the statistically significant differences in demographics among the prophylactics we investigated.

Adherence

Tables 3 and 4 display the adherence rates for each medication for both follow-up cohorts using MPR and PDC. Approximately 30% of patients were adherent at the end of 6 months and 14% at 12 months

when ≥80% MPR was used to measure adherence. Using PDC to calculate adherence provided even lower estimates of 24% and 14% for 6 and 12 months follow-up, respectively. Appendix 2 compares demographics between adherent and non-adherent groups stratified by follow-up time and the two adherence measurements used. Only age was found to differ significantly among adherent and non-adherent patients. Although asthma was significantly different using MPR calculation at 6 months this was not robust and did not hold for the 12 month cohort or for either of the cohorts using PDC calculations.

Results from the logistics regression models that included the covariates from Appendix 1 may also be found in Tables 3 and 4. Two models were generated to estimate unadjusted and adjusted estimates of odds ratios. Since topiramate had the largest sample size this was used as the referent group in each of the analyses. The models are as follows:

Unadjusted Model:

$$\exp\{\text{logit}[\pi(X)]\}=\beta_0+\beta_1\text{amitriptyline}+\beta_2\text{atenolol}+\beta_3\text{citalopram}+\beta_4\text{divalproex}+\beta_5\text{fluoxetine}+\beta_6\text{gabapentin}+\beta_7\text{metoprolol}+\beta_8\text{nadolol}+\beta_9\text{nortriptyline}+\beta_{10}\text{paroxetine}+\beta_{11}\text{propranolol}+\beta_{12}\text{sertraline}$$

Adjusted Model:

$$\exp\{\text{logit}[\pi(X)]\}=\beta_0+\beta_1\text{amitriptyline}+\beta_2\text{atenolol}+\beta_3\text{citalopram}+\beta_4\text{divalproex}+\beta_5\text{fluoxetine}+\beta_6\text{gabapentin}+\beta_7\text{metoprolol}+\beta_8\text{nadolol}+\beta_9\text{nortriptyline}+\beta_{10}\text{paroxetine}+\beta_{11}\text{propranolol}+\beta_{12}\text{sertraline}+\beta_{13}\text{age}+\beta_{14}\text{sex}+\beta_{15}\text{employestatus}+\beta_{16}\text{plantype}+\beta_{17}\text{region}+\beta_{18}\text{city}+\beta_{19}\text{cancer}+\beta_{20}\text{hypertension}+\beta_{21}\text{headache}$$

*Where $\pi(X)$ = Adherence (coded as 1/0 for yes/no)

Fluoxetine, paroxetine, citalopram, metoprolol, nadolol, atenolol, and gabapentin had point estimates that indicated better odds of adherence when compared to topiramate while amitriptyline, nortriptyline, sertraline, propranolol, and divalproex had worse odds of adherence. The medications that were associated with better adherence were also the least represented among the prophylactics. Small sample sizes mean larges confidence intervals that make these results not statistically significant. Amitriptyline was the only prophylactic that had a lower odds of adherence when compared to topiramate that was statistically significant in more than one analysis across multiple models. Gabapentin also showed a similar trend but was only statistically significant when the adjusted model was applied to adherence based on MPR.

Switching

Appendices 3 and 4 present the switch rates for the 6 and 12 month cohorts respectively. Results are stratified by the initial prophylactic as well as the prophylactic to which that the patient switched. The charts that comprise Figure 2 illustrate the proportion of patients that switched to and from each prophylactic. The most common prophylactic switched to and from was topiramate. Although the proportions for topiramate differed by whether patients were switching to or from, this prophylactic had the highest proportion in both of these analyses. Other medications that had significant switching did not experience this kind of match between switching behaviors. A large proportion of the patients who switched decided to replace amitriptyline and nortriptyline with another prophylactic, while an equally large proportion of patients who switched chose to convert to citalopram, gabapentin, or propranolol.

Graphs in Figure 3 illustrate the KM curves for each prophylactic and tables 6 and 7 present the results of the Cox PH models. Topiramate was the referent group and thus each hazard ratio can be interpreted as the chance of a switch occurring with a specific prophylactic divided by the chance of the switch

occurring with topiramate. Point estimates showed that the likelihood of switching was lower among all prophylactics compared to topiramate; however, these results were not statistically significant except for fluoxetine, which was significant only at the 12 month follow-up where the sample size for switching was only one.

ER Visits

Tables 8 and 9 present the number and proportion of patients who experienced an ER visit during the two follow-up periods. These results are stratified by adherence as well as prophylactic drug. A combination chart was used to illustrate the summary of the data shown in the aforementioned tables. (Figure 4) The number of patients with ER visits was much higher among non-adherent patients. Due to a larger proportion of patients who were non-adherent, these results may be misguiding. At 6 months, the proportion in the non-adherent group who experienced an ER visit is smaller than the proportion who experienced an ER visit in the adherent group. At 12 months, the proportions are similar between the adherent and non-adherent groups. To further investigate ER visits among these two groups the following logistic models were used to analyze the ER visit data:

Unadjusted Model:

$$\exp\{\text{logit}[\pi(X)]\}=\beta_0+\beta_1\text{adherence}$$

Adjusted Model:

$$\exp\{\text{logit}[\pi(X)]\}=\beta_0+\beta_1\text{adherence}+\beta_2\text{amitriptyline}+\beta_3\text{atenolol}+\beta_4\text{citalopram}+\beta_5\text{divalproex}+\beta_6\text{fluoxetine}+\beta_7\text{gabapentin}+\beta_8\text{metoprolol}+\beta_9\text{nadolol}+\beta_{10}\text{nortriptyline}+\beta_{11}\text{paroxetine}+\beta_{12}\text{propranolol}+\beta_{13}\text{sertraline}+\beta_{14}\text{age}+\beta_{15}\text{sex}+\beta_{16}\text{employestatus}+\beta_{17}\text{plantype}+\beta_{18}\text{region}+\beta_{19}\text{city}+\beta_{20}\text{cancer}+\beta_{21}\text{hypertension}+\beta_{22}\text{headache}$$

*Where π(X) = ER Visits (coded as 1/0 for yes/no)

Results of the models are shown in Table 10. Unadjusted and adjusted logistic regression models reveal that that there are no significant differences in odds of an ER visit between the adherent and non-adherent groups.

DISCUSSION

In this study we analyzed the adherence and switching rates of 13 commonly prescribed oral migraine prophylactics among chronic migraenours. This analysis used information from a large US healthcare database that included commercial and Medicare supplemental data from in-patient, outpatient, and pharmacy claims. Regardless of the medication used, adherence with oral migraine prophylactics dramatically declined over the 6 and 12 month follow-up periods. There has been some debate regarding the methods used to calculate adherence from claims data and it has been suggested that PDC is a more accurate method compared to MPR because it does not overestimate adherence. In our study we have calculated adherence rates using both methods. As expected, we found that PDC provided lower estimates of adherence at both 6 and 12 months when compared with MPR. The values from each calculation were carried forward, and all of the analyses shown in the results were completed using each method. Some of the outcomes varied slightly but overall the two methods produced similar results in our analyses.

Demographics were found to vary among the different prophylactics used. Overall the baseline characteristics of our patient sample were similar to those expected for a chronic migraine population: a largely female, middle-aged, working population living in a metropolitan area who suffers from one or more comorbidities. We did find that there was an abnormally high proportion of patients with cancer (approximately 40% among all cohorts) which has not been seen in other studies and that could not be

explained with the information we have. The inclusion of these covariates rarely changed the outcomes but nonetheless provided more accurate point estimates and confidence intervals for our results.

Our results are similar to other published studies that investigated adherence in migraine patients. Berger et al. reported adherence rates of 26.6% to 32.4% (6-month MPR) among the various classes of prophylactics which is comparable to our findings of 29.5% for the same time frame and method among all of the study medications.[20] Demographics were also similar between the two studies with the exception of the proportion of patients with comorbidities associated with cancer. The methods (study design, patient selection, coding, etc.) for attaining comorbidity data from both studies were similar and thus the reason for this finding has not yet been explored.

Since chronic migraine is a chronic problem for most patients, and oral prophylactics must be taken daily in order to adequately prevent migraine attacks, it is reasonable to compare adherence rates among CM patients with those of other chronic conditions that require the same type of oral daily medication therapy. Yeaw et al. used a national database of medical claims to compare adherence among 6 different chronic diseases over a 12-month follow-up period using PDC to calculate adherence.[14] Their findings ranged from 35% adherence for overactive bladder medications to 72% for oral antidiabetics which was considerably better than the 14% adherence presented in our results for chronic migraenours at 12 months of follow-up.

As is the case with large insurance claims database analyses our study is has some important limitations. One such major limitation of this dataset is that it does not represent the patients who actually take their medications. There is an assumption that once a patient picks up their medication from a pharmacy they are actually ingesting that medication as prescribed or at least as indicated by the refill patterns. Since we are using days' supply to calculate adherence there is also an assumption that the doctor prescribed the medication correctly and that days' supply is correct for the indication of migraine

or chronic migraine. Furthermore there is also an assumption that the doctor is correctly diagnosing patients and that the ICD-9-CM codes contained within the database for each patient accurately describe their disease. This latter may lead misclassification which is an important limitation in any observational study.

The MarketScan database has additional limitations. It does not, for example, provide any information on disease severity. Chronic migraine encompasses any patient who experiences ≥15 headache days per month; however, a patient who experiences 15 headache days per month compared to someone who has 30 headache days per month may have very different attitudes and behaviors related to their treatment. Additionally, headache episodes may vary in severity among the patients. This fact is not captured in diagnosis codes and thus not represented in this dataset. Separately, although not technically a limitation of the dataset we did not use the available data to calculate discontinuation rates. The results presented in our study are limited to switching rates which cannot be used to interpret discontinuation. Moreover, time-to-switch was only evaluated in those patients who actually completed a switch. Patients who did not discontinue their initial prophylactic and start another medication were not included in the calculation of KM curves and Cox PH models. This exclusion occurred because variables describing the time at which censoring occurred and the type of censoring that transpired (administrative, drop-out, or competing risks) were not available for this analysis. Lastly, although copay information is available in the MarketScan database we did not take advantage of this for our current analysis. Copays have been shown to be associated with adherence in a number of studies.[32] Although the medications in the analysis were all generics, and the copays are likely not to vary greatly between them, this may still be an important covariate to include in future analyses of the CM population. Our study is the first claims based analysis that characterizes chronic migraine patients and assesses oral prophylactic adherence, switching, and ER visits among this specific patient population. The sample used in the analysis is representative of commercial and Medicare supplemental populations of the entire US

and may be generalizable to any region therein. Having said that, this study reflects an insured population; these results may not be generalizable uninsured individuals or those who are insured through public programs.

The results presented herein provide new information for clinicians and various decision makers regarding adherence to oral prophylactics among chronic migraenours. Current guidelines highlight the importance of prophylactic treatment among patients who suffer from frequent headaches and also recommend that treatment is continued for at least one year.[11] Our results suggest that only a very small proportion of patients remain adherent at 12 months of follow-up, regardless of the prophylactic that is initiated. Switching data presented in this study may be of importance to clinicians as it highlights important behavioral trends among chronic migraine patients. Prescribing among clinicians clearly favors topiramate; however, our results showed that the highest proportion of patients who switched from any medication to another prophylactic were those who initiated topiramate first. A large number of CM patients experienced ER visits which further demonstrates the need for adequate treatment in this patient population. These key points should be taken into consideration by investigators and decision makers for future studies and policies.

CONCLUSION

Adherence to oral migraine prophylactics is low among the US chronic migraine population at both 6 and 12 months. A large proportion of patients switch between the prophylactics studied with the greatest switching occurring to and from topiramate. A significant proportion of chronic migraine patients experience ER visits but in our results we found that these visits were not associated with adherence.

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Figure 1. Patient Selection Process

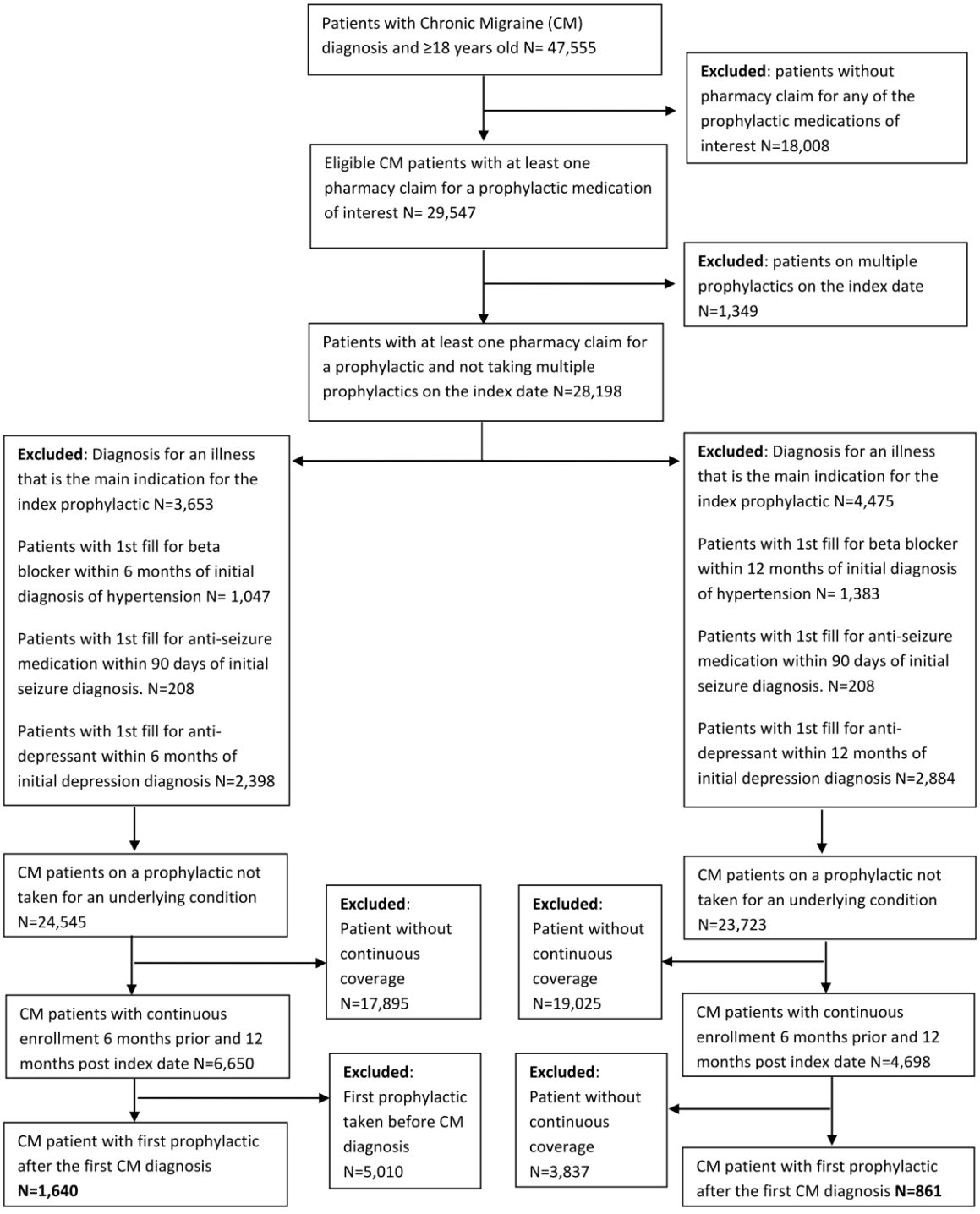


Table 1. Demographics and Clinical Characteristics of Chronic Migraine Patients by Initial Prophylactic, 6-Month Cohort

		Antidepressants						*Beta-Blockers*				*Antiepileptics*		
Demographics of CM Patients	Total N=1640	Amitriptyline N=246	Nortriptyline N=140	Citalopram N=134	Sertraline N=37	Fluoxetine N=54	Paroxetine N=19	Propranolol N=130	Metoprolol N=51	Nadolol N=41	Atenolol N=44	Gabapentin N=177	Topiramate N=480	Divalproex N=84
Age – Mean (SD)	40 (13)	38 (12)	41 (13)	38 (12)	40 (16)	39 (11)	41 (14)	37 (12)	46 (14)	40 (11)	42 (12)	46 (12)	37 (12)	41 (14)
Gender, n (%)														
Female	1348 (82)	208 (85)	103 (74)	120 (90)	31 (84)	50 (93)	16 (84)	97 (75)	40 (78)	35 (85)	34 (77)	141 (80)	414 (87)	59 (70)
Employment Status, n (%)														
Full-time	890 (54)	145 (59)	84 (60)	68 (51)	19 (51)	38 (70)	9 (47)	74 (57)	21 (41)	29 (71)	27 (61)	74 (42)	248 (52)	51 (61)
Part-time/Seasonal	15 (1)	2 (1)	2 (1)	1 (1)	1 (3)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	5 (1)	1 (1)
Early Retiree	48 (3)	4 (2)	3 (2)	5 (4)	0 (0)	2 (4)	2 (11)	1 (1)	3 (6)	2 (5)	2 (5)	12 (7)	10 (2)	2 (2)
Medicare Eligible Retiree	39 (2)	4 (2)	5 (4)	3 (2)	3 (8)	0 (0)	0 (0)	1 (1)	2 (4)	0 (0)	1 (2)	9 (5)	8 (2)	3 (4)
Retiree	18 (1)	3 (1)	2 (1)	0 (0)	0 (0)	2 (4)	0 (0)	1 (1)	1 (2)	0 (0)	0 (0)	5 (3)	3 (1)	1 (1)
COBRA	9 (<1)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	3 (2)	3 (1)	0 (0)
Long Term Disability	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)	0 (0)
Surviving Spouse/Dependent	4 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)
Other/Unknown	615 (38)	88 (36)	43 (31)	56 (42)	14 (38)	10 (19)	8 (42)	52 (40)	23 (45)	10 (24)	14 (32)	70 (40)	203 (42)	24 (29)
Employee Classification, n (%)														
Salary Non-Union	241 (15)	39 (16)	30 (12)	11 (8)	4 (11)	7 (13)	1 (5)	13 (10)	8 (16)	12 (29)	7 (16)	26 (15)	69 (14)	14 (17)
Salary Union	46 (3)	7 (3)	2 (1)	6 (4)	3 (8)	0 (0)	1 (5)	1 (1)	2 (4)	3 (7)	1 (2)	8 (5)	11 (2)	1 (1)
Salary Other	52 (3)	4 (2)	4 (3)	0 (0)	0 (0)	8 (15)	0 (0)	4 (3)	0 (0)	4 (10)	1 (2)	5 (3)	19 (4)	3 (4)
Hourly Non-Union	140 (9)	32 (13)	16 (11)	10 (7)	3 (8)	9 (17)	2 (11)	9 (7)	1 (2)	0 (0)	4 (9)	12 (7)	37 (8)	5 (6)
Hourly Union	138 (8)	20 (8)	10 (7)	11 (8)	3 (8)	4 (7)	1 (5)	12 (9)	5 (10)	1 (2)	4 (9)	13 (7)	45 (9)	9 (11)
Hourly Other	20 (1)	2 (1)	1 (1)	1 (1)	0 (0)	1 (2)	0 (0)	6 (5)	0 (0)	0 (0)	0 (0)	1 (<1)	4 (1)	4 (5)
Non-Union	106 (6)	16 (7)	10 (7)	12 (9)	1 (3)	5 (9)	0 (0)	8 (6)	3 (6)	7 (17)	2 (5)	10 (6)	26 (5)	4 (5)
Union	44 (3)	2 (1)	3 (2)	3 (2)	2 (5)	0 (0)	0 (0)	5 (4)	1 (2)	2 (5)	3 (7)	6 (3)	11 (2)	5 (6)
Unknown	853 (52)	124 (50)	64 (46)	80 (60)	21 (57)	20 (37)	14 (74)	72 (55)	31 (61)	12 (29)	22 (50)	96 (54)	258 (54)	39 (46)
Geographical Location, n (%)														
Northeast	230 (14)	37 (15)	25 (18)	14 (10)	2 (5)	4 (7)	2 (11)	24 (19)	9 (18)	5 (12)	11 (25)	17 (10)	71 (15)	9 (11)
North Central	444 (27)	67 (27)	29 (21)	37 (28)	13 (35)	11 (20)	6 (32)	31 (24)	12 (24)	14 (34)	11 (25)	65 (37)	114 (24)	34 (40)
South	628 (38)	90 (37)	52 (37)	53 (40)	15 (41)	28 (52)	6 (32)	51 (39)	17 (33)	18 (44)	12 (28)	49 (28)	210 (44)	26 (31)
West	329 (20)	52 (21)	34 (24)	30 (22)	7 (19)	10 (19)	5 (26)	22 (17)	12 (24)	4 (10)	10 (23)	46 (26)	81 (17)	14 (17)
Unknown	9 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	2 (2)	1 (2)	0 (0)	0 (0)	0 (0)	4 (<1)	1 (1)
Located in an "MSA"	1435 (88)	213 (87)	132 (94)	120 (90)	29 (78)	50 (93)	12 (63)	115 (88)	46 (90)	28 (68)	43 (98)	151 (85)	421 (88)	72 (86)

Located outside of an "MSA"	205 (13)	33 (13)	8 (6)	14 (10)	8 (22)	4 (7)	7 (37)	15 (12)	5 (10)	13 (14)	1 (2)	26 (15)	59 (12)	12 (14)
Health Plan Type, n (%)														
Comprehensive	47 (3)	7 (3)	6 (4)	3 (2)	3 (8)	0 (0)	1 (5)	1 (<1)	4 (8)	2 (5)	2 (5)	6 (3)	9 (2)	4 (5)
EPO	42 (3)	7 (3)	5 (4)	2 (1)	0 (0)	1 (2)	0 (0)	4 (3)	1 (2)	0 (0)	1 (2)	5 (3)	16 (3)	0 (0)
HMO	194 (12)	30 (12)	20 (14)	11 (8)	3 (8)	7 (13)	1 (5)	19 (15)	6 (12)	7 (17)	6 (14)	16 (9)	3 (<1)	7 (8)
POS	148 (9)	22 (9)	10 (7)	15 (11)	0 (0)	10 (19)	1 (5)	13 (10)	2 (4)	9 (22)	5 (11)	14 (8)	321 (67)	13 (15)
PPO	1065 (65)	160 (65)	80 (57)	92 (69)	29 (78)	28 (52)	15 (79)	83 (64)	36 (71)	20 (49)	25 (57)	120 (68)	34 (7)	54 (64)
POS w/Capitation	11 (<1)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	3 (2)	0 (0)	0 (0)	0 (0)	1 (<1)	60 (13)	2 (2)
CDHP	70 (4)	13 (5)	11 (8)	3 (2)	1 (3)	3 (6)	1 (5)	4 (3)	1 (2)	3 (7)	1 (2)	10 (6)	16 (3)	3 (4)
HDHP	26 (2)	3 (1)	3 (2)	5 (4)	0 (0)	1 (2)	0 (0)	1 (<1)	0 (0)	0 (0)	2 (5)	2 (1)	8 (2)	0 (0)
Other Diagnoses, n (%)														
Allergic Rhinitis	354 (22)	51 (21)	31 (22)	30 (22)	8 (22)	21 (39)	4 (21)	25 (19)	10 (20)	8 (20)	9 (20)	37 (21)	107 (22)	21 (25)
Asthma	249 (15)	34 (14)	21 (15)	17 (13)	1 (3)	9 (17)	4 (21)	15 (12)	12 (24)	7 (17)	4 (9)	36 (20)	77 (16)	12 (14)
Bipolar disorder	68 (4)	2 (1)	2 (1)	10 (7)	1 (3)	5 (9)	0 (0)	1 (<1)	4 (8)	2 (5)	4 (9)	9 (5)	22 (5)	6 (7)
Cancer	652 (40)	84 (34)	52 (37)	66 (49)	11 (30)	19 (35)	10 (53)	45 (35)	19 (37)	14 (34)	22 (50)	96 (54)	180 (38)	33 (39)
Congestive heart failure	21 (1)	0 (0)	2 (1)	2 (1)	1 (3)	0 (0)	1 (5)	1 (<1)	5 (10)	1 (2)	3 (7)	0 (0)	3 (<1)	2 (2)
Coronary heart disease	93 (6)	11 (4)	6 (4)	6 (4)	5 (14)	3 (6)	3 (16)	6 (5)	8 (16)	3 (7)	5 (11)	15 (8)	15 (3)	6 (7)
Depression	409 (25)	46 (19)	23 (16)	56 (42)	11 (30)	27 (50)	6 (32)	21 (16)	12 (24)	10 (24)	11 (25)	66 (37)	93 (19)	25 (30)
Diabetes	137 (8)	16 (7)	9 (6)	12 (9)	3 (8)	4 (7)	0 (0)	11 (8)	10 (20)	5 (12)	6 (14)	16 (9)	38 (8)	7 (8)
Epilepsy	45 (2)	6 (2)	5 (4)	2 (1)	2 (5)	1 (2)	0 (0)	1 (<1)	3 (6)	1 (2)	2 (5)	5 (3)	14 (3)	3 (4)
GERD	345 (21)	51 (21)	31 (22)	36 (27)	7 (19)	5 (9)	6 (32)	25 (19)	15 (29)	10 (24)	7 (16)	46 (26)	88 (18)	17 (20)
Hypertension	412 (25)	49 (20)	32 (23)	40 (30)	13 (35)	19 (35)	2 (10)	24 (18)	29 (57)	13 (32)	17 (39)	53 (30)	102 (21)	19 (23)
Headache (other than Migraine)	1257 (77)	193 (78)	115 (82)	106 (79)	27 (73)	39 (72)	11 (58)	81 (62)	37 (73)	30 (73)	31 (70)	141 (80)	368 (77)	75 (89)
Renal Failure	23 (1)	1 (<1)	3 (2)	3 (2)	0 (0)	0 (0)	0 (0)	0 (0)	3 (6)	1 (2)	0 (0)	4 (2)	6 (1)	2 (2)
Sleep Disorder	378 (23)	61 (25)	41 (29)	33 (25)	10 (27)	11 (20)	3 (16)	25 (19)	10 (19)	8 (20)	9 (20)	47 (27)	100 (21)	18 (21)

CM – chronic migraine, SD – standard deviation, COBRA – Consolidated Omnibus Budget Reconciliation Act, MSA – metropolitan statistical area, EPO – exclusive provider organization, HMO – health maintenance organization, POS – point of service, PPO – preferred provider organization, CDHP – consumer driven health plan, HDHP – high deductible health plan, GERD – gastro esophageal reflux disorder

Table 2. Demographics and Clinical Characteristics of Chronic Migraine Patients by Initial Prophylactic, 12-Month Cohort

		Antidepressants						*Beta-Blockers*				*Antiepileptics*		
Demographics of CM Patients	Total N=861	Amitriptyline N=139	Notriptyline N=71	Citalopram N=65	Sertraline N=18	Fluoxetine N=25	Paroxetine N=8	Propranolol N=73	Metoprolol N=23	Nadolol N=24	Atenolol N=18	Gabapentin N=96	Topiramate N=249	Divalproex N=50
Age – Mean (SD)	39.95 (13)	38.56 (13)	39.89 (13)	39.08 (11)	41.28 (14)	41.48 (9)	38.25 (15)	37.03 (12)	48.96 (3)	39.00 (11)	44.11 (12)	45.21 (13)	37.91 (12)	42.70 (13)
Gender														
Female	707 (82)	114 (82)	51 (72)	57 (88)	15 (83)	24 (96)	6 (75)	56 (77)	19 (83)	21 (88)	11 (61)	78 (81)	217 (87)	36 (72)
Employment Status														
Full-time	496 (58)	82 (59)	48 (68)	37 (57)	11 (61)	18 (72)	5 (63)	44 (60)	8 (35)	18 (75)	12 (67)	46 (48)	134 (54)	31 (62)
Part-time/Seasonal	11 (1)	1 (<1)	1 (14)	1 (2)	1 (6)	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)	4 (2)	0 (0)
Early Retiree	29 (3)	3 (2)	2 (3)	3 (5)	0 (0)	2 (8)	1 (13)	1 (1)	2 (9)	2 (8)	1 (6)	6 (6)	5 (2)	1 (2)
Medicare Eligible Retiree	20 (2)	4 (3)	1 (14)	1 (2)	1 (6)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (6)	6 (6)	4 (2)	1 (2)
Retiree	12 (1)	3(2)	1 (14)	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)	3 (3)	2 (<1)	1 (2)
COBRA	3 (<1)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (<1)	0 (0)
Long Term Disability	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)
Surviving Spouse/Dependent	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Other/Unknown	286 (33)	46 (33)	18 (25)	22 (34)	5 (28)	3 (12)	2 (25)	27 (37)	11 (48)	4 (17)	4 (22)	30 (31)	99 (40)	15 (30)
Employee Classification														
Salary Non-Union	131 (15)	21 (15)	15 (21)	6 (9)	2 (11)	4 (16)	1 (13)	5 (7)	3 (13)	9 (38)	3 (17)	16 (17)	39 (16)	7 (14)
Salary Union	31 (4)	5 (4)	1 (1)	5 (8)	1 (6)	0 (0)	1 (13)	0 (0)	0 (0)	3 (13)	0 (0)	4 (4)	10 (4)	1 (2)
Salary Other	28 (3)	2 (1)	3 (4)	0 (0)	0 (0)	3 (12)	0 (0)	3 (4)	0 (0)	3 (13)	1 (6)	3 (3)	7 (3)	3 (6)
Hourly Non-Union	70 (8)	20 (14)	8 (11)	4 (6)	1 (6)	4 (16)	0 (0)	3 (4)	0 (0)	0 (0)	3 (17)	8 (8)	18 (7)	1 (2)
Hourly Union	80 (9)	12 (9)	6 (8)	5 (8)	3 (17)	3 (12)	0 (0)	6 (8)	3 (13)	0 (0)	2 (11)	7 (7)	28 (11)	5 (10)
Hourly Other	7 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (4)	0 (0)	0 (0)	0 (0)	1 (1)	1 (<1)	2 (4)
Non-Union	62 (7)	10 (7)	5 (7)	6 (9)	1 (6)	3 (12)	0 (0)	6 (8)	3 (13)	4 (17)	1 (6)	5 (5)	13 (5)	3 (6)
Union	18 (2)	1 (<1)	1 (1)	2 (3)	0 (0)	0 (0)	0 (0)	3 (4)	0 (0)	1 (4)	2 (11)	3 (3)	2 (<1)	3 (6)
Unknown	434 (50)	68 (49)	32 (45)	37 (57)	10 (56)	8 (32)	6 (75)	44 (60)	14 (61)	4 (17)	6 (33)	49 (51)	131 (53)	25 (50)
Geographical Location														
Northeast	122 (14)	25 (18)	13 (18)	8 (12)	2 (11)	1 (4)	0 (0)	12 (16)	7 (30)	3 (13)	4 (22)	10 (10)	32 (13)	5 (10)
North Central	251 (29)	38 (27)	18 (25)	20 (31)	5 (28)	5 (20)	3 (38)	19 (26)	4 (17)	10 (42)	5 (28)	37 (39)	66 (27)	21 (42)
South	319 (37)	49 (35)	26 (37)	24 (37)	7 (39)	14 (56)	3 (38)	25 (34)	8 (35)	9 (38)	5 (28)	23 (24)	109 (44)	16 (32)
West	167 (19)	27 (19)	14 (20)	13 (20)	4 (22)	5 (20)	2 (25)	17 (23)	4 (17)	2 (8)	4 (22)	26 (27)	41 (16)	7 (14)
Unknown	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (2)
Located in an "MSA"	755 (88)	114 (82)	68 (96)	59 (91)	15 (83)	23 (92)	7 (88)	62 (85)	21 (91)	16 (67)	18 (100)	83 (86)	225 (90)	42 (84)

Located outside of an "MSA"	106 (12)	25 (18)	3 (4)	6 (9)	3 (17)	2 (8)	1 (13)	11 (15)	2 (9)	8 (33)	0 (0)	13 (14)	24 (10)	8 (16)
Health Plan Type														
Comprehensive (2)	27 (3)	5 (4)	2 (3)	2 (3)	1 (6)	0 (0)	1 (13)	1 (1)	1 (4)	2 (8)	2 (11)	6 (6)	3 (1)	1 (2)
EPO (3)	16 (2)	4 (3)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	2 (2)	8 (3)	0 (0)
HMO (4)	107 (13)	17 (12)	12 (17)	5 (8)	1 (6)	5 (20)	1 (13)	11 (15)	2 (9)	2 (8)	3 (17)	10 (10)	31 (12)	6 (12)
POS (5)	85 (10)	13 (9)	7 (10)	10 (15)	0 (0)	4 (16)	1 (13)	8 (11)	2 (9)	5 (21)	1 (6)	7 (7)	20 (8)	7 (14)
PPO (6)	561 (67)	90 (65)	45 (63)	42 (65)	15 (83)	13 (52)	5 (63)	49 (67)	16 (70)	14 (58)	9 (50)	62 (65)	167 (67)	33 (66)
POS w/Capitation (7)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
CDHP (8)	27 (3)	6 (4)	2 (3)	3 (5)	0 (0)	0 (0)	0 (0)	1 (1)	1 (4)	1 (4)	0 (0)	6 (6)	5 (2)	2 (4)
HDHP (9)	11 (1)	2 (1)	0 (0)	1 (2)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	2 (11)	2 (2)	4 (2)	0 (0)
Other Diagnoses														
Allergic Rhinitis	196 (23)	32 (23)	17 (24)	13 (20)	5 (28)	5 (20)	2 (25)	19 (26)	7 (30)	4 (17)	2 (11)	17 (18)	58 (23)	13 (26)
Asthma	131 (15)	21 (15)	8 (11)	10 (15)	1 (6)	4 (16)	2 (25)	7 (10)	8 (35)	2 (8)	1 (6)	22 (23)	41 (12)	4 (8)
Bipolar disorder	35 (4)	1 (<1)	2 (3)	1 (2)	0 (0)	2 (8)	0 (0)	1 (1)	2 (9)	2 (8)	1 (6)	7 (7)	14 (56)	2 (4)
Cancer	363 (42)	48 (35)	29 (41)	29 (45)	6 (33)	11 (44)	5 (63)	24 (33)	9 (39)	10 (42)	10 (56)	57 (59)	101 (41)	24 (48)
Congestive heart failure	9 (1)	0 (0)	2 (3)	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)	3 (13)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (2)
Coronary heart disease	54 (6)	5 (4)	4 (6)	5 (8)	4 (22)	0 (0)	2 (25)	4 (5)	5 (22)	2 (8)	3 (17)	7 (7)	7 (3)	5 (10)
Depression	212 (25)	24 (17)	2 (3)	23 (35)	5 (28)	12 (48)	2 (25)	13 (18)	5 (22)	6 (25)	2 (11)	38 (40)	56 (22)	12 (24)
Diabetes	75 (9)	8 (6)	3 (4)	8 (12)	3 (17)	1 (4)	0 (0)	7 (10)	3 (13)	4 (17)	3 (17)	10 (10)	22 (9)	3 (6)
Epilepsy	20 (2)	2 (1)	1 (1)	1 (2)	1 (6)	1 (4)	0 (0)	1 (1)	1 (4)	0 (0)	0 (0)	2 (2)	8 (3)	2 (4)
GERD	201 (23)	32 (23)	18 (25)	19 (29)	4 (22)	3 (12)	1 (13)	14 (19)	9 (39)	5 (21)	2 (11)	21 (22)	59 (24)	13 (26)
Hypertension	221 (26)	31 (22)	17 (24)	17 (26)	8 (44)	10 (40)	2 (25)	13 (18)	15 (65)	6 (25)	7 (39)	25 (26)	59 (24)	11 (22)
Headache (other than Migraine)	671 (78)	108 (78)	63 (89)	49 (75)	13 (72)	17 (68)	7 (88)	49 (67)	17 (74)	18 (75)	13 (72)	79 (82)	193 (78)	43 (86)
Renal Failure	14 (2)	1 (<1)	2 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)	2 (2)	5 (2)	2 (4)
Sleep Disorder	210 (24)	38 (27)	14 (20)	16 (25)	5 (28)	4 (16)	1 (13)	14 (19)	5 (21)	3 (13)	2 (11)	24 (25)	60 (24)	10 (20)

CM – chronic migraine, SD – standard deviation, COBRA – Consolidated Omnibus Budget Reconciliation Act, MSA – metropolitan statistical area, EPO – exclusive provider organization, HMO – health maintenance organization, POS – point of service, PPO – preferred provider organization, CDHP – consumer driven health plan, HDHP – high deductible health plan, GERD – gastro esophageal reflux disorder

Table 3. Logistic Regression Model Results for Adherence by Initial Prophylactic, 6-Month Cohort

		MPR					*PDC*				
Initial Prophylactic	N	Mean MPR (SD)	N Adherent ≠	% Adherent ≠≠	Unadjusted Odds of Adherence (99% CI)	Adjusted Odds of Adherence (99% CI)	Mean PDC (SD)	N Adherent ≠	% Adherent ≠≠	Unadjusted Odds of Adherence (99% CI)	Adjusted Odds of Adherence (99% CI)
Amitriptyline	246	.44 (.33)	60	24.4%	0.72 (0.46 - 1.14)	0.70 (0.44 - 1.12)	.39 (.30)	47	19.1%	**0.60 (0.36 - 0.98)**	**0.57 (0.34 - 0.94)**
Nortriptyline	140	.43 (.33)	33	23.6%	0.69 (0.39 - 1.23)	0.67 (0.37 - 1.20)	.41 (.30)	30	21.4%	0.69 (0.38 - 1.24)	0.63 (0.34 - 1.16)
Citalopram	134	.56 (.33)	44	32.8%	1.10 (0.64 - 1.88)	1.09 (0.63 - 1.89)	.45 (.29)	28	20.9%	0.67 (0.36 - 1.22)	0.68 (0.36 - 1.28)
Sertraline	37	.48 (.32)	10	27.0%	0.83 (0.31 - 2.23)	0.86 (0.32 - 2.33)	.45 (.29)	6	16.2%	0.49 (0.15 - 1.59)	0.49 (0.15 - 1.62)
Fluoxetine	54	.58 (.35)	20	37.0%	1.32 (0.61 - 2.84)	1.30 (0.58 - 2.92)	.56 (.34)	20	37.0%	1.49 (0.69 - 3.21)	1.55 (0.69 - 3.50)
Paroxetine	19	.54 (.37)	9	47.4%	2.02 (0.60 - 6.77)	2.00 (0.59 - 6.81)	.60 (.37)	10	52.6%	2.81 (0.84 - 9.43)	2.70 (0.78 - 9.27)
Propranolol	130	.47 (.33)	32	24.6%	0.73 (0.41 - 1.31)	0.75 (0.42 - 1.35)	.46 (.30)	27	20.8%	0.66 (0.36 - 1.22)	0.64 (0.34 - 1.21)
Metoprolol	51	.54 (.34)	18	35.3%	1.22 (0.55 - 2.71)	1.15 (0.50 - 2.62)	.50 (.30)	11	21.6%	0.69 (0.28 - 1.73)	0.57 (0.22 - 1.50)
Nadolol	41	.57 (.34)	17	41.5%	1.59 (0.68 - 3.73)	1.55 (0.65 - 3.69)	.56 (.37)	14	34.1%	1.31 (0.54 - 3.18)	1.25 (0.51 - 3.09)
Atenolol	44	.55 (.35)	16	36.4%	1.28 (0.55 - 2.98)	1.09 (0.45 - 2.64)	.55 (.33)	15	34.1%	1.31 (0.55 - 3.09)	1.20 (0.49 - 2.94)
Gabapentin	177	.50 (.36)	58	32.8%	1.09 (0.67 - 1.77)	1.08 (0.66 - 1.79)	.40 (.30)	33	18.6%	0.58 (0.33 - 1.01)	**0.53 (0.30 - 0.96)**
Divalproex	84	.45 (.33)	20	23.8%	0.70 (0.35 - 1.42)	0.64 (0.31 - 1.33)	.40 (.30)	15	17.9%	0.55 (0.25 - 1.20)	0.49 (0.22 - 1.11)
Topiramate	480	.50 (.34)	146	30.4%	Referent	Referent	.48 (.32)	134	27.9%	Referent	Referent
Total	1637	.29 (.46)	483	29.5%			.24 (.43)	390	23.8%		
*Goodness of Fit**					**1.000**	**0.328**				**1.000**	**0.251**

N – number, SD – standard deviation, MPR – medication possession ratio, PDC – proportion of days covered
** Goodness of fit analysis reported as chi² test – p-values greater than 0.05 are considered statistically significant*
Bolded values are those values that are statistically significant
≠Adherent is defined by MPR or PDC ≥80%
≠≠Non-adherent is defined by MPR or PDC <80%

Table 4. Logistic Regression Model Results for Adherence by Initial Prophylactic, 12-Month Cohort

		MPR					*PDC*				
Initial Prophylactic	N	Mean MPR (SD)	N Adherent ≠	% Adherent ≠	Unadjusted Odds of Adherence (99% CI)	Adjusted Odds of Adherence (99% CI)	Mean PDC (SD)	N Adherent ≠	% Adherent ≠	Unadjusted Odds of Adherence (99% CI)	Adjusted Odds of Adherence (99% CI)
Amitriptyline	139	.28 (.30)	16	11.5%	0.47 (0.22 - 1.05)	**0.36 (0.15 - 0.86)**	.27 (.29)	14	10.1%	0.45 (0.20 - 1.03)	**0.37 (0.15 - 0.90)**
Nortriptyline	71	.37 (.34)	14	19.7%	0.90 (0.38 - 2.13)	0.85 (0.35 - 2.11)	.34 (.29)	12	16.9%	0.82 (0.33 - 2.03)	0.79 (0.30 - 2.05)
Citalopram	65	.33 (.30)	8	12.3%	0.51 (0.18 - 1.46)	0.43 (0.14 - 1.34)	.31 (.27)	7	10.8%	0.49 (0.16 - 1.47	0.41 (0.12 - 1.35)
Sertraline	18	.33 (.29)	2	11.1%	0.46 (0.06 - 3.28)	0.36 (0.05 - 2.77)	.33 (.28)	2	11.1%	0.50 (0.07 - 3.62)	0.41 (0.05 - 3.20)
Fluoxetine	25	.41 (.32)	2	8.0%	0.32 (0.05 - 2.21)	0.29 (0.04 - 2.10)	.39 (.30)	2	8.0%	0.35 (0.05 - 2.44)	0.33 (0.05 - 2.40)
Paroxetine	8	.51 (.35)	1	12.5%	0.52 (0.03 - 8.42)	0.55 (0.03 - 9.30)	.48 (.32)	1	12.5%	0.57 (0.04 - 9.29)	0.62 (0.04 - 10.47)
Propranolol	73	.36 (.31)	10	13.7%	0.58 (0.22 - 1.52)	0.53 (0.19 - 1.43)	.34 (.29)	6	8.2%	0.36 (0.11 - 1.16)	0.34 (0.10 - 1.12)
Metoprolol	23	.49 (.31)	3	13.0%	0.55 (0.11 - 2.83)	0.24 (0.03 - 1.83)	.47 (.29)	3	13.0%	0.60 (0.12 - 3.13)	0.27 (0.04 - 2.03)
Nadolol	24	.46 (.36)	6	25.0%	1.22 (0.34 - 4.36)	1.03 (0.27 - 3.91)	.44 (.34)	6	25.0%	1.34 (0.37 - 4.82)	1.17 (0.31 - 4.46)
Atenolol	18	.50 (.37)	5	27.8%	1.40 (0.34 - 5.76)	1.33 (0.31 - 5.82)	.35 (.32)	4	22.2%	1.15 (0.25 - 5.23	1.09 (0.23 - 5.28)
Gabapentin	96	.33 (.32)	14	14.6%	0.62 (0.27 - 1.45)	0.47 (0.19 - 1.15)	.31 (.29)	12	12.5%	0.57 (0.24 - 1.40)	0.42 (0.16 - 1.08)
Divalproex	50	.25 (.28)	5	10.0%	0.41 (0.11 - 1.45)	0.25 (0.06 - 1.04)	.24 (.25)	3	6.0%	0.26 (0.05 - 1.25)	0.20 (0.04 - 1.00)
Topiramate	249	.39 (.34)	52	20.9%	Referent	Referent	.37 (.33)	48	19.3%	Referent	Referent
Total	859	.16 (.37)	138	29.5%			.14 (.39)	120	14.0%		
*Goodness of Fit**					1.000	0.328				1.000	0.251

N – number, SD – standard deviation, MPR – medication possession ratio, PDC – proportion of days covered

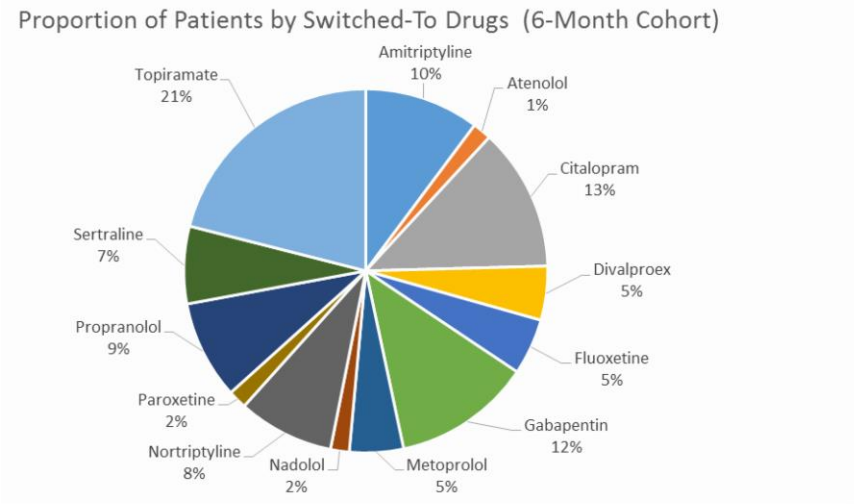
** Goodness of fit analysis reported as chi² test – p-values greater than 0.05 are considered statistically significant*

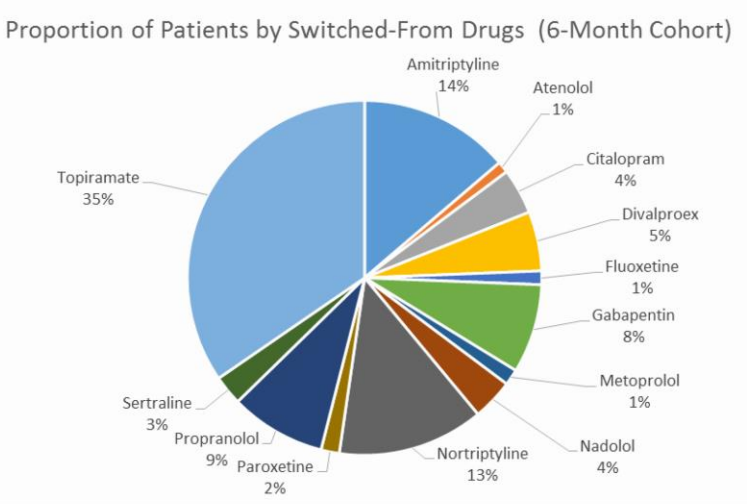
Bolded values are those values that are statistically significant

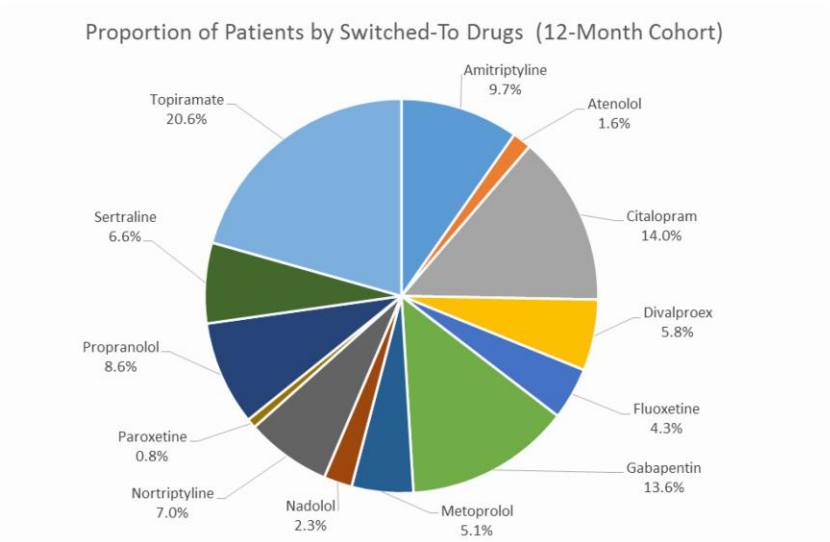
≠Adherent is defined by MPR or PDC ≥80%

≠≠Non-adherent is defined by MPR or PDC <80%

Figure 2. Switching By Initial (Switched-From) Prophylactic, Switched-To Prophylactic, and Follow-Up Time







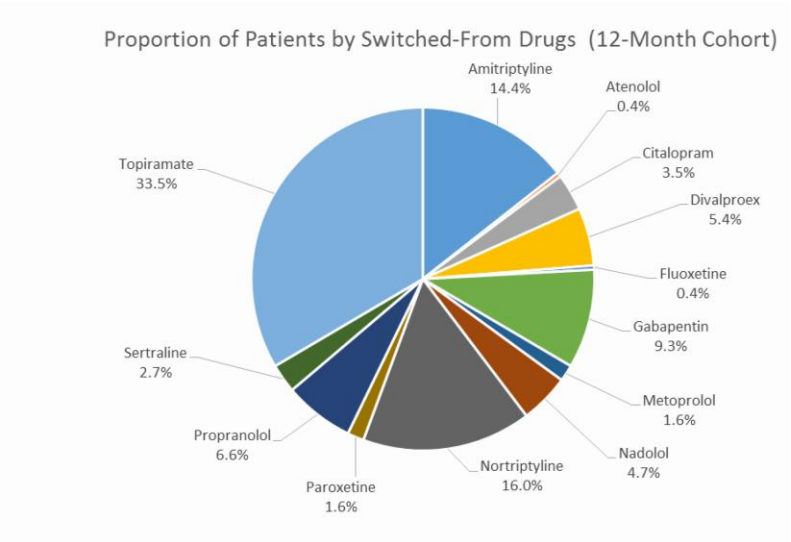


Table 5. Cox Proportional Hazard Regression Model Results for Adherence by Initial Prophylactic, 6-Month Cohort

Initial Prophylactic	*N*	*N Switched*	*Proportion Switched*	*Unadjusted Hazard Ratio (99% CI)*	*Test of Proportional Hazard Assumption**	*Adjusted Hazard Ratio (99% CI)*	*Test of Proportional Hazard Assumption*		
Amitriptyline	246	49	19.9%	0.86 (0.55 - 1.36)	0.861	0.85 (0.53 - 1.35)	0.843	Age	0.867
Nortriptyline	140	41	29.3%	0.83 (0.48 - 1.44)	0.609	0.85 (0.49 - 1.49)	0.519	Sex	0.382
Citalopram	134	61	45.5%	0.76 (0.46 - 1.24)	0.702	0.77 (0.46 - 1.28)	0.700	Employee Status	0.239
Sertraline	37	33	89.2%	0.58 (0.23 - 1.42)	0.013	0.58 (0.23 - 1.43)	0.017	Regions	0.925
Fluoxetine	54	24	44.4%	0.62 (0.32 - 1.22)	0.029	0.63 (0.31 - 1.26)	0.021	City	0.606
Paroxetine	19	8	42.1%	1.47 (0.51 - 4.21)	0.287	1.55 (0.53 - 4.58)	0.318	Plan Type	0.243
Propranolol	130	42	32.3%	0.64 (0.34 - 1.20)	0.183	0.64 (0.33 - 1.21)	0.214	Cancer	0.626
Metoprolol	51	23	45.1%	0.73 (0.37 - 1.48)	0.194	0.75 (0.36 - 1.56)	0.268	Depression	0.957
Nadolol	41	8	19.5%	0.78 (0.33 - 1.86)	0.170	0.80 (0.33 - 1.92)	0.150	HTN	0.603
Atenolol	44	8	18.2%	1.25 (0.58 - 2.71)	0.418	1.17 (0.52 - 2.66)	0.483	Headache	0.963
Gabapentin	177	59	33.3%	0.74 (0.45 - 1.22)	0.620	0.75 (0.45 - 1.26)	0.690	**Global**	**0.508**
Topiramate	480	101	21.0%	Referent	N/A	Referent	N/A		
Divalproex	84	23	27.4%	1 (Collinear)	N/A	1 (Collinear)	N/A		

N – number, SD – standard deviation, MPR – medication possession ratio, PDC – proportion of days covered

** Proportional hazard assumption test reported as chi^2 test – p-values greater than 0.05 are considered statistically significant*

Bolded values are those values that are statistically significant

✗Adherent is defined by MPR or PDC ≥80%

✗✗Non-adherent is defined by MPR or PDC <80%

Table 6. Cox Proportional Hazard Regression Model Results for Adherence by Initial Prophylactic, 12-Month Cohort

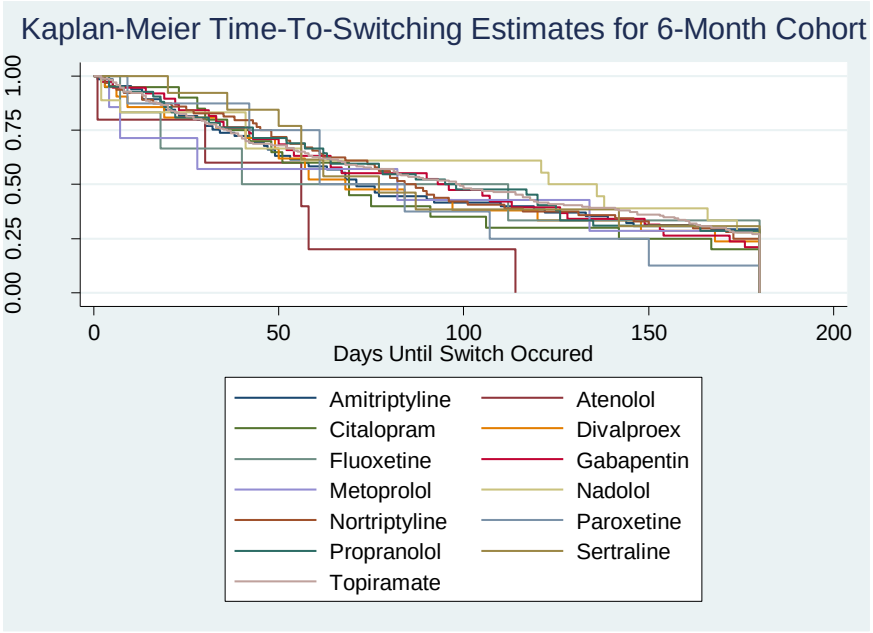
Initial Prophylactic	*N*	*N Switched*	*Proportion Switched*	*Unadjusted Hazard Ratio (99% CI)*	*Test of Proportional Hazard Assumption**	*Adjusted Hazard Ratio (99% CI)*	*Test of Proportional Hazard Assumption*		
Amitriptyline	139	37	26.6%	0.63 (0.34 - 1.16)	0.337	0.63 (0.33 - 1.20)	0.215	Age	0.905
Nortriptyline	71	41	57.7%	0.78 (0.36 - 1.64)	0.420	0.85 (0.39 - 1.86)	0.297	Sex	0.756
Citalopram	65	9	13.8%	0.80 (0.41 - 1.55)	0.813	0.85 (0.42 - 1.70)	0.613	Employee Status	0.322
Sertraline	18	7	38.9%	0.34 (0.08 - 1.40)	0.868	0.38 (0.09 - 1.62)	0.865	Regions	0.177
Fluoxetine	25	1	4.0%	**0.30 (0.10 - 0.84)**	**0.582**	**0.31 (0.10 - 0.93)**	0.399	City	0.571
Paroxetine	8	4	50.0%	1.63 (0.24 - 10.86)	0.972	1.85 (0.26 - 13.24)	0.956	Plan Type	0.586
Propranolol	73	17	23.3%	0.52 (0.21 - 1.31)	0.973	0.55 (0.21 - 1.47)	0.890	Cancer	0.775
Metoprolol	23	4	17.4%	0.66 (0.28 - 1.67)	0.828	0.68 (0.25 - 1.89)	0.983	Depression	0.615
Nadolol	24	12	50.0%	0.72 (0.25 - 2.07)	0.842	0.73 (0.25 - 2.14)	0.973	HTN	0.966
Atenolol	18	1	5.6%	0.82 (0.23 - 2.91)	0.854	0.83 (0.22 - 3.11)	0.701	Headache	0.983
Gabapentin	96	24	25.0%	0.85 (0.44 - 1.63)	0.958	0.88 (0.45 - 1.73)	0.921	**Global**	**0.993**
Topiramate	50	14	28.0%	1 (Collinear)	N/A	1 (Collinear)	N/A		
Divalproex	249	86	34.5%	Referent	N/A	Referent	N/A		

N – number, SD – standard deviation, MPR – medication possession ratio, PDC – proportion of days covered

** Proportional hazard assumption test reported as chi^2 test – p-values greater than 0.05 are considered statistically significant*

Bolded values are those values that are statistically significant

Figure 3. Kaplan-Meier Curves for Time-To-Switch Estimates by Follow-Up Time



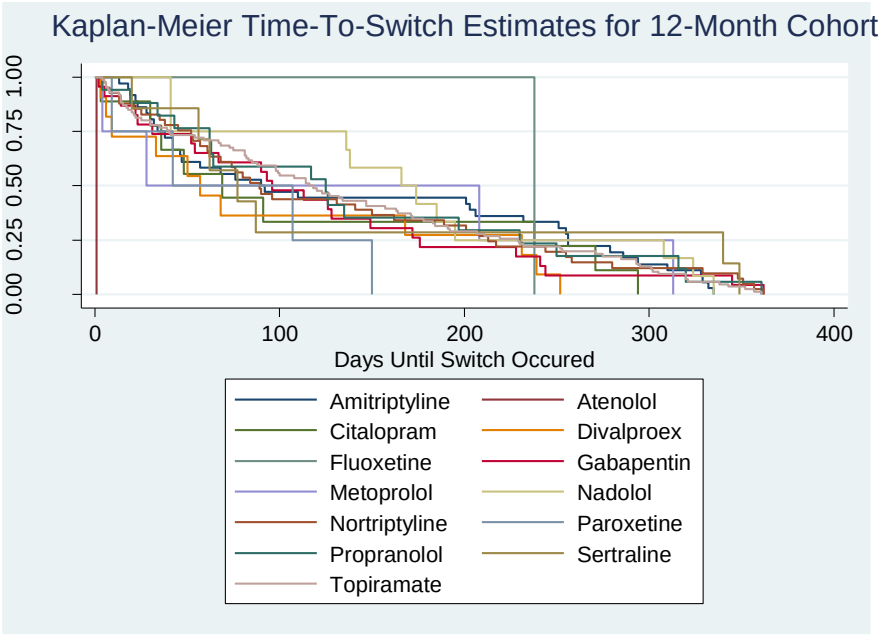


Table 7. ER Visits by Adherence and Initial Prophylactic, 6-Month Cohort

	PDC						*MPR*					
Prophylactic Medication	**N Adherent✗**	**N Non-adherent✗✗**	**N Adherent w/≥1 ER Visits**	**Proportion of Adherent Patients With ER Visits**	**N Non-Adherent w/≥1 ER Visits**	**Proportion of Non-Adherent Patients With ER Visits**	**N Adherent✗**	**N Non-adherent✗✗**	**N Adherent w/≥1 ER Visits**	**Proportion of Adherent Patients With ER Visits**	**N Non-Adherent w/≥1 ER Visits**	**Proportion of Non-Adherent Patients With ER Visits**
Amitriptyline	47	199	2	4%	13	7%	60	186	5	8%	10	5%
Nortriptyline	30	110	0	0%	8	7%	33	107	0	0%	8	7%
Citalopram	28	106	0	0%	5	5%	44	90	3	7%	2	2%
Sertraline	6	31	0	0%	3	10%	10	27	1	10%	2	7%
Fluoxetine	20	34	4	20%	4	12%	20	34	2	10%	6	18%
Paroxetine	10	9	2	20%	2	22%	9	10	1	11%	3	30%
Propranolol	27	103	0	0%	4	4%	32	98	0	0%	4	4%
Metoprolol	11	40	1	9%	7	18%	18	33	4	22%	4	12%
Nadolol	14	27	1	7%	1	4%	17	24	1	6%	1	4%
Atenolol	15	29	0	0%	0	0%	16	28	0	0%	0	0%
Gabapentin	33	144	8	24%	11	8%	58	119	10	17%	9	8%
Divalproex	15	69	0	0%	7	10%	20	64	0	0%	7	11%
Topiramate	134	346	6	4%	16	5%	146	334	6	4%	16	5%
Total	390	1247	24	6%	81	6%	483	1154	33	7%	72	6%

N – number, SD – standard deviation, MPR – medication possession ratio, PDC – proportion of days covered
✗Adherent is defined by MPR or PDC ≥80%
✗✗Non-adherent is defined by MPR or PDC <80%

Table 8. ER Visits by Adherence and Initial Prophylactic, 12-Month Cohort

	PDC						*MPR*					
Prophylactic Medication	**N Adherent**	**N Non-adherent**	**N Adherent w/≥1 ER Visits**	**Proportion of Adherent Patients With ER Visits**	**N Non-Adherent w/≥1 ER Visits**	**Proportion of Non-Adherent Patients With ER Visits**	**N Adherent**	**N Non-adherent**	**N Adherent w/≥1 ER Visits**	**Proportion of Adherent Patients With ER Visits**	**N Non-Adherent w/≥1 ER Visits**	**Proportion of Non-Adherent Patients With ER Visits**
Amitriptyline	14	125	2	14%	8	6%	16	123	3	19%	7	6%
Nortriptyline	12	59	0	0%	6	10%	14	57	0	0%	6	11%
Citalopram	7	58	0	0%	1	2%	8	57	0	0%	1	2%
Sertraline	2	16	0	0%	0	0%	2	16	0	0%	0	0%
Fluoxetine	2	23	0	0%	1	4%	2	23	0	0%	1	4%
Paroxetine	1	7	0	0%	2	29%	1	7	0	0%	2	29%
Propranolol	6	67	0	0%	1	1%	10	63	0	0%	1	2%
Metoprolol	3	20	0	0%	1	5%	3	20	0	0%	1	5%
Nadolol	6	18	1	17%	1	6%	6	18	1	17%	1	6%
Atenolol	4	14	0	0%	0	0%	5	13	0	0%	0	0%
Gabapentin	12	84	1	8%	11	13%	14	82	2	14%	10	12%
Divalproex	3	47	0	0%	4	9%	5	45	0	0%	4	9%
Topiramate	48	201	3	6%	10	5%	52	197	4	8%	9	5%
Total	120	739	7	6%	46	6%	138	721	10	7%	43	6%

N – number, SD – standard deviation, MPR – medication possession ratio, PDC – proportion of days covered
⚡Adherent is defined by MPR or PDC ≥80%
⚡⚡Non-adherent is defined by MPR or PDC <80%

Figure 4. Summary of ER Visits by Adherence Status, Adherence Measure, and Follow-Up Time

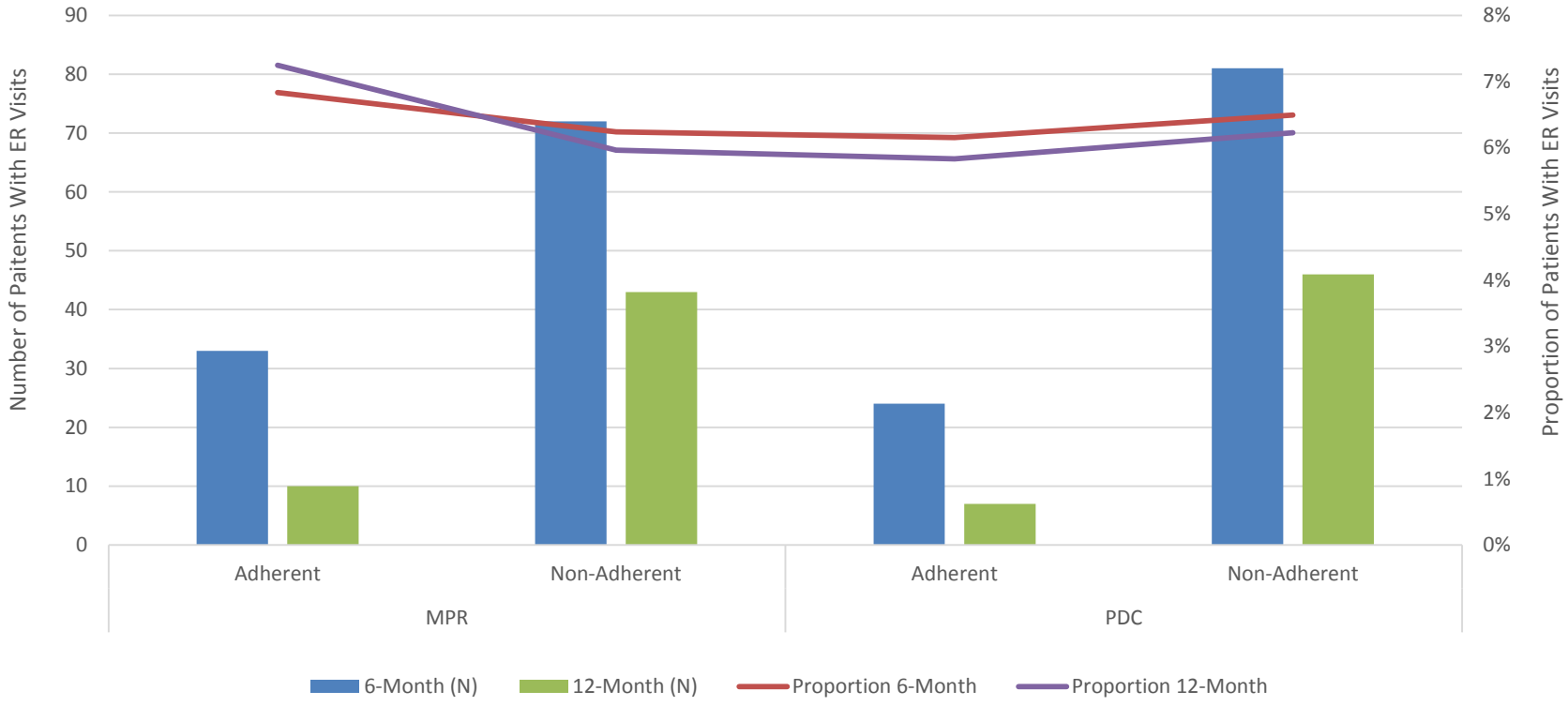


Table 9. Logistic Regression Model Results for ER Visits by Adherence Measure and Follow-Up Time

	6- Month			*12-Month*		
	MPR (99% CI)	PDC (99% CI)	Goodness of Fit (p-value)*	MPR (99% CI)	PDC (99% CI)	Goodness of Fit (p-value)*
Unadjusted Model	1.09 (0.71 - 1.68)	0.94 (0.58 - 1.50)	**1.000**	1.21 (0.59 - 2.47)	0.92 (0.40 - 2.08)	**1.000**
Adjusted Model	1.06 (0.68 - 1.64)	0.99 (0.61 - 1.62)	**0.326**	1.30 (0.60 - 2.85)	1.098 (0.46 - 2.57)	**0.125**

MPR – medication possession ratio, PDC – proportion of days covered

** Goodness of fit analysis reported as chi² test – p-values greater than 0.05 are considered statistically significant and are bolded*

Appendix 1. Model Covariate Selection for Regression and Cox Models

	6-Month Cohort		*12-Month Cohort*		*Actual Model*
Covariate	p-value*	Included in Model	p-value*	Included in Model	Included
Age	<.0001	Yes	<.0001	Yes	Yes
Sex	<.001	Yes	0.014	Yes	Yes
Employee Status	0.001	Yes	0.161	No	Yes
Employee Classification	<0.001	Yes	0.005	Yes	No
Geographical Region	0.009	Yes	0.402	No	Yes
MSA vs. Non-MSA	<0.001	Yes	0.014	Yes	Yes
Health Plan Type	0.085	Yes	0.577	No	Yes
Allergic Rhinitis	1.000	No	0.935	No	No
Asthma	0.214	No	0.062	Yes	No
Bipolar disorder	0.005	Yes	0.222	No	No
Cancer	0.001	Yes	0.036	Yes	Yes
Congestive heart failure	<0.001	Yes	<0.000	Yes	No
Coronary heart disease	0.002	Yes	<0.000	Yes	No
Depression	<0.001	Yes	0.001	Yes	Yes
Diabetes	0.26	No	0.444	No	No
Epilepsy	0.823	No	0.941	No	No
GERD	0.154	No	0.650	No	No
Hypertension	<0.001	Yes	0.002	Yes	Yes
Headache (other than Migraine)	0.001	Yes	0.198	No	Yes
Renal Failure	0.177	No	0.840	No	No
Sleep Disorder	0.672	No	0.339	No	No
Included Covariates	14		10		10

MSA – metropolitan statistical area, GERD – gastro esophageal reflux disorder
**p-value calculated using t-test for age and chi^2 test for all categorical variables*

Appendix 2. Demographics and Clinical Characteristics of Chronic Migraine Patients by Initial Prophylactic and Adherence Measure

	MPR								*PDC*							
	12 Month Cohort				6 Month Cohort				12 Month Cohort				6 Month Cohort			
Demographics of CM Patients	**Total N=861**	**Adherent N=140**	**Non-Adherent N=721**	**p-value***	**Total N=1640**	**Adherent N=486**	**Non-Adherent N=1154**	**p-value***	**Total N=861**	**Adherent N=154**	**Non-Adherent N=707**	**p-value***	**Total N=1640**	**Adherent N=393**	**Non-Adherent N=1247**	**p-value***
Age – Mean (SD)	39.95 (13)	44.16 (12)	39.13 (13)	**<.0001**	39.50 (13)	40.2 (12)	39.2 (13)	0.145	39.95 (13)	44.47 (12)	39.20 (13)	**<.0001**	39.50 (13)	41.21 (13)	38.96 (13)	**0.002**
Gender				0.992				0.605				0.472				0.849
Female	707 (82)	115 (82)	592 (82)		1348 (82)	404 (83)	947 (82)		707 (82)	103 (74)	604 (85)		1348 (82)	325 (83)	1026 (82)	
Employment Status				0.102				0.532				**0.035**				0.455
Full-time	496 (58)	82 (59)	414 (57)		890 (54)	271 (56)	619 (54)		496 (58)	70 (50)	426 (60)		890 (54)	222 (56)	668 (54)	
Part-time/Seasonal	11 (1)	2 (1)	9 (1)		15 (<1)	5 (1)	10 (<1)		11 (1)	2 (1)	9 (1)		15 (1)	5 (1)	10 (<1)	
Early Retiree	29 (3)	3 (2)	26 (4)		48 (3)	18 (4)	30 (3)		29 (3)	3 (2)	26 (4)		48 (3)	12 (3)	36 (3)	
Medicare Eligible Retiree	20 (2)	6 (4)	14 (2)		39 (2)	10 (2)	29 (3)		20 (2)	6 (4)	14 (2)		39 (2)	8 (2)	31 (2)	
Retiree	12 (1)	4 (3)	8 (1)		18 (1)	7 (1)	11 (<1)		12 (1)	4 (3)	8 (1)		18 (1)	6 (1)	12 (<1)	
COBRA	3 (<1)	2 (1)	1 (<1)		9 (<1)	4 (<1)	5 (<1)		3 (<1)	2 (1)	1 (<1)		9 (<1)	4 (1)	5 (<1)	
Long Term Disability	2 (<1)	0 (0)	2 (<1)		2 (<1)	1 (<1)	1 (<1)		2 (<1)	0 (0)	2 (<1)		2 (<1)	1 (<1)	1 (<1)	
Surviving Spouse/Dependent	2 (<1)	0 (0)	2 (<1)		4 (<1)	0 (0)	4 (<1)		2 (<1)	0 (0)	2 (<1)		4 (<1)	0 (0)	4 (<1)	
Other/Unknown	286 (33)	41 (29)	245 (34)		615 (38)	170 (35)	445 (39)		286 (33)	35 (25)	251 (35)		615 (38)	135 (34)	480 (38)	
Employee Classification				0.683				0.685				0.505				0.563
Salary Non-Union	131 (15)	27 (19)	104 (14)		241 (15)	73 (15)	168 (15)		131 (15)	23 (16)	108 (15)		241 (15)	58 (15)	183 (15)	
Salary Union	31 (4)	7 (5)	24 (3)		46 (3)	19 (4)	27 (2)		31 (4)	7 (5)	24 (3)		46 (3)	15 (4)	31 (2)	
Salary Other	28 (3)	2 (1)	26 (4)		52 (3)	17 (4)	35 (3)		28 (3)	1 (<1)	27 (4)		52 (3)	13 (3)	39 (3)	
Hourly Non-Union	70 (8)	11 (8)	59 (8)		140 (9)	38 (8)	102 (9)		70 (8)	10 (7)	60 (8)		140 (9)	31 (8)	109 (9)	
Hourly Union	80 (9)	15 (11)	65 (9)		138 (8)	42 (9)	96 (8)		80 (9)	14 (10)	66 (9)		138 (8)	36 (9)	102 (8)	
Hourly Other	7 (<1)	1 (<1)	6 (<1)		20 (1)	5 (1)	15 (1)		7 (<1)	1 (<1)	6 (<1)		20 (1)	3 (<1)	17 (1)	
Non-Union	62 (7)	9 (6)	53 (7)		106 (6)	36 (7)	70 (6)		62 (7)	7 (5)	55 (8)		106 (6)	32 (8)	74 (6)	
Union	18 (2)	2 (1)	16 (2)		44 (2)	14 (3)	30 (3)		18 (2)	2 (1)	16 (2)		44 (3)	12 (3)	32 (3)	
Unknown	434 (50)	66 (47)	368 (51)		853 (52)	242 (50)	611 (53)		434 (50)	57 (41)	377 (53)		853 (52)	193 (49)	660 (53)	
Geographical Location				0.441				0.315				0.337				0.117
Northeast	122 (14)	20 (14)	102 (14)		230 (14)	67 (14)	163 (14)		122 (14)	20 (14)	102 (14)		230 (14)	54 (14)	176 (14)	
North Central	251 (29)	45 (32)	206 (29)		444 (27)	146 (30)	298 (26)		251 (29)	35 (25)	216 (31)		444 (27)	118 (30)	326 (26)	
South	319 (37)	43 (31)	276 (38)		628 (38)	172 (35)	456 (40)		319 (37)	37 (26)	282 (40)		628 (38)	132 (34)	496 (40)	
West	167 (19)	32 (23)	135 (19)		329 (20)	97 (20)	232 (20)		167 (19)	30 (21)	137 (19)		329 (20)	85 (22)	244 (20)	
Unkown	2 (<1)	0 (0)	2 (<1)		9 (<1)	4 (<1)	5 (<1)		2 (<1)	0 (0)	2 (<1)		9 (<1)	4 (1)	5 (<1)	

Located in an "MSA"	755 (88)	121 (86)	634 (88)	0.620	1435 (88)	428 (88)	1007 (87)	0.653	755 (88)	105 (75)	650 (92)	0.556	1435 (88)	343 (87)	1092 (88)	0.878
Located outside of an "MSA"	106 (12)	19 (14)	87 (12)		205 (13)	58 (12)	147 (13)		106 (12)	17 (12)	89 (13)		205 (13)	50 (13)	155 (12)	
Health Plan Type				0.860				0.233				0.565				0.084
Comprehensive	27 (3)	5 (4)	22 (3)		47 (3)	11 (2)	36 (3)		27 (3)	5 (4)	22 (3)		47 (3)	8 (2)	39 (3)	
EPO	16 (2)	3 (2)	13 (2)		42 (3)	12 (2)	30 (3)		16 (2)	1 (<1)	15 (2)		42 (3)	13 (3)	29 (2)	
HMO	107 (13)	14 (10)	93 (13)		194 (12)	56 (12)	138 (12)		107 (13)	12 (9)	95 (13)		194 (12)	40 (10)	154 (12)	
POS	85 (10)	10 (7)	75 (10)		148 (9)	36 (7)	112 (10)		85 (10)	8 (6)	77 (11)		148 (9)	31 (8)	117 (9)	
PPO	561 (67)	96 (69)	465 (64)		1065 (65)	334 (69)	731 (63)		561 (67)	87 (62)	474 (67)		1065 (65)	263 (67)	802 (64)	
POS w/Capitation	1 (<1)	0 (0)	1 (<1)		11 (<1)	2 (<1)	9 (<1)		1 (<1)	0 (0)	1 (<1)		11 (<1)	1 (<1)	10 (<1)	
CDHP	27 (3)	3 (2)	24 (3)		70 (4)	13 (3)	57 (5)		27 (3)	2 (1)	25 (4)		70 (4)	12 (3)	58 (5)	
HDHP	11 (1)	2 (1)	9 (1)		26 (2)	8 (2)	18 (2)		11 (1)	2 (1)	9 (1)		26 (2)	11 (3)	15 (1)	
Other Diagnoses																
Allergic Rhinitis	196 (23)	28 (20)	168 (23)	0.394	354 (22)	97 (20)	257 (22)	0.299	196 (23)	24 (17)	172 (24)	0.379	354 (22)	81 (21)	273 (22)	0.590
Asthma	131 (15)	16 (11)	115 (16)	0.173	249 (15)	58 (12)	191 (17)	**0.017**	131 (15)	14 (10)	117 (17)	0.214	249 (15)	47 (12)	202 (16)	0.041
Bipolar disorder	35 (4)	3 (2)	32 (4)	0.208	68 (4)	19 (4)	49 (4)	0.755	35 (4)	2 (1)	33 (5)	0.143	68 (4)	11 (3)	57 (5)	0.124
Cancer	363 (42)	58 (41)	305 (42)	0.848	652 (40)	197 (40)	455 (39)	0.676	363 (42)	53 (38)	310 (44)	0.757	652 (40)	162 (41)	490 (39)	0.496
Congestive heart failure	9 (1)	7 (5)	2 (<1)	0.626	21 (1)	10 (2)	11 (<1)	0.069	9 (1)	2 (1)	7 (1)	0.486	21 (1)	7 (2)	14 (1)	0.311
Coronary heart disease	54 (6)	12 (9)	42 (6)	0.220	93 (6)	32 (7)	61 (5)	0.299	54 (6)	12 (9)	42 (6)	0.800	93 (6)	30 (8)	63 (5)	0.054
Depression	212 (25)	30 (21)	182 (25)	0.338	409 (25)	127 (26)	282 (24)	0.469	212 (25)	26 (19)	186 (26)	0.360	409 (25)	85 (22)	324 (26)	0.082
Diabetes	75 (9)	14 (10)	61 (8)	0.554	137 (8)	43 (9)	94 (8)	0.639	75 (9)	14 (10)	61 (9)	0.242	137 (8)	40 (10)	97 (8)	0.134
Epilepsy	20 (2)	5 (4)	15 (2)	0.284	45 (3)	17 (4)	28 (2)	0.225	20 (2)	5 (4)	15 (2)	0.160	45 (3)	14 (4)	31 (2)	0.255
GERD	201 (23)	32 (23)	169 (23)	0.881	345 (21)	97 (20)	248 (21)	0.487	201 (23)	28 (20)	173 (24)	0.912	345 (21)	76 (19)	269 (22)	0.344
Hypertension	221 (26)	36 (26)	185 (26)	0.989	412 (25)	124 (26)	288 (25)	0.812	221 (26)	32 (23)	189 (27)	0.878	412 (25)	105 (27)	307 (25)	0.403
Headache (other than Migraine)	671 (78)	106 (76)	565 (78)	0.489	1257 (77)	371 (76)	886 (77)	0.848	671 (78)	94 (67)	577 (82)	0.800	1257 (77)	295 (75)	962 (77)	0.395
Renal Failure	14 (2)	2 (1)	12 (2)	0.840	23 (1)	9 (2)	14 (1)	0.315	14 (2)	2 (1)	12 (2)	0.990	23 (1)	8 (2)	15 (1)	0.221
Sleep Disorder	210 (24)	36 (26)	174 (24)	0.690	378 (23)	116 (24)	262 (23)	0.609	210 (24)	30 (21)	180 (25)	0.956	378 (23)	88 (22)	290 (23)	0.723

CM – chronic migraine, SD – standard deviation, COBRA – Consolidated Omnibus Budget Reconciliation Act, MSA – metropolitan statistical area, EPO – exclusive provider organization, HMO – health maintenance organization, POS – point of service, PPO – preferred provider organization, CDHP – consumer driven health plan, HDHP – high deductible health plan, GERD – gastro esophageal reflux disorder
** p-value calculated using t-test for age and chi2 test for all categorical variables*
Statistically significant p-values are bolded

Appendix 3. Switch Rates and Days to Switching by Initial Prophylactic and Prophylactic Switched-To, 6-Month Cohort

Initial Prophylactic	*Started Initial Prophylactic*	*Switched From Initial Prophylactic*		*Days to Switching (SD)*	*Switched To Amitriptyline*		*Switched To Atenolol*		*Switched To Citalopram*		*Switched To Divalproex*		*Switched To Fluoxetine*		*Switched To Gabapentin*		*Switched To Metoprolol*		*Switched To Nadolol*		*Switched To Nortriptyline*		*Switched To Paroxetine*		*Switched To Propranolol*		*Switched To Sertraline*		*Switched To Topiramate*	
	N	N	%	Days	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Amitriptyline	246	49	20%	119 (107)	0	0%	0	0%	6	12%	1	2%	3	6%	7	14%	2	4%	0	0%	7	14%	1	2%	5	10%	6	12%	28	57%
Atenolol	44	8	18%	52 (42)	1	13%	0	0%	0	0%	1	13%	0	0%	0	0%	1	13%	0	0%	1	13%	0	0%	0	0%	1	13%	0	0%
Citalopram	134	61	46%	103 (87)	2	3%	0	0%	0	0%	0	0%	2	3%	2	3%	0	0%	0	0%	1	2%	1	2%	0	0%	5	8%	7	11%
Divalproex	84	23	27%	83 (87)	0	0%	0	0%	2	9%	0	0%	1	4%	5	22%	0	0%	0	0%	2	9%	1	4%	3	13%	2	9%	10	43%
Fluoxetine	54	24	44%	116 (118)	0	0%	0	0%	3	13%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	4%	2	8%
Gabapentin	177	59	33%	111 (92)	7	12%	1	2%	5	8%	2	3%	2	3%	0	0%	2	3%	1	2%	3	5%	0	0%	2	3%	1	2%	13	22%
Metoprolol	51	23	45%	111 (116)	1	4%	0	0%	2	9%	1	4%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	4%	1	4%	1	4%
Nadolol	41	8	20%	133 (108)	4	50%	0	0%	1	13%	0	0%	2	25%	3	38%	3	38%	0	0%	0	0%	0	0%	0	0%	0	0%	5	63%
Nortriptyline	140	41	29%	120 (99)	2	5%	2	5%	7	17%	4	10%	3	7%	11	27%	2	5%	1	2%	0	0%	0	0%	9	22%	1	2%	22	54%
Paroxetine	19	8	42%	91 (64)	0	0%	0	0%	4	50%	0	0%	1	13%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	2	25%	1	13%
Propranolol	130	42	32%	127 (107)	7	17%	2	5%	7	17%	1	2%	1	2%	4	10%	1	2%	1	2%	3	7%	2	5%	0	0%	2	5%	11	26%
Sertraline	37	33	89%	142 (125)	0	0%	0	0%	4	12%	0	0%	1	3%	5	15%	0	0%	0	0%	1	3%	1	3%	0	0%	0	0%	1	3%
Topiramate	480	101	21%	121 (97)	25	25%	3	3%	20	20%	13	13%	8	8%	22	22%	12	12%	5	5%	23	23%	2	2%	22	22%	11	11%	0	0%
Total	1637	480	29%	117 (99)	49	10%	8	2%	61	13%	23	5%	24	5%	59	12%	23	5%	8	2%	41	9%	8	2%	42	9%	33	7%	101	21%

N – number, SD – standard deviation

Appendix 4. Switch Rates and Days to Switching by Initial Prophylactic and Prophylactic Switched-To, 12-Month Cohort

Initial Prophylactic	*Started Initial Prophylactic*	*Switched From Initial Prophylactic*		*Days to Switching (SD)*	*Switched To Amitriptyline*		*Switched To Atenolol*		*Switched To Citalopram*		*Switched To Divalproex*		*Switched To Fluoxetine*		*Switched To Gabapentin*		*Switched To Metoprolol*		*Switched To Nadolol*		*Switched To Nortriptyline*		*Switched To Paroxetine*		*Switched To Propranolol*		*Switched To Sertraline*		*Switched To Topiramate*	
	N	N	%	Days	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Amitriptyline	139	37	27%	143 (120)	0	0%	0	0%	4	11%	0	0%	1	3%	5	14%	2	5%	0	0%	4	11%	1	3%	3	8%	6	16%	11	30%
Atenolol	18	1	6%	1	0	0%	0	0%	0	0%	1	100%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Citalopram	65	9	14%	120 (114)	1	11%	0	0%	0	0%	0	0%	1	11%	1	11%	0	0%	0	0%	0	0%	0	0%	0	0%	2	22%	4	44%
Divalproex	50	14	28%	80 (98)	0	0%	0	0%	1	7%	0	0%	0	0%	3	21%	0	0%	0	0%	1	7%	0	0%	2	14%	1	7%	6	43%
Fluoxetine	25	1	4%	238	0	0%	0	0%	1	100%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Gabapentin	96	24	25%	118 (105)	5	21%	0	0%	4	17%	1	4%	0	0%	0	0%	1	4%	1	4%	1	4%	0	0%	0	0%	1	4%	10	42%
Metoprolol	23	4	17%	138 148)	0	0%	0	0%	2	50%	1	25%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	25%	0	0%
Nadolol	24	12	50%	174 (106)	2	17%	0	0%	0	0%	0	0%	1	8%	2	17%	2	17%	0	0%	0	0%	0	0%	0	0%	0	0%	5	42%
Nortriptyline	71	41	58%	135 (112)	2	5%	2	5%	5	12%	3	7%	2	5%	7	17%	0	0%	0	0%	0	0%	0	0%	5	12%	0	0%	15	37%
Paroxetine	8	4	50%	77 (63)	0	0%	0	0%	2	50%	0	0%	1	25%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	25%
Propranolol	73	17	23%	145 (114)	3	18%	1	6%	3	18%	1	6%	1	6%	2	12%	1	6%	1	6%	1	6%	1	6%	0	0%	1	6%	1	6%
Sertraline	18	7	39%	142 (140)	0	0%	0	0%	2	29%	0	0%	0	0%	4	57%	0	0%	0	0%	1	14%	0	0%	0	0%	0	0%	0	0%
Topiramate	249	86	35%	141 (109)	12	14%	1	1%	12	14%	8	9%	4	5%	11	13%	7	8%	4	5%	10	12%	0	0%	12	14%	5	6%	0	0%
Total	861	257	30%	135 (111)	25	10%	4	2%	36	14%	15	6%	11	4%	35	14%	13	5%	6	2%	18	7%	2	1%	22	9%	17	7%	53	21%

N – number, SD – standard deviation