Treatment Patterns, Discontinuation, and Switching of Acute Medications for Migraine: A Cross-Sectional Survey

Chiemeka Ike

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Emily Beth Devine
Zachary Marcum

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Abstract

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Chiemeka Ike
Chair of the Supervisory Committee:
Associate Professor, Emily Beth Devine
School of Pharmacy

BACKGROUND: Migraine is an episodic neurological disorder that poses significant burden on patients and the physicians who manage their therapy. Treatment patterns for acute medications for migraine are not well characterized using claims databases alone. A variety of treatment approaches are taken by physicians and patients to find the optimal acute migraine medication. Only a few studies have evaluated the role of cardiovascular risk in migraine treatment selection. Generally, there is some understanding that cardiovascular disease risk may play a role in acute medication selection but few studies have explored this subgroup of patients in depth. Using Adelphi survey data, our research attempts to fill these gaps. The objective of this study was to characterize treatment patterns of discontinuation, switching, and satisfaction with acute medications for migraine using cross-sectional survey data from patients and physicians.

METHODS: Adelphi administered three surveys, the Physician Workload Questionnaire (PWQ), Patient Record Form (PRF), and Patient Self-Completion Questionnaire (PSC). We analyzed data from all three surveys. Survey respondents were migraineurs regardless of treatment history. We characterized physician demographics and workload patterns as well as patient demographics and migraine specific characteristics. Additionally, we characterized treatment patterns for discontinuation or switching. We also assessed physician-reported reasons for discontinuation or switching as well as patient-reported side effects currently experienced. We calculated the level of satisfaction for both physicians and patients with current acute medications for

migraine. We then explored characteristics of patients that were associated with triptan treatment failure, discontinuation in the past due to side effects, and discontinuation in the past due to lack of efficacy. In our secondary analyses, we focused on treatment patterns among patients with increased cardiovascular (CV) risk.

RESULTS: Physicians (N=431) completed a Patient Record Form (PRF) on up to 10 patients each with migraine for whom they were making treatment decisions. A total of 4,254 PRFs were completed. Over 70% of the patients were female, 47% were on acute medications only, 39% were on acute and preventive medications, 4% were on preventive medications only, and 11% were on no current treatment. At completion of data collection, patients had spent an average of 1,023 days on their current acute medication, while an average of 81 days elapsed between the most recently discontinued or switched acute medication and the start of the current medication. Sumatriptan and Ibuprofen were the two medications with the highest proportion of patients experiencing prior use with 23% and 16%, respectively. Physicians reported lack of efficacy as the most common reason for discontinuation or switching acute medications for migraine. Tiredness/fatigue was the most commonly reported side effect patients experienced while taking acute medications for migraine. On a seven-point Likert scale, over 60% of physicians and over 60% of patients were satisfied or extremely satisfied with their prescribed acute medications for migraine. The adjusted odds of treatment failure on a triptan were significantly higher for obese versus patients with normal BMI (OR = 1.438, 95% CI 1.083 to 1.991), significantly higher for episodic versus chronic patients (OR = 2.535, 95% CI 1.873 to 3.431), and significantly higher for those with current severe migraine (OR = 2.346, 95% CI 1.079 to 3.219) or current moderate migraine (OR = 1.529, 95% CI 1.169 to 2.015), each compared to mild migraine. Twelve percent of patients cited their most common reason for discontinuation or switching their triptan medication was after asking their doctor. For our subgroup analysis, patients with CV risk followed similar trends as the entire patient sample in the PRF with regards to demographics, the proportion of patient experiencing prior use, physician reasons for discontinuation or switching, and physician-reported level of satisfaction. Out of 611 patients characterized as having CV risk, 163 patients (27%) failed to achieve pain freedom at two hours post-dose while on a triptan.

CONCLUSION: Our findings show that patients had spent, on average, three months on their current acute medication for migraine while almost three months elapsed between the most recently discontinued or switched acute medication and the start of current medication. Triptans were the most common class of medications with the highest proportion of patients experiencing prior use which is consistent with current guidelines and their place in therapy. Lack of efficacy was cited most commonly by physicians as their reason for discontinuation or switching. Tiredness/fatigue was the most commonly reported side effect experienced by patients which may also be indicative of the triptan side effect profile. Physicians and patients were generally satisfied with current acute medications for migraine. Treatment failure while on a triptan was significantly associated with obesity, episodic migraine, and severe or moderate migraine. These migraine-specific characteristics may suggest patients with higher migraine burden in general. Finally, almost a third of patients with CV risk failed to achieve two-hour headache freedom on a triptan post-dose on more than half of occasions. Our study revealed that patients with CV risk may not be receiving adequate migraine relief from triptans.

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INTRODUCTION

Migraine is an neurological disorder characterized by a severe throbbing headache generally associated with nausea and, photophobia, sound sensitivity and low tolerance to sudden head movement. The spectrum of migraine disorders is classified at diagnosis as episodic or chronic migraine. Chronic migraine is defined as headaches occurring on 15 or more days per month for at least three months, occurring in a patient with lifetime history of at least five prior migraine attacks which has the features of migraine without aura and/or respond to migraine-specific treatment on at least 8 days per month and not attributed to medication overuse or another causative disorder.[1] Episodic migraine is characterized by those with migraine who have one to 14 headache days per month.[2] Migraine patients can also be categorized as having migraine with or without aura.[3] Migraine affects 39 million men, women and children in the US and 1 billion worldwide. Migraine affects women disproportionately, with 28 million female migraine sufferers in the US. Migraine disorders are associated with significant healthcare and lost productivity costs estimated at $36 billion annually in the U.S.[4] Treatment approaches include acute or preventive treatment or a combination of both. Acute medications for migraine include medication triptans, ergotamine derivatives/ergots, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and a combination of these medications (Appendix 1). Preventive therapies commonly used for migraine include beta-blockers, calcium channel blockers, anticonvulsants, or antidepressant medications.

In 2015, the American Headache Society (AHS) released clinical guidance for the treatment of acute migraine.[5] These guidelines provide specific recommendations based on the strength of evidence for certain drug classes categorized as “Effective/Level A”, “Probably effective/Level B”, and “Possibly effective/Level C”. Triptans carry a Level A recommendation. Ergotamine and other forms of dihydroergotamine carry a Level B recommendation. Nonspecific medications such as acetaminophen, NSAIDs, butorphanol nasal spray, sumatriptan/naproxen, and the combination of acetaminophen/aspirin/caffeine carry a Level A recommendation. In addition to effectiveness, the guidelines also recommend that clinicians consider potential side effects, risk of adverse events, and potential contraindications when making prescribing decisions. The guidelines stop short of providing guidance for specific medications in each of these instances.

When prescribing medications for acute migraine attacks, clinicians must consider migraine phenotype, frequency, severity, medication efficacy, comorbidities treatment history, and tolerability. The current approach of selecting acute treatments for migraine is largely driven by patient characteristics and physician preferences, which leads to large practice variation. Triptans are often considered first-line therapy. A 2015 review article examined treatment approaches for episodic migraine where an acute migraine medication is chosen based on severity of the attack and the resulting disability. The authors recommended that triptans should be chosen as initial therapy for a patient with severe attacks while acetaminophen or an NSAID may be an appropriate initial choice for a patient with less severe attacks.[6] Yet, triptans are contraindicated in patients with certain cardiovascular (CV) comorbidities. Similarly, pregnancy and breastfeeding patients are cautioned against using NSAIDs, as NSAID use after the 30th week of gestation has been found to be associated to premature closure of the ductus arteriosus and potentially associated with complications such as pulmonary hypertension.[7] Acetaminophen would typically be considered as a better option for acute treatment in these women. Further, the AHS guidelines consider opioids such as butorphanol, codeine/acetaminophen, and tramadol/ acetaminophen as “probably effective” but do not recommend them for routine use.[5]

Several studies have evaluated treatment and discontinuation patterns in the context of acute migraine treatment, each enrolling between 120 and 40,000 adult migraine patients.[8-12] All studies evaluated triptans alone or in combination with opioids, ergots, NSAIDs or over-the-counter (OTC) medications. Three retrospective claims database analyses evaluated discontinuation, switching and persistence over two years primarily among new triptan users. Chen et al reported that among Taiwanese adults, 26% discontinued a triptan, 34% were persistent users, and 41% switched to an NSAID, acetaminophen or ergotamine.[9] In the study by Katić et al, among US adults, 26% discontinued their newly prescribed triptan, 46% patients were

persistent users, and 67% switched to NSAIDs or opioids.[10] In a European study by Ng-Mak, 87% of patients discontinued their triptan, 14% were persistent users and less than 3% switched to a different class of medications.[11] Two cross-sectional surveys conducted in the US, examined patient reasons for triptan discontinuation and noted lack of effect and occurrence of side effects as the top two reasons for discontinuation.[8,12] Similarly, a prospective cohort study of migraine patients from Austria on newly prescribed triptans concluded that majority of patients switched or discontinued their medication due to insufficient treatment response, preference for other acute medications, or the occurrence of adverse effects.[13] A longitudinal survey of US migraine patients prescribed triptans and opioids found that opioid use was associated with an increased risk of medication discontinuation compared to triptans. In the same study, older age was a significant predictor of triptan discontinuation while migraine pain recurrence, concerns about drug interactions, and side effects were common reasons for triptan discontinuation.[14] Collectively, these studies provide information largely for US migraineurs using triptans for treatment of acute migraine attacks.

Further, of the seven aforementioned studies, only two evaluated the role of cardiovascular risk in migraine treatment selection. One of these studies mentioned that cardiovascular disease risk may play a role in adherence to triptans and found that patients with diabetes mellitus tended to discontinue their triptan, although the authors did not provide any plausible explanations for this phenomenon.[9] The second study briefly highlights the shortcomings in current migraine-specific treatments and the limited use of triptans, particularly among those with cardiovascular disease (i.e. myocardial infarction, arrhythmias) or cardiovascular risk (i.e. diabetes mellitus, obesity).[10]

We aim to fill some of these gaps. Our study is multinational, encompasses all available acute and preventive medications for migraine, uses data collected from patients and physicians, and characterizes treatment patterns in this overall population as well as in a subgroup with CV risk. The primary objective of this study was to characterize treatment patterns, patient-reported side effects experienced, physician and patient-reported level of satisfaction with prescribed acute medications, along with patient characteristics (e.g. migraine history, number of headache days per month) associated with triptan discontinuation or treatment failure while on a triptan using cross-sectional survey data. Our study offers the unique opportunity to compare physicians and patient views about reasons for discontinuation and switching. Finally, we conducted subgroup analyses in patients with known CV risk.

METHODS

Data source and study population

We analyzed cross-sectional survey data collected by Adelphi Real World® (Adelphi). Adelphi conducts national and multi-country observational studies through their initiative titled, "Disease Specific Programmes™ (DSPs). DSPs are Adelphi's proprietary, real-world evidence (RWE) generation programmes. Each DSP focuses on one disease state. In this initiative, Adelphi employees administer surveys that capture clinical practice patterns for each DSP. Each survey is administered in multiple countries/regions that can include France, Germany, Italy, Spain, United Kingdom (UK), United States (US), Japan, China, Australia and Latin America. A typical survey sample includes approximately 700 physicians (primary care and specialists). Physicians are identified from public lists of healthcare professionals and sampled according to selection criteria predefined for a specific DSP. Physician eligibility for participation is determined by specialty, whether they are responsible for making treatment decisions, and their patient workload in a typical week (in total and with the relevant condition). Physicians who meet these predefined eligibility criteria are subsequently invited to participate in the full DSP. Physician participation is voluntary. For each DSP, approximately 150 to 200 physicians are recruited from the US and 80 to 100 physicians from each of the other participating countries. Physicians are asked to recruit a predetermined number of consecutively consulting patients with the disease condition of interest, forming a convenience sample. There is no requirement for patient samples to be representative of the population with regard to race, socioeconomic status, or age. For each of their patients, each physician completes a patient record form (PRF). Patients whose information is recorded in a PRF are invited to confidentially complete a patient questionnaire (PSC) independently from their physician. The PSC questionnaire includes detailed questions on demographics, disease symptoms, comorbid conditions and treatment satisfaction, all from the patient's perspective.[15]

For the migraine DSP, between August and December 2017, Adelphi recruited 431 general practitioners (GPs)/primary care physician (PCPs) and neurologists across the US, UK, France and Germany. Physicians were recruited using public lists of health care professionals, and field-based interviewers; and were eligible if they were licensed and were making treatment decisions for patients suffering from migraines. For inclusion, PCPs must have made treatment decisions for ≥10 patients with migraine per month while neurologists must have made treatment decisions for ≥20 patients with migraine per month. Each physician was asked to recruit ten consecutive migraineurs who attended their clinic for any reason. Within this there was an oversample patient it may be worth mentioning. The 10th patient provided by each physician had to be receiving at least their second line of preventive therapy. Physicians were compensated to participate in the migraine DSP according to fair market research rates reflective of their time involvement. To meet eligibility criteria, patients were required to be ≥ 18 years of age and must have a physician confirmed diagnosis of migraine. Data were collecting using three surveys, the Physician Workload Questionnaire (PWQ), the PRF, and the Patient Self-Completed Questionnaire (PSC), each administered once. The PWQ was completed by physicians, and estimated workload, both total numbers of patients actively seen in the practice and those seen for migraine. The PRF contained detailed questions about patient demographics, diagnoses, severity of condition, number of headache days, comorbid conditions, treatment history (acute and preventive), and general questions about patients' migraine therapy. The PSC patient sample represented a subset of the PRF sample. The PSC captured similar information as that recorded on the PRF, only from the patient perspective with a big focus on quality of life. Consenting patients completed the PSCs independently of their physician, immediately after consultation.[14]

Evaluation Plan

Using Adelphi survey results, we first characterized physician demographics and workload patterns as reported in the PWQ. These variables included physician specialty, demographic characteristics, and proportion of patients seen by physicians in each type of practice setting (Table 1a). We defined chronic migraine in our analysis as 15 or more total headache days (including migraine, tension, rebound) over the last 3 months while episodic migraine was defined as total headache days of 0 to 14 headache days per month. Using demographic

variables captured in the PRF, we next characterized patient demographics, type of migraine (with or without aura), spectrum of migraine frequency, (episodic versus chronic), migraine severity over the past three months, types of migraine medications (acute/preventive), frequency of headache symptoms, number of migraine-related headache days per month (HDM) at diagnosis, and other clinical characteristics. We report these for both the total migraine sample and by subgrouping according to type of current migraine medication used along four dimensions: acute treatment only, acute and preventive treatment, preventive treatment only, and no current treatment (Table 1b). In our primary analysis, we included data from all survey responders, physicians who completed the PRF (regardless of whether there was a corresponding PSC or not) and patients who completed the PSC. When the same or a similar question was asked in both forms, we report the findings from each and qualitatively compare these to each other. We used questions from the PRF or the PSC to answer our research questions of interest with the goal of characterizing treatment, discontinuation and switching patterns. We captured physician-reported reasons for discontinuation, describe side effects experienced by patient self-report, satisfaction and drivers of satisfaction.

Treatment, Discontinuation and Switching Patterns

From the PRF, we characterized treatment patterns for the medication currently used, as well as up to three previously used medications, in reverse chronologic order, by start date. We also characterized treatment patterns for discontinuation or switching. The Adelphi survey captured each new line of therapy previously prescribed for each patient. A new line of therapy was considered a drug add-on, a discontinuation or a switch and did not include a dosage change. Discontinuation was defined as ceasing or discontinuing an acute medication for migraine. Switching was defined as initiation a different class of acute medication for migraine, not including dosage or formulation change. We characterized the proportion of patients who experienced prior use of any acute medication for migraine. We then characterized the average number of days of the gap that occurred between discontinuation/switching of the most recently prescribed medication and initiation of the currently prescribed medication. By the way the survey questions were worded, we were unable to distinguish between the two. Finally, by drug class and then by generic drug name, we characterized the proportion of patients who experienced prior use of any acute medication, regardless of overlap.

Reasons for discontinuation (physicians) and currently experienced side effects (patients)

Also from the PRF, we characterized physicians' current issues or reasons for discontinuation of prescribed acute medications. We report these in three ways: 1) using the categories of lack of efficacy, occurrence of side effects, and other; 2) listing the top five reasons, and 3) providing the complete list of reasons. Patients self-reported side effects of their currently used medications. We report the top five reasons and also provide the complete list.

Satisfaction

We calculated the level of both physician and patient satisfaction with patients' current acute medication for migraine, captured from the PRF and PSC, respectively. This information was captured on a 7-point Likert scale, ranging from extremely satisfied to extremely dissatisfied. When physicians were dissatisfied, we report the drivers of dissatisfaction and, for those who were dissatisfied, their most likely next course of action. Patients provided an estimate of their own likelihood of continuing their acute medication, based on their experience. This last question was reported on a 5-point Likert scale ranging from definitely yes to definitely no.

Triptan use

Next, focusing on triptan use, we defined three outcomes we captured from the PRF: treatment failure (defined as lack of headache freedom on more than 50% of occasions for a patient currently or previously on a triptan in the last six months), triptan discontinuation in the past due to side effects, and triptan discontinuation in the past for lack of efficacy. We calculated the proportion of patients who experienced each outcome separately; and then estimated the association between each characteristic and the outcome of treatment failure, while controlling for the other characteristics. These characteristics were selected from the

demographics table for their direct clinical relevance. We also report patient-reported reasons for discontinuing a triptan or switching to another triptan.

Secondary Analysis – CV Risk Population

We were especially interested in evaluating patients who had underlying cardiovascular (CV) risk, therefore, we conducted a secondary analysis in this subgroup of patients. To define and identify CV risk we reviewed both the Contraindications and Warnings/Precautions sections of the FDA Drug Labels of four representative triptan medications (almotriptan, eletriptan, sumatriptan, and zolmitriptan).[16-19] We applied this resulting list to the list of comorbidities collected using the Adelphi PRF, creating one-to-one matches to define the subgroup (Appendix 2). We then conducted our same analyses in this subgroup. In addition, to assess patients' understanding of CV risk from their perspective, we characterized CV risk severity (mild, moderate, severe) using a question from the PSC.

Analysis

The unit of analysis was the patient. For each patient characteristic, we evaluated and report the amount of missing data. For all our independent and outcome variables, we excluded "don't know" or missing responses. We summarized continuous variables using means and standard deviations (SDs), categorical variables using counts and proportions. All proportions were rounded to whole numbers. To evaluate associations between patient characteristics and each outcome of interest we used the Chi-square test of independence. In both the PRF and the PSC, satisfaction was rated on a 7-point Likert scale, ranging from extremely satisfied to extremely dissatisfied. Patients reported their likelihood of continuing their acute medication on a 5-point Likert scale ranging from definitely yes to definitely no. We used chi-2 tests to test the significance of the bivariate association between each selected patient characteristic and each outcome of interest; and multivariable logistic regression to estimate the association between all selected patient characteristics and each outcome of interest. Each selected patient characteristic was assessed for its potential as a confounder; those that were thought to be cofounders were included in the final models. If a patient were found to have any one of the CV risk factors listed in the Drug Label, they were classified as having CV risk. Analyses were conducted in R software version 3.4.3. Statistical test results were considered significant at an alpha level of 0.05. The data used in our analysis was collected by a third-party vendor. Therefore, it did not meet the federal definition of human subjects' research and did not obtain approval from the University of Washington Investigational Review Board.

RESULTS

Four hundred and thirty-one physicians completed the PWQ survey. This same number of physicians completed the PRF for their respective 4,254 patients. Lastly, 2,239 patients completed the PSC survey.

Characteristics of the Physician Population (Physician Baseline Data)

Among our sample of 431 physicians, 59% (N=256) practiced as a primary care physician (PCP) or general practitioner (GP) and 41% (N=175) were neurologists. Reflecting the sampling strategy, a greater proportion of physicians were from the US, with approximately equal proportions from each of the other countries. Approximately 70% of physicians were male. Neurologists cared for patients largely in the hospital setting, while PCPs cared for patients largely in the settings of private and public offices. A very small proportion of physicians were currently involved in clinical trials related to migraine. Physicians made treatment decisions for an average of 41 patients per month. PCPs managed a much larger number of patients for any health condition (including patients without migraine), when compared to neurologists, while neurologists managed a greater number of patients for migraine. The mean number of migraine patients diagnosed in the last 12 months was 51 patients. Neurologists managed a greater number of patients on acute migraine medications, preventive medications, and the combination of acute and preventive medications than PCPs (Table 1a).

Primary Analysis

Characteristics of the Patient Population (Patient Baseline Data)

Physicians completed the PRF for a total of 4,254 patients. Forty-seven percent (n=2,001) of patients were taking acute medications only, 39% (n=1646) were taking acute and preventive medications, 4% (n=152) were taking preventive medications only, and 11% (n=455) were not currently receiving treatment. The mean age of patient respondents was 40 years while the mean age at migraine diagnosis was 33 years. The majority of patients were female (73%). The mean body mass index (BMI) among patients was 26 kg/m2. The majority of patients were employed full-time and had never smoked. The mean number of years since migraine diagnosis was four years. The majority (90%) of patients were episodic migraineurs. Thirty-six percent of the patients experienced migraine with aura, 58% experienced migraine without aura, and 10% collectively experienced menstrual migraine and/or menstrually-related migraine (5% for each type). Physicians categorized the migraine severity of over 60% of their patients as “moderate.” In the last 3 months, 43% of patients had three or fewer total headache days per month (HDM), 32% had 4-7 total HDM, 16% had 8-14 HDM, and 10% had more than 15 total HDM. For migraine-related HDM, in the last 3 months, 52%, 30%, 13%, and 5% of patients had three or fewer, 4-7, 8-14, and more than 15 migraine-related HDM, respectively. Over 90% patients experienced three or fewer rebound HDM in the last 3 months. On average, patients experienced 5 migraine symptoms, while the mean number of total HDM and migraine-related HDM in the last 3 months were 6 and 5, respectively. The mean systolic blood pressure was 124 mmHg while the mean diastolic blood pressure was 76 mmHg. The mean total cholesterol for the patient sample was 130 mg/dl. Among US patients, 76% were Caucasian, while 89% were Caucasian among European Union (EU) patients (Table 1b).

Treatment patterns, discontinuation or switching

Of the 4,254 patients in the PRF, physicians reported that 3,694 (87%) patients had ever received an acute medication. The proportion of patients that received any three previously discontinued or switched acute medications was 8%, 1%, and <1%, respectively. Physicians reported that 1,259 out of 4,254 patients (30%) had experienced prior use of a prescribed acute medication at any time (Figure 1a/1b). The average number of days spent on current acute medication was 1023 (1509) days. The average number of days spent on any of the three previously discontinued or switched acute medications was 1,074 (1,575), 1,038 (1.517), 520 (646) days, respectively. Overall, the average number of days spent on any the three previously prescribed acute medications was 887 (253) days. An average gap that represented discontinuation or switching between the most recently prescribed medication and initiation of the current medication was 81 (346) days. Out of the 2,239 patients who completed the PSC survey, 1,820 patients (82%) reported that they were currently on acute medications for migraine, 345 (15%) stated they were not on acute medications, and 74 (3%) patients did not indicate if they were currently taking an acute medication for migraine (Table 2). The medication classes most commonly previously prescribed were triptans (n=580; 46%), NSAIDS, (n=376; 30%), ergot alkaloids (n=30; 2%) and other (n=273; 22%) (Figure 1a). The generic medications most commonly previously prescribed were sumatriptan (n=295 patients; 23%), followed by ibuprofen (n=199; 16%) and paracetamol (acetaminophen) (n=156; 12%) (Figure 1b).

Reasons for discontinuation (physicians) and side effects (patients)

Among 1,300 patients for whom physicians answered this question, the overarching current reasons for discontinuing a patient's acute medication were lack of efficacy (n=578; 45%), side effects (n=476; 37%), and other (n=246; 19%). (Figure 2a). The top five most commonly reported reasons were lack of efficacy (n=441); 25%, headache recurrence within 24 hours (n=261; 15%), tiredness/fatigue (n=134; 8%), drowsiness/sedation (n=128; 7%), and medication overuse headache (n= 100; 6%) (Figure 2b). Appendix 3 characterizes the complete list of reasons for discontinuation of acute medications for migraine. Of 1,820 responses, 1,281 patients (70%) reported they experienced side effects while on their current medication. The top five side effects reported by patients were tiredness/fatigue (n=257; 14%), drowsiness/sedation (n=224; 17%), dizziness (n=197; 15%), nausea/vomiting (n=119; 9%), and dry mouth (n=91; 7%) (Figure 2c). Appendix 3 lists all patient-reported current side effects.

Satisfaction

There was a total of 3,651 physician satisfaction responses. The majority (>60%) of physicians were satisfied or extremely satisfied with their patients' current acute medication (Figure 3). Physicians provided drivers of dissatisfaction for 839 patients with regards to their current prescribed acute medication. The drivers of dissatisfaction in decreasing order were lack of efficacy (n=408; 49%), diminished efficacy over time (n=278; 33%), other (n=106; 13%), number of side effects experienced (n=102; 12%), mode of administration (n=28; 3%), and severity of side effects experienced (n=17; 2%). However, when physicians answered what would be their most likely next course of action should the patient's medication prove sub-optimal, 1,697 out of 3,651 (46%) responded they would switch the current acute medication, while 200 (5%) indicated their next course of action would be to switch formulations. Only 28 (< 1%) physicians responded that discontinuation would be their next course of action. Over 60% of patients were satisfied or extremely satisfied with their prescribed medication (Figure 4). When patients were asked whether they would like to continue using their prescribed medication 995 of 2,239 (44%) responded "definitely yes", 637 (29%) responded "probably", while 31 patients (1.4%) responded as "definitely not" or "probably not." Five-hundred and seventy-six patients (26%) either did not respond to this question or responded as "don't know."

Triptan use

Of the 4,254 patient responses from the PRF, there was a statistically significant difference between those who discontinued a triptan in the past due to lack of efficacy and total HDM ($p<0.001$); and between those who experienced treatment failure while on a triptan and type of migraine ($p<0.05$), BMI category, spectrum of migraine frequency, type of migraine treatment, migraine severity, total HDM for past three months, migraine-

related HDM for past three months, and rebound (all p<0.001). There were no significant differences between those who discontinued a triptan in the past due to side effects and any characteristic. (Table 3). Table 4 summarizes the results from the adjusted/multivariable logistic regression using patient data obtained from the PRF survey. The adjusted odds of treatment failure on a triptan were significantly higher for obese versus patients with normal BMI (OR =1.438, 95% CI 1.083 to 1.991), significantly higher for episodic versus chronic patients (OR = 2.535, 95% CI 1.873 to 3.431), and significantly higher for those with current severe migraine (OR = 2.346, 95% CI 1.079 to 3.219) or current moderate migraine (OR = 1.529, 95% CI 1.169 to 2.015), each compared to mild migraine. A total of 1,458 patients reported their reasons for discontinuation/switching their triptan medication. The largest proportion of patients discontinued or switched their triptan medication after asking their doctor (n=171; 12%), followed by the side effect of tiredness/fatigue (n=133; 9%), dizziness (n=108; 7%), drowsiness/sedation (n=90; 6%), or due to a doctor recommended break (n=75; 5%) (Figure 5) (The survey question did not ask patients to state what, specifically, they asked their doctor). Appendix 3, Figure 5a has a comprehensive list of patient-reported reasons for discontinuation or switching their triptan medication).

Secondary Analysis

Characteristics of patients with cardiovascular (CV) risk

Of the 4,254 patients represented in the PRF sample, we characterized 611 patients (14%) as having increased CV risk. Physicians reported that 49 out of 611 patients (8%) had never received a triptan because of the warnings, precautions and/or contraindications. Among the 2,239 patients who completed the PSC, 567 patients (73%) indicated that they perceived their CV risk to be “mild”, 181 (23%) indicated their risk as “moderate”, and 25 (3%) as “severe.” Physicians completed the PRF for a total of 611 patients characterized as having CV risk. Thirty-eight percent (n=233) of patients were taking acute medications only, 53% (n=323) were taking acute and preventive medications, 3% (n=16) were taking preventive medications only, and 6% (n=39) were not currently receiving treatment. The mean age of patient respondents was 53 years while the mean age at migraine diagnosis was 44 years. The majority of patients were female (67%). The mean body mass index (BMI) among patients was 28 kg/m2. The majority of patients were employed full-time and had never smoked. The mean number of years since migraine diagnosis was eight years. The majority (87%) of patients were episodic migraineurs. Forty-three percent of the patients experienced migraine with aura, 55% experienced migraine without aura, and 6% collectively experienced menstrual and/or menstrually-related migraine (3% for each type). About 15% categorized their current migraine severity as “moderate.” In the last 3 months, 41% of patients had three or fewer total HDM, 29% had 4-7 total HDM, 17% had 8-14 HDM, and 13% had more than 15 total HDM. For migraine-related HDM, in the last 3 months, 52%, 30%, 12%, and 6% of patients had three or fewer, 4-7, 8-14, and more than 15 migraine-related HDM, respectively. Over 90% patients experienced three or fewer rebound HDM in the last 3 months. On average, patients experienced 5 migraine symptoms, while the mean number of total HDM and migraine-related HDM in the last 3 months were 7 and 5, respectively. The mean systolic blood pressure was 135 mmHg while the mean diastolic blood pressure was 82 mmHg. The mean total cholesterol for the patient sample was 145 mg/dl. Among US patients, 72% were Caucasian, while 85% were Caucasian among European Union (EU) patients (Table 5). Out of 611 patients characterized as having CV risk, 476 (78%) patients had hypertension, 6% had arrhythmias, and 4% had reynaud’s disease (Table 6).

Treatment patterns, discontinuation or switching (among patients with CV risk)

Of the 611 patients characterized as having CV risk in the PRF, physicians reported that 561 (92%) patients had ever received an acute medication. The proportion of patients that received any three previously discontinued or switched acute medications were 11%, 1%, and <1%, respectively. Physicians reported that 236 out of 611 patients (39%) had experienced prior use of a prescribed acute medication at any time. The average number of days spent on current acute medication was 1,315 (1,766) days. The average number of days spent on any of the three previously discontinued or switched acute medications was 1,852 (2,570), 2,035 (1,516) days and no patients had received a third previously discontinued or switched acute medication, respectively. Overall, the

average number of days spent on the three previously prescribed acute medications was 1,944 (91) days. An average gap that represented discontinuation or switching between the most recently prescribed medication and initiation of the current medication was 168 (427) days (Table 7). The medication classes most commonly previously prescribed were comprised of triptans, NSAIDS, ergot alkaloids, and other (Figure 6a). The medications most commonly previously prescribed were sumatriptan (n=67; 28%), followed by ibuprofen (n=29; 12%) and paracetamol (acetaminophen) (n=25; 11%) (Figure 6b). Among patients with CV risk, there were 322 patient responses in the PSC for whether they were currently on acute medications. Two hundred and seventy patients (84%) reported that they were currently on acute medications for migraine, 18 (6%) stated they were not on acute medications, and 11 (4%) patients did not indicate if they were currently taking an acute medication for migraine.

Reasons for discontinuation (physicians) and side effects (patients) (among patients with CV risk)

Among 387 patients with CV risk for whom physicians answered this question, among the top five current issues/reasons for discontinuation, lack of efficacy (n=79; 20.4%) was the most commonly reported current issue/reason for discontinuation of acute medications, followed by headache recurrence within 24 hours (n=42; 11%), tiredness/fatigue (n=33; 9%), drowsiness/sedation (n=30; 8%), and gastrointestinal side effects (n=23; 6%) (Figure 7a) (see Appendix 3, Figure 7ai for comprehensive list). Of 322 responses, 280 patients (87%) reported they experienced side effects while on their current medication. The top five side effects reported by patients were tiredness/fatigue (n=52; 19%), drowsiness/sedation (n=47; 17%), dizziness (n=37; 13%), nausea/vomiting (n=25; 9%), and dry mouth (n=24; 9%) (Figure 7b) (Appendix 3, Figure 7bi lists all patient-reported current side effects).

Satisfaction (among patients with CV risk)

Physicians responded to the satisfaction question for 557 patients with CV risk. The majority (>60%) of physicians were satisfied or extremely satisfied with their patients' current medication (Figure 8). Among patients with CV risk, 142 physicians provided drivers of dissatisfaction for their patient's current prescribed acute medication. The drivers of dissatisfaction in descending order were lack of efficacy (n=60; 42%), diminished efficacy over time (n=58; 41%), number of side effects experienced (n=21; 15%), other (n=11; 8%), mode of administration (n=5; 4%), and severity of side effects experienced (n=3; 2%). However, when physicians answered what would be their most likely next course of action should the patient's medication prove sub-optimal, 244 out of 558 (44%) responded they would switch the current acute medication, while 36 (6%) indicated their next course of action would be to switch formulations. Physicians responded that discontinuation would be their next course of action for 7 patients (1%). Among patients with CV risk, about 160 out of 322 (50%) of patients who responded were satisfied or extremely satisfied with their prescribed medication (Figure 9). When patients were asked whether they would like to continue using their prescribed medication out of 133 out of 322 (41%) patients who answered this question responded, "definitely yes", 101 (31%) responded "probably", while 5 patients (2%) responded as "definitely not" or "probably not." Eighty-three patients (26%) either did not respond to this question or responded as "don't know."

Triptan use (among patients with CV risk)

Among patients with CV risk, 356 patients reported their reasons for discontinuation/switching their triptan medication. The largest proportion of patients discontinued or switched their triptan medication after asking their doctor (n=32; 9%), followed by the side effect of tiredness/fatigue (n=27; 8%), dizziness (n=27; 8%), drowsiness/sedation (n=20 6%), or due to a doctor recommended break (n=16; 4%) (Figure 10) (Appendix 3) (The survey question did not ask patients to state what, specifically, they asked their doctor.) Figure 10a is a full list of patient-reported reasons for discontinuation or switching triptan medication). Out of 611 patients we characterized as having CV risk, 163 patients (27%) failed to achieve pain freedom at two hours post-dose on > 50% of the time while on a triptan.

DISCUSSION

Primary Analysis

Treatment patterns, discontinuation or switching

The proportion of patients on previously prescribed medication decreased from the first through the third previously used medication. This is likely because of the extent of recall required for the latter previously used medications. The average number of days spent on each of the medications increased from first through the third previously used medication. Also, this may be because of the smaller observations for the latter previously used medications. On average, patients stayed on any of the three previously discontinued or switched medications for 2 years. Among patients who used up to three acute medications previously, an average gap of 3 months passed between discontinuation or switching of their first most recently prescribed medication and initiation of the current medication. About 30% of patients in our sample were not treatment naïve. Sumatriptan and ibuprofen were the most commonly prescribed medications.

Reasons for discontinuation (physicians) and side effects (patients)

Physicians' main reason for discontinuing a patient's prescribed acute medication for migraine was lack of efficacy. Seventy percent of patients reported experiencing side effects while taking their current medication.

Satisfaction

Physicians were mostly satisfied with patient's current acute medication for migraine. The top three drivers of dissatisfaction were lack of efficacy, diminished efficacy over time, and other. However, if a patient's medication proved sub-optimal, almost 50% of physicians would switch their patient's medication. Almost half of patients were satisfied with their prescribed medication. About 45% of patients reported that they were definitely going to continue using their prescribed acute medication for migraine. Both physicians and patients were relatively satisfied with the current acute medication.

Triptan use

Treatment failure was largely associated with characteristics that describe migraine (type, spectrum, type of treatment, severity, and HDM). Treatment failure while on a triptan was significantly higher for those patients who were obese and with a higher migraine headache burden (episodic, and moderate or severe).

Secondary Analysis

Characteristics of the subgroup with CV risk

Compared to the patients in the overall PRF sample, patients with increased CV risk, fewer patients were on acute medications only or were not currently on treatment, whereas a higher proportion of patients were taking both acute and preventive medications or preventive medications only. Patients with increased CV risk were older and had a higher mean age at migraine diagnosis. Among patients with increased CV risk, the majority were female, had slightly higher BMI, were employed full-time and had never smoked; similar to all patients represented in the PRF. The mean number of years since migraine diagnosis was twice that of entire patient sample. Similarly, the majority of patients were episodic migraineurs. A higher proportion of patients experienced migraine with aura compared to the entire patient sample, however migraine without aura, menstrual and menstrually-related migraine had lower proportion of patients compared to the entire patient sample. A much smaller proportion of patients categorized their current migraine severity as moderate. Patients with increased CV risk were similar to the larger patient sample with regards to total HDM, migraine-related HDM, rebound HDM in the last three months, mean number of migraine symptoms, mean number of total HDM, and migraine-related HDM in the last three months. However, we found that patients with CV risk had higher mean systolic blood pressure, diastolic blood pressure, and total mean cholesterol. Additionally, we found similar characteristics for ethnicity/race among US and EU patients.

Treatment patterns, discontinuation or switching

The trend for the proportion of patients on previously prescribed medication was similar for the secondary analysis. Again, this may be because of the extent of recall required for the latter previously used medications. The average number of days spent on each of the medications increased from first through the third previously used medication similar to the primary analysis. Also, this may be because of the smaller observations for the latter previously used medications. On average, patients stayed on all three previously discontinued or switched medications for 5 years. Among patients with CV risk who used up to three acute medications previously, an average gap of 6 months passed between discontinuation or switching of their first most recently prescribed medication and initiation of the current medication. About 40% of patients in our sample with CV risk were not treatment naïve. Sumatriptan and ibuprofen were the most commonly prescribed medications among patients with CV risk.

Satisfaction

Physicians were mostly satisfied with patient's current acute medication for migraine. The top three drivers of dissatisfaction were lack of efficacy, diminished efficacy over time, and other. However, if a patient's medication proved sub-optimal, less than half of physicians indicated they would switch their patient's medication, and a very small percentage would switch formulations.

Triptan use

Almost a third of patients with CV risk failed to achieve pain freedom while on triptan.

Comparison with literature

The Migraine DSP is different from other large studies of migraine in the US and worldwide. The American Migraine Prevalence and Prevention (AMPP) AMPP study[20], the Chronic Migraine Epidemiology and Outcomes (CaMEO) study[21], and the International Burden of Migraine Study (IBMS)[22] have all assessed the burden of migraine. The AMPP was a population-based study that used annual postal survey data collected over five years. The CaMEO study used a web-based survey to collect data every three months over a 15-month period. The IBMS was also a web-based, large international cross-sectional survey of persons across North America, South America, Europe and Asia with chronic and episodic migraine. The conduct of the Migraine DSP was methodologically different from the other migraine studies because it uses "real world" data that reflects current clinical practice. Our study focuses primarily on treatment patterns for acute medications for migraine treatment and satisfaction levels from physicians and patients. Additionally, we sought to characterize similar treatment patterns and level of satisfaction with current acute medications among patients with CV risk.

Triptans are the most widely used drug class, often in combination with other agents. Discontinuation and switching are both used to characterize patient characteristics in relation to acute treatment of migraine. The studies that have explored treatment patterns and disease burden in migraine have varying definitions, time periods of observation, and methods for assessing outcomes for discontinuation and switching. Chen et al reported that care by a neurologist (specialist) was associated with triptan use. On average, a greater proportion of patients discontinued triptan therapy than switched.[11] Generally, there is a wide range when it comes to proportion or rates of discontinuation and switching. The current literature highlights the gaps that remain in the evidence describing treatment patterns, switching or cycling of acute migraine medications.

Approximately 10 to 13% of all physicians answered, "don't know" when asked about patients' treatment failure at two hours post-dose on more than half of occasions, triptan discontinuation in the past due to lack of efficacy, and triptan discontinuation in the past due to side effects. Excluding "don't know" was unlikely to bias our estimates of the influence of "yes" versus "no. However, this reduced our sample size and thus reduced statistical power with regard to the remaining patient characteristic variables.

This paper adds to the understanding of treatment patterns for migraine. Triptans followed by NSAIDs were the class of medication with the highest proportion of patients having experienced prior use. This finding is consistent with the 2015 AHS guidelines on the acute treatment of migraine in adults. The AHS guidelines give

a Level A recommendation (effective) for specific medications such as triptans while ergotamine and other forms of dihydroergotamine have a Level B recommendation (probably effective).[8]

Lack of efficacy was cited as the most common reason for physician discontinuing or switching a patient's treatment, while patients reported discontinuing or switching after asking their physician. Tiredness/fatigue was the most common patient-reported side effects experienced which is indicative of the side effect profile of triptans as a class. Our results were similar to the Chen et al study[11] which cited common reasons for discontinuation as inadequate treatment response or pain relief and side effects. Physicians and patients were generally satisfied with their current acute medication even though a large proportion of physicians reported current issues while patients reported side effects experienced on current acute medications. This may be because patients and physicians have largely accepted the current available therapies and see impending improvement in their migraine management. Factors associated with switching or discontinuation of acute migraine medications included episodic migraine, migraine with aura, and increased migraine severity.

In our study, we were able to assess current treatment patterns among the CV patient population for whom triptan use is contraindicated or for which there is a warning/precaution against use in the drug label. The AMPP study assessed the prevalence of CV events among individuals with episodic migraine in the US. In this study, the highest prevalence of CV events and/or procedures was in those age 60 or older. In patients over 60 years, 22% reported CV events or conditions.[23] We found a slightly lower prevalence of CV risk (14%) in our migraine patient population compared to the AMPP study. According to a recently published Danish matched cohort study, migraine, particularly migraine with aura may be an important risk factor for cardiovascular diseases such myocardial infarction, ischemic stroke, hemorrhagic stroke, venous thromboembolism, and atrial fibrillation.[24] In our study, migraine with aura was associated with a significantly higher risk of treatment failure on triptan compared to patients characterized as experiencing migraine without aura. Among patients with increased CV risk, 27% of patients failed to achieve two-hour headache pain freedom post-dose more than 50% of the time.

Strengths and Limitations

Unique to our study is that we delve deeper into understanding the role of CV risk in acute medication selection, particularly by characterizing treatment patterns, physician-reported current issues with acute medications, medications with the highest proportion of patients experiencing prior use, and physician-reported satisfaction with current acute medications among patient with CV risk.

One of the main strengths of this study was that the Adelphi Migraine DSP dataset provides physicians' actual treatment and prescribing decisions/patterns unlike a trial setting which is not always representative of clinical practice.. The Migraine DSP is multinational and includes all consulting patients regardless of insurance coverage. Another strength was that each patient included in this analysis had a physician-reported diagnosis of migraine. It is important to note that amongst the variables collected, the Migraine DSP via the PRF survey includes clinical characteristics, which allowed us to analyze the subgroup of patients with CV risk. Finally, the Migraine DSP contains complete treatment history, and reasons for discontinuation or switching acute medications.

Our results are limited by the cross-sectional nature of the study, and potential selection bias by physicians who chose to participate in the study. Selection bias may play a factor in physicians' willingness to participate and how physicians recruited consecutive patients. Although the DSP process sought to minimize selection bias by encouraging participating physicians to collect data on a series of consecutive patients, this was contingent on physicians' integrity. Additionally, since the study participation sites were selected based on the volume of patients with migraine routinely seen, generalization to all patients with migraine is somewhat limited. One major limitation of our study is its inability to distinguish between discontinuation and switching in some of our analysis. Specifically, from the metric we used to characterize treatment discontinuation or switching, we could not distinguish whether the gap time between discontinuation of the most recently prescribed medication and initiation of the currently prescribed medication explained the gap between discontinuation or

switching. Moreover, when we calculated proportions of patients that experienced prior use of each class of acute medication for migraine, the prior use of medications indicated such as sumatriptan and ibuprofen were not mutually exclusive. Due to the observational nature of the Migraine DSP, any significant difference of an outcome using bivariate analyses between patient subgroups may be due to confounding. Lastly, we cannot rule out residual confounding in our multivariable analyses.

Future Work

One helpful direction for future studies would be to include additional risk factors with clinician input that may be more comprehensive for cardiovascular risk. For example, a patient with unrecognized CAD that may be predicted by the presence of obesity, hypercholesterolemia, smoking status, obesity, or diabetes, strong family was not classified at having CV risk in our study unless they had a history of or were currently suffering from a CV event. In doing this, we may be able to fully capture the burden of migraine in patients with CV risk. In addition, future work in the PSC survey deployment could endeavor to capture CV clinical characteristics to make side-by-side comparisons from patients and physicians among patients with CV risk.

CONCLUSION

Our findings show that during the survey time period, patients had spent, on average, three months on their current acute medication for migraine while almost three months elapsed between the most recently discontinued or switched acute medication and the start of current medication. Triptans were the most common class of medications with the highest proportion of patients experiencing prior use which is consistent with current guidelines and their place in therapy. Lack of efficacy was cited most commonly by physicians as their reason for discontinuation or switching. Tiredness/fatigue was the most commonly reported side effect experienced by patients which may also be indicative of the triptan side effect profile. Physicians and patients were generally satisfied with current acute medications for migraine. Treatment failure while on a triptan was significantly associated with episodic migraine, migraine with aura, and severe or moderate migraine. These migraine-specific characteristics may suggest patients with higher migraine burden in general. Finally, almost a third of patients with CV risk failed to achieve two-hour headache freedom on a triptan post-dose on more than half of occasions. Our study revealed that patients with CV risk may not be getting adequate migraine relief from triptans.

REFERENCES

1. Olesen J, Bousser MG, Diener HC, et al. New appendix criteria open for a broader concept of chronic migraine. Cephalalgia. 2006; 26:742–746. doi: 10.1111/j.1468-2982.2006.01172.
2. Katsarava Z, Buse DC, Manack AN, Lipton RB. Defining the differences between episodic migraine and chronic migraine. Curr Pain Headache Rep. 2012; 16:86–92.
3. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1- 211.
4. Migraine Facts. Migraine Research Foundation website. Accessed on June 4, 2018. http://migraineresearchfoundation.org/about-migraine/migraine-facts/).
5. Marmura MJ, Silberstein SD, Schwedt TJ. The Acute Treatment of Migraine in Adults: The American Headache Society Evidence Assessment of Migraine Pharmacotherapies. Headache. 2015;55(1):3–20.
6. Becker WJ. Acute Migraine Treatment in Adults. Headache. 2015; 55:778.
7. Schoenfeld A, Bar Y, Merlob P, Ovadia Y. NSAIDS: maternal and fetal considerations. Am J Reprod Immunol 1992; 28:141.
8. Wells RE, Markowitz SY, Baron EP, et al. Identifying the factors underlying discontinuation of triptans. Headache. 2014; 54:278-289.
9. Chen TB, Chen YT, Fuh JL et al. Treatment adherence among new triptan users: A 2-year cohort study in Taiwan. J Headache Pain. 2014; 15:48.
10. Katic BJ, Rajagopalan S, Ho TW et al. Triptan persistency among newly initiated users in a pharmacy claims database. Cephalalgia. 2011; 31:488-500.
11. Ng-Mak DS, Chen YT, Ho TW et al. Results of a 2-year retrospective cohort study of newly prescribed triptan users in European nationwide practice databases. Cephalalgia 2012; 32:875.
12. Landy SH, Turner IM, Runken MC et al. A cross-sectional survey to assess the migraineur's medication decision-making beliefs: determining when a migraine is triptan-worthy. Headache. 2013;53(7):1134-46.
13. Fischer M, Frank F, Willie G et al. Triptans for Acute Migraine Headache: Current Experience With Triptan Use and Prescription Habits in a Tertiary Care Headache Outpatient Clinic: An Observational Study. Headache. 2016; 56(6):952-60.
14. Holland S, Fanning KM, Serrano D et al. Rates and reasons for discontinuation of triptans and opioids in episodic migraine: results from the American Migraine Prevalence and Prevention (AMPP) study. J Neurol Sci. 2013;326(1-2):10-17.
15. Anderson P, Benford M, Harris N et al. Real-world physician and patient behaviour across countries: Disease-Specific Programmes – a means to understand. Current Medical Research and Opinions 2008; 24(11):3063-3072. doi:10.1185/03007990802457040.
16. Almotriptan (Axert® tablets) [Package Insert]. Kalamazoo, MI: Pharmacia and Upjohn Co., 2001.
17. Eletriptan (Replax® tablets) [Package insert]. New York, NY: Pfizer, 2002.
18. Sumatriptan (Imitrex® tablets) [Package insert]. Research Triangle Park, NC: GlaxoSmithKline, 1992.
19. Zolmitriptan (Zomig® tablets) [Package Insert]. Wilmington, DE: Zeneca Pharmaceuticals, 1997.
20. Diamond S, Bigal ME, Silberstein S, et al. Patterns of diagnosis and acute and preventive treatment for migraine in the United States: Results from the American Migraine Prevalence and Prevention study. Headache. 2007; 47:355-363.
21. Adams AM, Serrano D, Buse DC, et al. The impact of chronic migraine: The Chronic Migraine Epidemiology and Outcomes (CaMEO) Study methods and baseline results. Cephalalgia. 2015; 35:563-578.
22. Payne KA, Varon SF, Kawata AK, et al. The International Burden of Migraine Study (IBMS): Study design, methodology, and baseline cohort characteristics. Cephalalgia. 2011; 31:1116-1130.
23. Buse DC, Reed ML, Fanning KM et al. Cardiovascular events, conditions, and procedures among people with episodic migraine in the US Population: results from the American migraine prevalence and prevention (AMPP) study. Headache. 2016; 57: 31–44.

24. Adelborg K, Szépligeti SK, Holland-Bill L et al. Migraine and risk of cardiovascular diseases: Danish population-based matched cohort study. BMJ 2018; 360: k96. doi: 10.1136/bmj.k96.

TABLES

Table 1a: Physician Characteristics by Specialty †

Physician Characteristics (N, %)	**Total N (%)**	**Neurologist (n=175)**	**PCP/GP (n=256)**
Male sex, n (%)	289 (67%)	123 (70%)	166 (65%)
Country, n (%)			
France	98 (23%)	44 (25%)	54 (21%)
Germany	91 (21%)	40 (23%)	51 (20%)
UK	90 (21%)	40 (23%)	50 (20%)
US	152 (35%)	51 (29%)	101 (40%)
Practice Setting Type, %			
Patients seen at Public Hospital (%)	19%	41%	4%
Patients seen at Private Hospital (%)	3%	4%	1%
Patients seen at Public Office (%)	36%	28%	41%
Patients seen at Private Office (%)	42%	27%	52%
Patients seen at Other practice setting (%)	1%	0%	1%
Clinical Trial experience in migraine, n (%)			
Currently involved in clinical trials	10 (2%)	7 (4%)	3 (1%)
Have been involved in clinical trials but not currently	131 (30%)	76 (43%)	55 (22%)
Never been involved in clinical trials	290 (67%)	92 (53%)	198 (77%)
Total number of migraine patients you make treatment decisions for per month, mean (SD)	41 (37)	56 (35)	31 (34)
Total number of patients you manage for any health condition, mean (SD)	1519 (1047)	1415 (1113)	1589 (996)
Total number of migraine patients currently managed by you personally, mean (SD)	195 (381)	311 (559)	115 (123)
Number of migraine patients diagnosed in the last 12 months, mean (SD)	51 (140)	97 (209)	20 (24)
Total number of patients with a migraine diagnosis receiving no prescribed medication, mean (SD)	15 (31)	15 (34)	15 (30)
Total number of patients with a migraine diagnosis receiving acute only medication, mean (SD)	58 (71)	71(83)	49 (61)
Total number of patients with a migraine diagnosis receiving preventive only medication, mean (SD)	29 (87)	50 (131)	15 (27)
Total number of patients with a migraine diagnosis receiving acute and preventive medication, mean (SD)	92 (273)	175 (410)	36 (50)

Physician Characteristics (N, %)	**Total N (%)**	**Neurologist (n=175)**	**PCP/GP (n=256)**
Total number of patients with a migraine diagnosis that you recommended over-the-counter (OTC) medication, mean (SD)	18 (44)	16 (34)	19 (50)

EU = European Union; N=total number of patient responses for variable; n = number of patients with characteristic; PCP/GP=Primary Care Physician/General Practitioner; SD = standard deviation; UK = United Kingdom; US = United States.
% = percent of patients with characteristic
† = Physician Workload Questionnaire (PWQ)

Table 1b: Patient Characteristics Stratified by type of migraine treatment (acute only, acute and preventive, preventive only, no current treatment) (N=4,254) ∞

Patient Characteristics	Total N (%)	Acute only (N=2001)	Acute and preventive (N=1646)	Preventive only (N=152)	No current treatment (N=455)
Age (years), mean (SD)	39.8 (13.5)	39.0 (13.4)	42.4 (13.0)	40.4 (13.4)	34.06 (13.7)
Age (years) categories, n (%) **Ŧ =5**					
< 40 years	2204 (52%)	1105 (55%)	703 (43%)	77 (51%)	319 (70%)
40 – 59 years	1669 (39%)	716 (36%)	788 (48%)	61 (40%)	104 (23%)
> 60 years	376 (9%)	177 (9%)	155 (9%)	14 (9%)	30 (7%)
Age at diagnosis (years), mean (SD)	32.8 (11.9)	32.5 (11.7)	33.2 (11.7)	37.0 (12.7)	31.71 (12.4)
Age at diagnosis (years categories, n (%) **Ŧ = 1,786**					
< 40 years	1713 (74%)	806 (75%)	598 (72%)	54 (62%)	255 (77%)
40 – 59 years	552 (24%)	247 (23%)	212 (26%)	28 (15%)	65 (20%)
> 60 years	62 (3%)	27 (3%)	18 (2%)	5 (6%)	12 (4%)
Female sex, n (%)	3101 (73%)	1452 73%)	1220 (74%)	111 (73%)	318 (70%)
BMI (kg/m2), mean (SD)	25.3 (4.49)	25.0 (4.42)	25.9 (4.8)	25.4 (4.1)	24.8 (4.4)
BMI (kg/m2) categories, n (%)					
Normal	2234 (53%)	1093 (55%)	805 (49%)	83 (55%)	253 (56%)
Overweight	1488 (35%)	694 (35%)	596 (36%)	46 (30%)	152 (33%)
Obese	532 (13%)	214 (11%)	245 (15%)	23 (15%)	50 (11%)
Employment status, n (%) **Ŧ =128**					
Employed	2879 (70%)	1397 (71%)	1123 (71%)	100 (75%)	259 (58%)
Unemployed	185 (5%)	79 (4%)	82 (5%)	5 (4%)	19 (4%)
Other	1062 (26%)	487 (25%)	377 (24%)	29 (22%)	169 (38%)
Duration of smoking (years), mean (SD)	13.7 (10.3)	13.7 (10.6)	15.8 (10.3)	12.0 (6.6)	7.9 (6.7)
Smoking status, n (%) **Ŧ =241**					
Current smoker	703 (17%)	378 (19%)	237 (14%)	16 (11%)	72 (16%)
Former smoker	749(18%)	328 (16%)	348 (21%)	24 (16%)	49 (11%)
Never smoked	2561 (60%)	1188 (59%)	983 (60%)	92 (61%)	298 (66%)
Don't know	241 (6%)	107 (5%)	78 (5%)	20 (13%)	36 (8%)

Patient Characteristics	Total N (%)	Acute only (N=2001)	Acute and preventive (N=1646)	Preventive only (N=152)	No current treatment (N=455)
Time since migraine diagnosis (years), mean (SD)	4.4 (6.8)	4.16 (7.0)	6.25 (7.1)	2.19 (3.5)	0.84 (3.7)
Spectrum of migraine frequency, n (%) **Ŧ = 4**					
Episodic migraine	3823 (90%)	1908 (95%)	1370 (83%)	119 (78%)	426 (94%)
Chronic migraine	427 (10%)	91 (5%)	275 (17%)	33 (22%)	28 (6%)
Type of migraine headache, n (%)					
Migraine with aura	1550 (36%)	664 (33%)	704 (43%)	50 (33%)	132 (29%)
Migraine without aura	2469 (58%)	1178 (59%)	915 (56%)	88 (58%)	288 (63%)
Menstrual migraine	229 (5%)	123 (6%)	71 (4%)	9 (6%)	26 (6%)
Menstrually-related migraine	199 (5%)	107 (5%)	63 (4%)	6 (4%)	23 (5%)
Migraine severity (including migraine, tension, rebound, banded) over the last 3 months, n (%) **Ŧ = 57**					
Mild	680 (16%)	330 (17%)	237 (14%)	20 (13%)	93 (20%)
Moderate	2622 (62%)	1294 (65%)	977 (59%)	87 (57%)	264 (58%)
Severe	895 (21%)	363 (18%)	413 (25%)	35 (23%)	84 (19%)
Don't know	57 (1%)	14 (1%)	19 (1%)	10 (7%)	14 (3%)
Total HDM (including migraine, tension, rebound, banded) over the last 3 months, n (%)					
0-3 days	1810 (43%)	984 (49%)	538 (33%)	46 (30%)	242 (53%)
4-7 days	1348 (32%)	669 (34%)	504 (31%)	39 (26%)	136 (30%)
8-14 days	665 (16%)	255 (13%)	328 (20%)	34 (22%)	48 (11%)
15 + days	427 (10%)	427 (10%)	275 (17%)	33 (22%)	28 (6%)
Migraine-related HDM (including migraine, tension, rebound, banded) over the last 3 months, n (%)					
0-3 days	2202 (52%)	1173 (59%)	692 (42%)	57 (38%)	280 (62%)
4-7 days	1292 (30%)	596 (30%)	518 (32%)	57 (38%)	121 (27%)
8-14 days	541 (13%)	181 (9%)	303 (18%)	21 (14%)	36 (8%)
15 + days	215 (5%)	49 (3%)	132 (8%)	17 (11%)	17 (4%)

Patient Characteristics	**Total N (%)**	**Acute only (N=2001)**	**Acute and preventive (N=1646)**	**Preventive only (N=152)**	**No current treatment (N=455)**
Rebound (medication overuse) HDM (including migraine, tension, rebound, banded) over the last 3 months, n (%)					
0-3 days	4012 (94%)	1934 (97%)	1496 (91%)	135 (89%)	447 (98%)
4-7 days	151 (4%)	41 (2%)	89 (5%)	15 (10%)	6 (1%)
8-14 days	51 (1%)	13 (1%)	35 (2%)	2 (1%)	1 (0.2%)
15 + days	40 (1%)	13 (1%)	26 (2%)	0 (0%)	1 (0.2%)
Current number of migraine symptoms, mean (SD)	5.0 (2.5)	4.7 (2.3)	5.6 (2.5)	4.1 (2.5)	4.3 (2.6)
Total HDM over the last 3 months (including migraine, tension, rebound), mean (SD)	6.1 (5.9)	4.9 (4.4)	7.7 (6.9)	9.0 (8.3)	4.8 (5.0)
Migraine-related HDM over the last 3 months, mean (SD)	4.7 (4.5)	4.0 (3.5)	5.8 (5.3)	5.9 (5.8)	3.9 (3.8)
Current Systolic Blood Pressure (mmHg), mean (SD)	124.2 (13.4)	123.8 (12.9)	125.8 (13.6)	124.2 (12.6)	120.5 (14.4)
Current Diastolic Blood Pressure(mmHg), mean (SD)	76.4 (9.6)	76.3 (9.2)	76.8 (9.7)	77.0 (9.1)	75.3 (10.5)
Total cholesterol (mg/dl), mean (SD)	129.5 (88.9)	128.0 (88.3)	131.0 (91.2)	145.4 (80.1)	123.95 (83.7)
Country, n (%)					
France	925 (22%)	452 (23%)	353 (21%)	13 (9%)	107 (24%)
Germany	900 (21%)	539 (27%)	255 (16%)	32 (21%)	74 (16%)
UK	910 (21%)	340 (17%)	371 (23%)	68 (45%)	131 (29%)
US	1519 (36%)	670 (34%)	667 (41%)	39 (26%)	143 (31%)
US Ethnicity/Race, n (%) **Ŧ = 2735**					
White/Caucasian	1147 (76%)	513 (34%)	502 (33%)	27 (2%)	105 (7%)
Non-White	372 (25%)	157 (10%)	165 (11%)	12 (1%)	38 (3%)
EU Ethnicity/Race, n (%) **Ŧ = 1519**					
White/Caucasian	2443 (89%)	1190 (44%)	883 (32%)	101 (4%)	269 (10%)
Non-White	292 (12%)	141 (5%)	96 (4%)	12 (1%)	43 (2%)

Patient Characteristics	Total N (%)	Acute only (N=2001)	Acute and preventive (N=1646)	Preventive only (N=152)	No current treatment (N=455)
BMI: body mass index; kg/m2 = kilogram per meter squared; EU = European Union; EU Ethnicity(Non-White): Afro-Caribbean, Hispanic/Latino, Asian (Indian, Asian-other, Chinese), Mixed Race, Middle Eastern, Other; HDM = headache days per month; n = number of patients with characteristic; N=total number of patient responses for variable; n = number of patients with characteristic, N=number of patient responses for variable; SD = standard deviation; UK = United Kingdom; US = United States; US Ethnicity/Race (Non-White): African American, Hispanic/Latino, Asian (Indian, Chinese, Other), Mixed Race, Middle Eastern, Native American. % = percent of patients with characteristic ∞ = Patient Record Form (PRF) Ŧ = number of missing observations					

Table 2: Treatment patterns, discontinuation or switching (current and previously discontinued) acute medications

Acute Medication	n, (%)	Time (days), mean (SD)
Patient Record Form (PRF) (n=4,254)		
Ever	3,694 (87%)	
Current	NA	1,023 (1,509)
First previously used medication	376 (8%)	1,074 (1,575)
Second previously used medication	47 (1%)	1,038 (1,517)
Third previously used medication	6 (<1%)	520 (646)
Previously used medication in any timeframe	1,259 (30%)	887 (253)
Gap time between most recent previous and initiation of current	NA	81 (346)
Patient Self-Completed Questionnaire (PSC) (n=2,239)		
Current	1,820 (82%)	NA
Not taking currently	345 (15%)	NA
Not stated	74 (3%)	NA

PRF = Patient Record Form
PSC = Patient Self-Completed Questionnaire
NA = Not Applicable

Table 3: Patient Characteristics by Triptan Discontinuation or failure ∞

Variable	Triptan Discontinuation in past due to lack of efficacy (N=39)	Triptan Discontinuation in past due to side effects (N=47)	Treatment Failure on Triptan (N=981)
	n (%)	n (%)	n (%)
Age categories (years)			
Ŧ =5			
<40 years old (N=2204)	13 (33%)	16 (34%)	448 (46%)
40-59 years old (N=1669)	25 (64%	18 (38%)	448 (46%)
>60 years old (N=376)	9 (23%)	5 (11%)	85 (9%)
Age categories at diagnosis (years)			
Ŧ =1786			
<40 years old (N=1713)	12 (31%)	10 (21%)	346 (35%)
40-59 years old (N=552)	4 (10%)	5 (11%)	123 (13%)
>60 years old (N=62)	0 (0%)	0 (0%)	8 (1%)
Sex			
Male (N=1153)	7 (18%)	8 (17%)	253 (26%)
Female (N=3101)	32 (82%)	39 (83%)	728 (74%)
BMI categories			
Normal (N=2234)	18 (46%)	16 (34%)	474 (48%)***
Overweight (N=1488)	8 (21%)	9 (19%)	145 (15%)***
Obese (N=532)	13 (33%)	22 (47%)	362 (37%)***
Employment status			
Ŧ = 128			
Employed (N=2879)	29 (74%)	27 (57%)	671 (68%)
Unemployed (N=185)	1 (3%)	6 (13%)	43 (4%)
Other (N=1062)	8 (21%)	10 (21%)	227 (23%)
Smoking status			
Ŧ = 241			
Current smoker (N=703)	2 (5%)	6 (13%)	153 (16%)
Former smoker (N=749)	12 (31%)	11 (23%)	199 (20%)
Never smoked (N=2561)	24 (62%)	29 (62%)	588 (60%)
Ethnicity/Race (US)			
Ŧ = 2,735			
White/Caucasian (N=1147)	15 (39%)	19 (40%)	301 (31%)
Non-White (N=372)	3 (8%)	4 (9%)	95 (10%)

Variable	Triptan Discontinuation in past due to lack of efficacy (N=39)	Triptan Discontinuation in past due to side effects (N=47)	Treatment Failure on Triptan (N=981)
	n (%)	n (%)	n (%)
Ethnicity/Race (EU)			
Ŧ = 1,519			
White/Caucasian (N=2443)	20 (51%)	22 (47%)	537 (55%)
Non-White (N=292)	1 (3%)	2 (4%)	48 (5%)
Spectrum of migraine frequency			
Ŧ = 4			
Episodic migraine (N=3823)	32 (85%)	37 (79%)	815 (83%)***
Chronic migraine (N=427)	7 (15%)	10 (21%)	166 (17%)***
Type of migraine headache			
Migraine with aura (N=1550)	13 (33%)	23 (49%)	423 (43%)*
Migraine without aura (N=2414)	23 (59%)	23 (49%)	513 (52%)*
Neither (N=290)	3 (8%)	1 (2%)	45 (5%)*
Type of migraine treatment			
Acute and preventive (N=1646)	21 (54%)	35 (75%)	600 (61%)***
Acute only (N=2001)	8 (21%)	7 (15%)	365 (37%)***
Preventive only (N=152)	6 (15%)	0 (0%)	9 (1%) ***
No current treatment (N=455)	4 (10%)	5 (11%)	7 (%)***
Migraine severity over the last 3 months			
Ŧ = 57			
Mild (N=680)	5 (13%)	7 (15%)	95 (10%)***
Moderate (N=2622)	19 (49%)	27 (57%)	590 (60%)***
Severe (N=895)	13 (33%)	11 (23%)	290 (30%)***
Total HDM over the last 3 months			
0-3 days (N=1810)	13 (33%)*	20 (43%)	282 (29%)***
4-7 days (N=1348)	11 (28%)*	13 (28%)	316 (32%)***
8-14 days (N=665)	8 (21%)*	10 (21%)	217 (22%)***
15 + days (N=427)	7 (18%)*	4 (9%)	166 (17%)***
Migraine-related HDM over the last 3 months			
0-3 days (N=2202)	15 (39%)	22 (47%)	375 (38%)***
4-7 days (N=1292)	17 (44%)	16 (34%)	337 (34%)***
8-14 days (N=541)	1 (3%)	4 (9%)	186 (19%)***
15 + days (N=215)	6 (15%)	5 (11%)	83 (9%)***

Variable	Triptan Discontinuation in past due to lack of efficacy (N=39)	Triptan Discontinuation in past due to side effects (N=47)	Treatment Failure on Triptan (N=981)
	n (%)	n (%)	n (%)
Rebound (medication overuse) HDM over the last 3 months			
0-3 days (N=4012)	35 (90%)	42 (89%)	880 (90%)***
4-7 days (N=151)	4 (10%)	4 (9%)	58 (6%)***
8-14 days (N=51)	0 (0%)	0 (0%)	27 3%)***
15 + days (N=40)	0 (0%)	1 (2%)	16 (2%)***

BMI = body mass index; kg/m2 = kilogram per meter squared; BMI categories: BMI 18.5 to < 25kg/m2 (Normal), BMI 25 to < 30 kg/m2 (Overweight), BMI > 30kg/m2 (Obese); Employment status (Other) = Student, Homemaker, Retired, and Long-term sick leave; EU = European Union; EU Ethnicity(Non-White): Afro-Caribbean, Hispanic/Latino, Asian (Indian, Asian-other, Chinese), Mixed Race, Middle Eastern, Other; HDM = headache days per month; n = number of patients with characteristic; N = number of patient responses for variable; US = United States; US Ethnicity/Race (Non-White): African American, Hispanic/Latino, Asian (Indian, Chinese, Other), Mixed Race, Middle Eastern, Native American.
Chronic migraine = 15+ total HDM over the last 3 months
Episodic migraine = 0-14 total HDM over the last 3 months
%= percent of patients with characteristic
$\chi 2$ =Chi-square was used to determine proportion of patients by outcomes (triptan discontinuation in the past due to lack of efficacy, side effects, and treatment failure while on triptan)
*$p < 0.05$ across groups
** $p < 0.01$ across groups
*** $p < 0.001$ across groups
∞ = PRF (Patient Record Form)
Ŧ = number of missing observations

Table 4: Association Between Patient Characteristics and Treatment Failure on Triptan∞

Variable	Treatment Failure on Triptan (N=981) OR (95% CI)
Age categories (years)	
40-59 years	1.074 (0.889, 1.298)
> 60 years	0.936 (0.664, 1.320)
<40 years	Ref
Sex	
Female	1.070 (0.868, 1.317)
Male	Ref
BMI categories	
Overweight	1.144 (0.940, 1.400)
Obese	1.438 (1.083, 1.991)*
Normal	Ref
Employment status	
Employed	0.933 (0.600, 1.454)
Other	1.125 (0.696, 1.820)
Unemployed	Ref
Smoking status	
Current smoker	0.990 (0.769, 1.272)
Former smoker	1.189 (0.950, 1.490)
Never smoked	Ref
Spectrum of migraine frequency	
Episodic migraine	2.535 (1.873, 3.431)***
Chronic migraine	Ref
Type of migraine	
Migraine with aura	1.188 (0.993, 1.422)
Migraine without aura	Ref
Migraine severity over the last 3 months	
Severe	2.346 (1.709, 3.219)***
Moderate	1.529 (1.169, 2.015)**
Mild	Ref

BMI = body mass index; kg/m2 = kilogram per meter squared; BMI categories: BMI 18.5 to < 25kg/m2 (Normal), BMI 25 to < 30 kg/m2 (Overweight), BMI > 30kg/m2 (Obese); CI = confidence interval; Employment status (Other) = Student, Homemaker, Retired, and Long-term sick leave; HDM = headache days per month; N = number of patient responses for variable; OR = Odds Ratio; Ref = referent category.
Chronic migraine = 15+ total HDM over the last 3 months
Episodic migraine = 0-14 total HDM over the last 3 months
Adjusted/Multivariable Logistic Regression
*p < 0.05
** p <0.01
*** p<0.001
∞ = PRF (Patient Record Form)

Table 5: Patient Characteristics by CV risk Stratified by type of migraine treatment (acute only, acute and preventive, preventive only, no current treatment (N=611) ∞

Patient Characteristics	Total N (%)	Acute only (N=233)	Acute and preventive (N=323)	Preventive only (N=16)	No current treatment (N=39)
Age (years), mean (SD)	53.1 (12.7)	54.7 (12.5)	52.2 (12.3)	51.8 (15.2)	52.6 (14.8)
Age (years) categories, n (%) **Ŧ = 4**					
< 40 years	74 (12%)	20 (9%)	44 (14%)	4 (25%)	6 (16%)
40 – 59 years	355 (59%)	128 (56%)	202 (63%)	6 (38%)	19 (50%)
> 60 years	51 (12%)	82 (36%)	77 (24%)	6 (38%)	13 (34%)
Age at diagnosis (years), mean (SD)	43.6 (13.6)	46.0 (13.9)	41.4 (12.1)	48.0 (17.0)	46.9 (15.4)
Age at diagnosis (years categories, n (%)					
< 40 years	111 (41%)	27 (31%)	73 (50%)	3 (30%)	8 (29%)
40 – 59 years	130 (5%)	49(56%)	62 (43%)	5 (50%)	14 (50%)
> 60 years	29 (11%)	11 (13%)	10 (7%)	2 (20%)	6 (21%)
Female sex, n (%)	410 (67%)	148 (64%)	225 (70%)	12 (75%)	25 (64%)
BMI (kg/m2), mean (SD)	27.9 (5.0)	27.6 (4.5)	28.3 (5.3)	27.6 (4.6)	26.5 (5.3)
BMI (kg/m2) categories, n (%)					
Normal	181 (30%)	75 (32%)	85 (26%)	7 (44%)	14 (36%)
Overweight	259 (42%)	96 (41%)	142 (44%)	4 (25%)	8 (21%)
Obese	171 (28%)	62 (27%)	96 (30%)	5 (31%)	17 (44%)
Employment status, n (%) **Ŧ =25**					
Employed	360 (61%)	139 (62%)	190 (62%)	9 (60%)	22 (56%)
Unemployed	25 (4%)	6 (3%)	17 (6%)	0 (0%)	2 (5%)
Other	201 (34%)	81 (36%)	99 (32%)	6 (40%)	15 (39%)
Duration of smoking (years), mean (SD)	19.8 (12.7)	25.7 (12.6)	17.2 (11.6)	NA	11.0 (12.0)
Smoking status, n (%) **Ŧ = 20**					
Current smoker	95 (16%)	39 (17%)	48(15%)	1 (6%)	7 (18%)
Former smoker	175 (29%)	64 (28%)	94 (29%)	4 (25%)	13 (33%)
Never smoked	321 (53%)	124 (53%)	168 (52%)	11 (69%)	18 (46%)
Don't know	20 (4%)	6 (3%)	13 (4%)	0 (0%)	1 (3%)
Time since migraine diagnosis (years), mean (SD)	7.7 (10.0)	8.8 (11.4)	8.5 (9.0)	1.23 (1.98)	2.7 (9.7)

Patient Characteristics	Total N (%)	Acute only (N=233)	Acute and preventive (N=323)	Preventive only (N=16)	No current treatment (N=39)
Spectrum of migraine frequency, n (%)					
Episodic migraine	533 (87%)	214 (92%)	274 (85%)	9 (82%)	35 (90%)
Chronic migraine	78 (13%)	19 (8%)	49 (15%)	2 (18%)	4 (10%)
Type of migraine headache, n (%)					
Migraine with aura	263 (43%)	80 (34%)	160 (50%)	6 (38%)	17 (44%)
Migraine without aura	334 (55%)	143 (61%)	161 (50%)	9 (56%)	21 (54%)
Menstrual migraine	16 (3%)	5 (2%)	7 (2%)	1 (6%)	3 (8%)
Menstrually-related migraine	16 (3%)	7 (3%)	8 (2%)	0 (0%)	1 (3%)
Migraine severity (including migraine, tension, rebound, banded) over the last 3 months, n (%) **Ŧ = 5**					
Mild	94 (15%)	32 (14%)	46 (14%)	5 (31%)	11 (28%)
Moderate	379 (15%)	170 (73%)	182 (56%)	9 (56%)	18 (46%)
Severe	133 (22%)	31 (13%)	91 (28%)	2 (13%)	9 (23%)
Don't know	5 (1%)	0 (0%)	4 (1%)	0 (0%)	1 (3%)
Total HDM (including migraine, tension, rebound, banded) over the last 3 months, n (%)					
0-3 days	249 (41%)	119 (51%)	108 (33%)	5 (31%)	17 (44%)
4-7 days	175 (29%)	64 (28%)	97 (30%)	2 (13%)	12 (31%)
8-14 days	106 (17%)	33 (14%)	62 (19%)	5 (31%)	6 (15%)
15 + days	81 (13%)	17 (7%)	56 (17%)	4 (25%)	4 (10%)
Migraine-related HDM (including migraine, tension, rebound, banded) over the last 3 months, n (%)					
0-3 days	320 (52%)	149 (64%)	143 (44%)	7 (44%)	21 (54%)
4-7 days	181 (30%)	59 (25%)	108 (33%)	4 (25%)	10 (26%)
8-14 days	74 (12%)	18 (8%)	48 (15%)	3 (19%)	5 (13%)
15 + days	36 (6%)	7 (3%)	24 (7%)	2 (13%)	3 (8%)

Patient Characteristics	**Total N (%)**	**Acute only (N=233)**	**Acute and preventive (N=323)**	**Preventive only (N=16)**	**No current treatment (N=39)**
Rebound (medication overuse) HDM (including migraine, tension, rebound, banded) over the last 3 months, n (%)					
0-3 days	563 (92%)	223 (96%)	286 (89%)	15 (94%)	39 (100%)
4-7 days	31 (5%)	4 (2%)	26 (8%)	1 (6%)	0 (0%)
8-14 days	10 (2%)	2 (1%)	8 (3%)	0 (0%)	0 (0%)
15 + days	7 (1%)	4 (2%)	3 (1%)	0 (0%)	0 (0%)
Current number of migraine symptoms, mean (SD)	5.2 (2.6)	4.6 (2.3)	5.7 (2.7)	3.9 (2.3)	4.9 (2.9)
Total HDM over the last 3 months (including migraine, tension, rebound), mean (SD)	6.8 (6.9)	5.3 (5.8)	7.9 (7.3)	10.8 (9.8)	5.3 (4.8)
Migraine-related HDM over the last 3 months, mean (SD)	4.9 (5.2)	3.8 (4.3)	5.6 (5.6)	6.6 (8.1)	4.4 (4.2)
Current Systolic Blood Pressure (mmHg), mean (SD)	134.9 (13.8)	134.8 (13.1)	135.3 (13.7)	137.6 (18.9)	131.6 (17.6)
Current Diastolic Blood Pressure(mmHg), mean (SD)	82.3 (9.9)	81.9 (9.2)	82.7 (10.2)	85.3 (9.6)	80.8 (11.8)
Total cholesterol (mg/dl), mean (SD)	145.0 (92.7)	136.0 (94.6)	154.7 (91.0)	128.8 (85.1)	105.1 (90.7)
Country, n (%)					
France	100 (16%)	38 (16%)	53 (16%)	0 (0%)	9 (23%)
Germany	104 (17%)	50 (22%)	51 (16%)	0 (0%)	3 (8%)
UK	98 (16%)	36 (16%)	42 (13%)	10 (63%)	10 (26%)
US	309 (51%)	109 (47%)	177 (55%)	6 (38%)	17 (44%)
US Ethnicity/Race, n (%) **Ŧ =302**					
White/Caucasian	221 (72%)	73 (67%)	130 (73%)	6 (100%)	12 (71%)
Non-White	86 (28%)	36 (33%)	47 (27%)	0 (100%)	5 (29%)
EU Ethnicity/Race, n (%) **Ŧ = 309**					
White/Caucasian	258 (85%)	107 (86%)	128 (88%)	8 (80%)	15 (68%)
Non-White	44 (15%)	17 (14%)	18 (12%)	2 (20%)	7 (32%)

Patient Characteristics	Total N (%)	Acute only (N=233)	Acute and preventive (N=323)	Preventive only (N=16)	No current treatment (N=39)
BMI: body mass index; kg/m2 = kilogram per meter squared; Employment status (Other) = Student, Homemaker, Retired, and Long-term sick leave; EU = European Union; EU Ethnicity(Non-White): Afro-Caribbean, Hispanic/Latino, Asian (Indian, Asian-other, Chinese), Mixed Race, Middle Eastern, Other; HDM = headache days per month; n = number of patients with characteristic; N = total number of patient responses for variable; n = number of patients with characteristic; NA = not applicable; SD = standard deviation; UK = United Kingdom; US = United States; US Ethnicity/Race (Non-White): African American, Hispanic/Latino, Asian (Indian, Chinese, Other), Mixed Race, Middle Eastern, Native American. % = Percent of patients with characteristic ∞ = Patient Record Form (PRF) Ŧ = number of missing observations					

Table 6: Proportion of patients with CV Risk (N=611) ∞

CV Risk Characteristic	n (%)
Hypertension	476 (78%)
Arrhythmias	35 (6%)
Reynaud's disease	27 (4%)
Coronary artery disease (CAD)	23 (4%)
Peripheral vascular disease (PVD)	19 (3%)
Ischemic Heart Disease	14 (2%)
Angina	9 (2%)
Cerebrovascular disease	8 (1%)

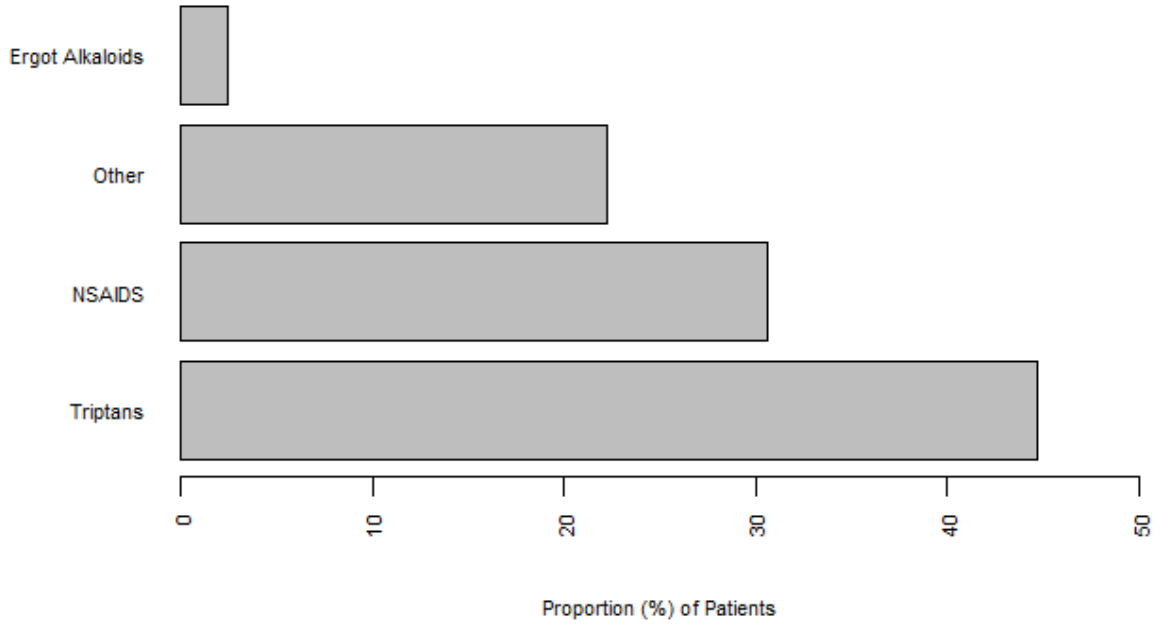
CAD = Coronary Artery Disease; CV = Cardiovascular;
PVD = Peripheral Vascular Disease.
N = number of patient responses for variable;
n = number of patients with characteristic.
∞ = PRF (Patient Record Form)

Table 7: Among patients with CV risk, treatment patterns, discontinuation or switching (current and previously discontinued) acute medications

Acute Medication	n, (%)	Time (days), mean (SD)
Patient Record Form (PRF) (n=611)		
Ever	561 (92%)	
Current	NA	1,315 (1,766)
First previously used medication	69 (11%)	1,852 (2,570)
Second previously used medication	7 (1%)	2,035 (1,516)
Third previously used medication	0 (0%)	NA
Previously used medication in any timeframe	236 (39%)	1,944 (91)
Gap time between most recent previous and initiation of current	NA	168 (427)
Patient Self-Completed Questionnaire (PSC) (n=322)		
Current	NA	NA
Not taking currently	NA	NA
Not stated	NA	NA
PRF = Patient Record Form PSC = Patient Self-Completed Questionnaire NA = Not Applicable		

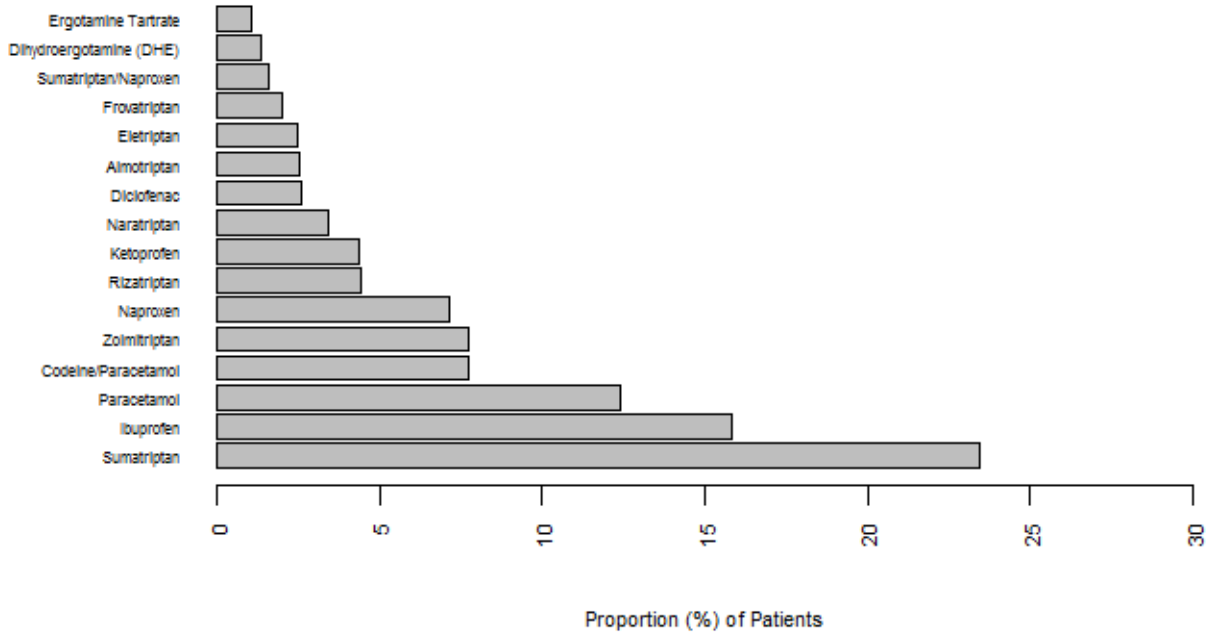
FIGURES

Figure 1a: Proportion of Patients Who Experienced Prior Use of A Maximum of Three Previously Prescribed Acute Medication Drug Class (N=1,259) ∞



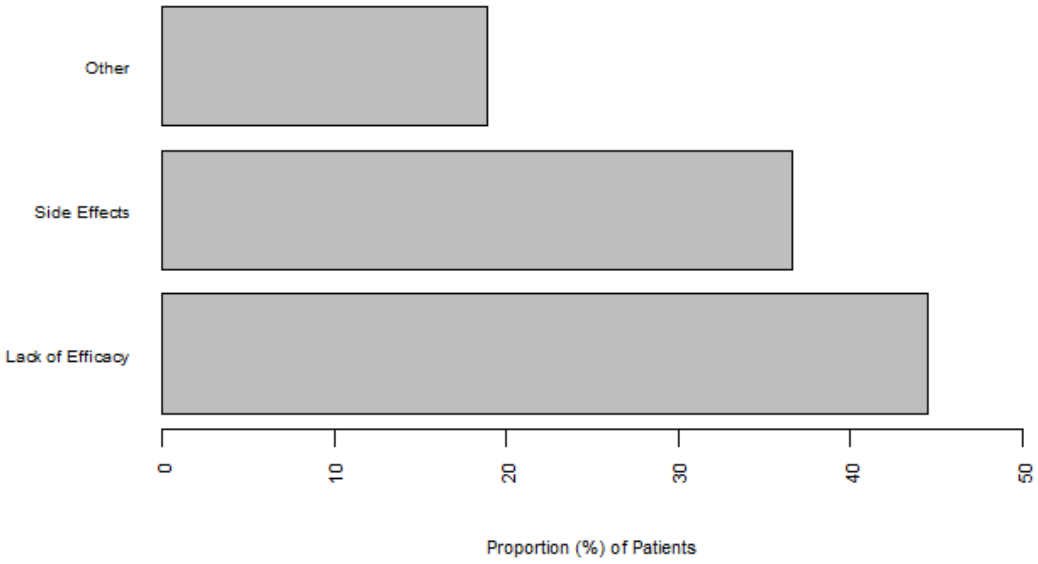
∞ = PRF (Patient Record Form)

Figure 1b: Proportion of Patients Who Experienced Prior Use of A Maximum of Three Previously Prescribed Acute Medications (N=1,259) ∞



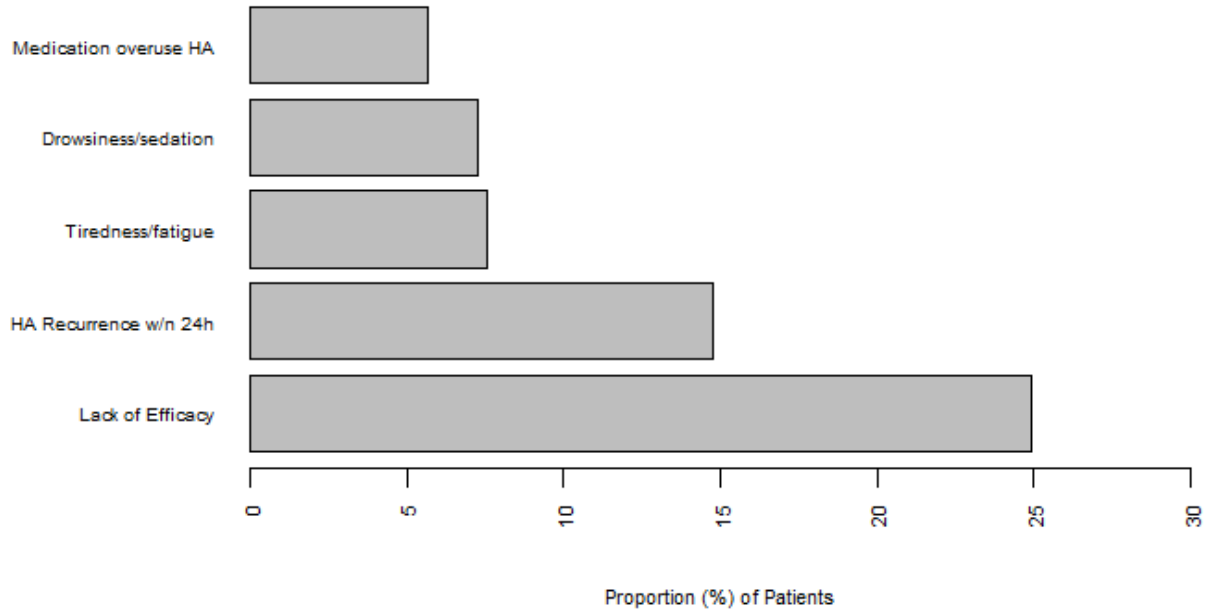
∞ = PRF (Patient Record Form)

Figure 2a: Physician-Reported: Current Issues/Reasons for Discontinuation of Current Acute Medications (high-level categories) (N=1,300) ∞



∞ = PRF (Patient Record Form)

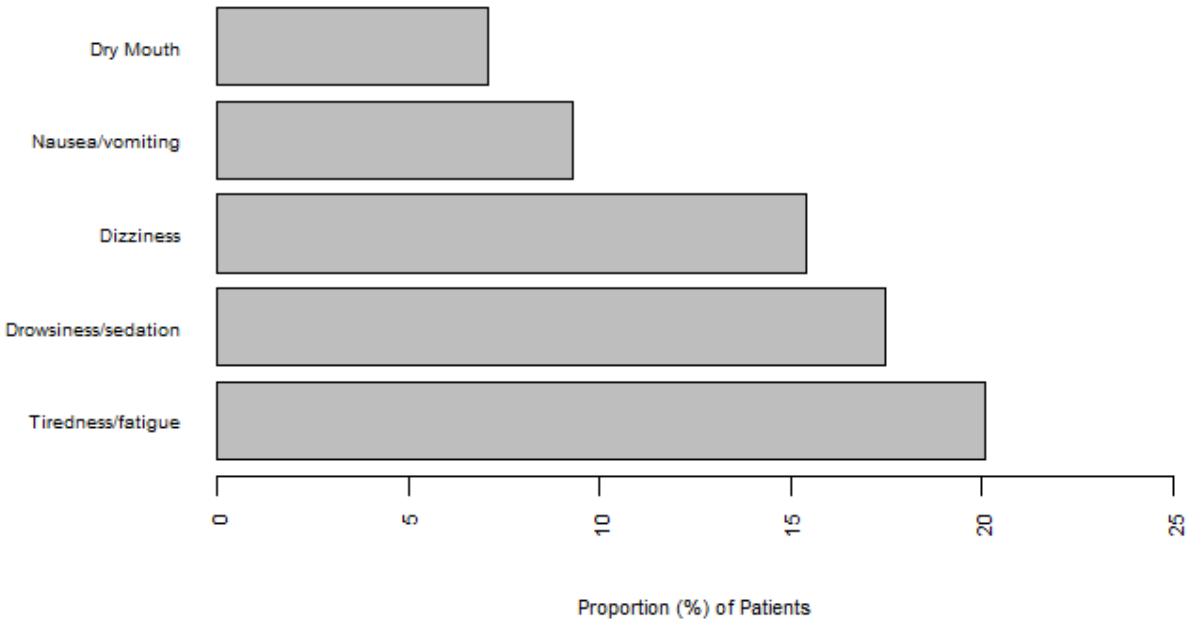
Figure 2b: Physician-Reported: Current Issues/Reasons for Discontinuation of Current Acute Medications (top five reasons) (N=1,768) ∞



∞ = PRF (Patient Record Form)

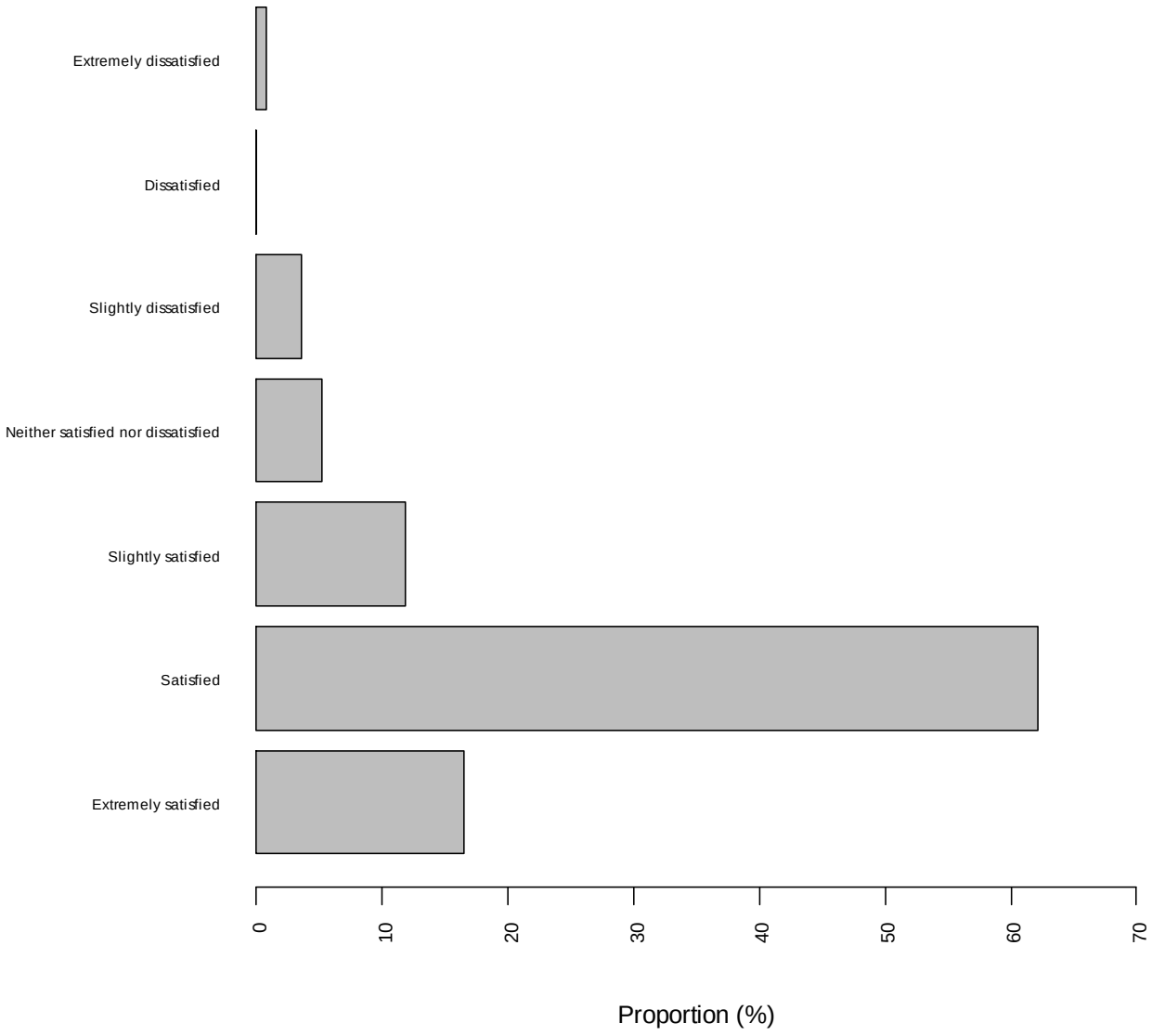
HA = Headache; w/n = within; 24h = 24 hours

Figure 2c: Patient-Reported Side Effects Experienced with Current Acute Medications (N=1,281) 🎗



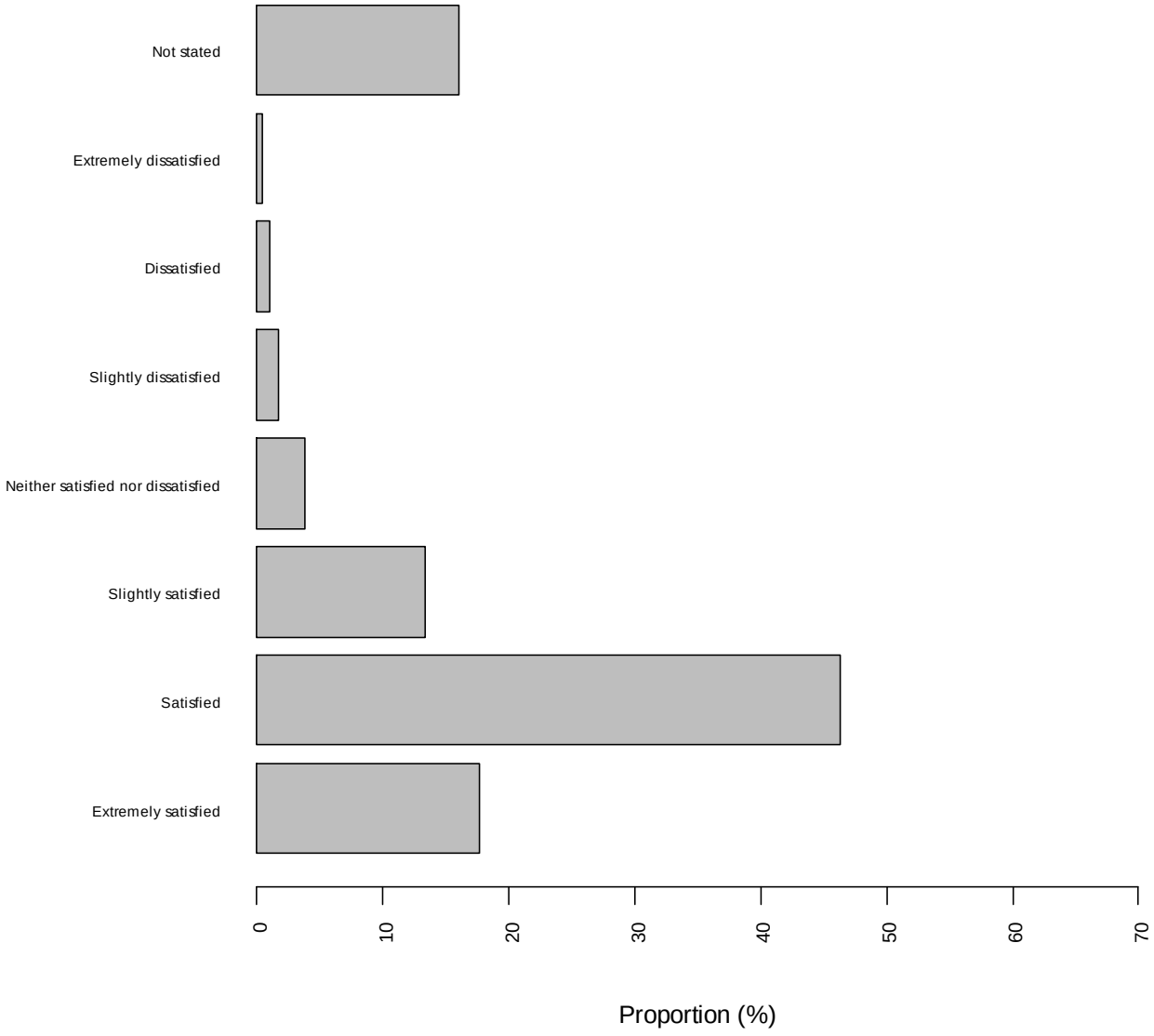
🎗 = PSC (Patient Self-Completed Questionnaire)

Figure 3: Physician-Reported Satisfaction with Current Acute Medications (N=3,651) ∞



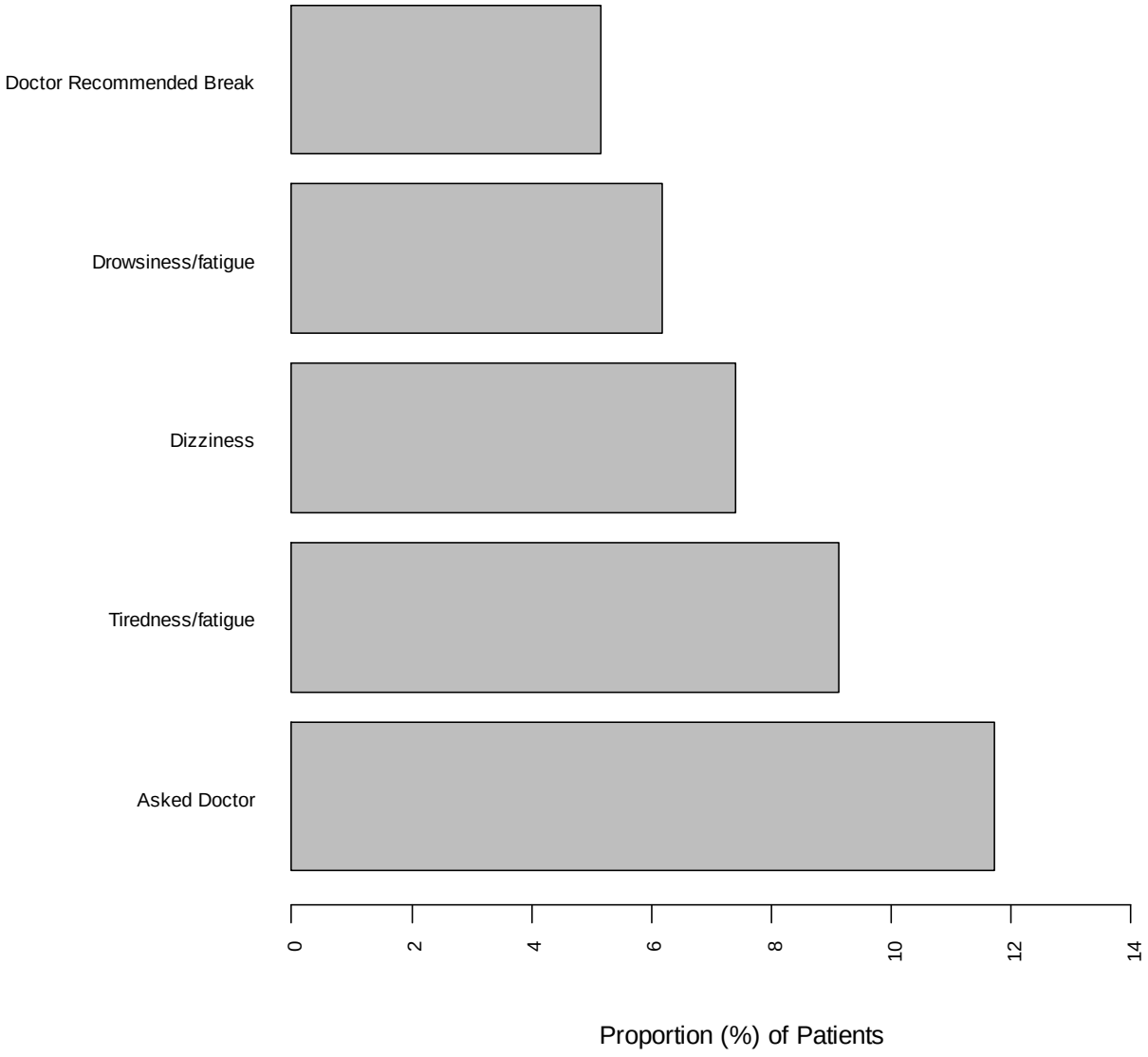
∞ = PRF (Patient Record Form)

Figure 4: Patient-Reported Satisfaction with Current Acute medications (N=2,239) 🎗



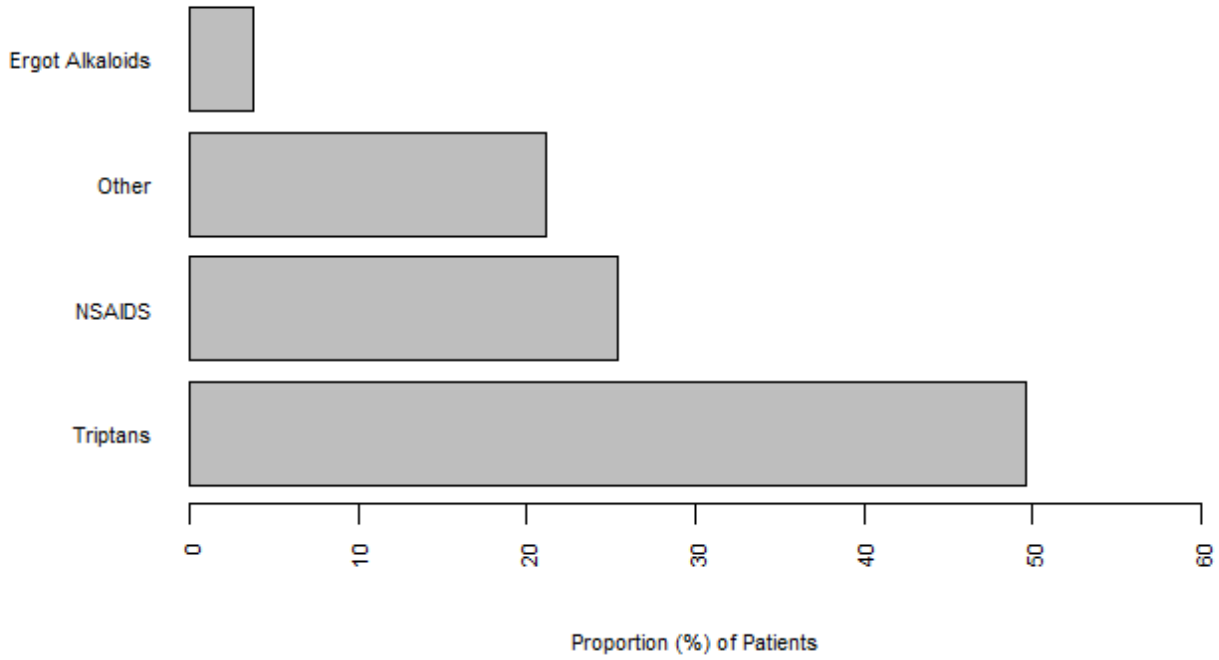
🎗 = PSC (Patient Self-Completed Questionnaire)

Figure 5: Patient-Reported Reasons for Discontinuation or Switching Triptan (N=1,458) ♟



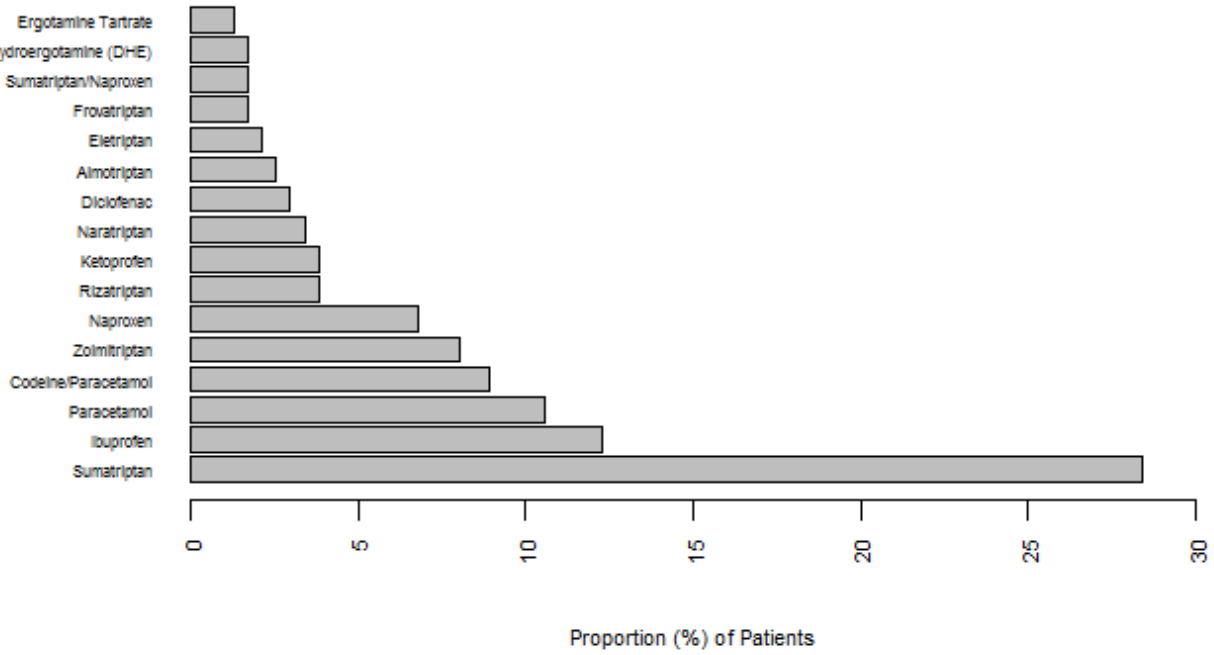
♟ = PSC (Patient Self-Completed Questionnaire)

Figure 6a: Among patients with CV risk, Physician Reported Proportion of Patients Who Experienced Prior Use of At Least Three Previously Prescribed Acute Medication Drug Classes (N=236) ∞



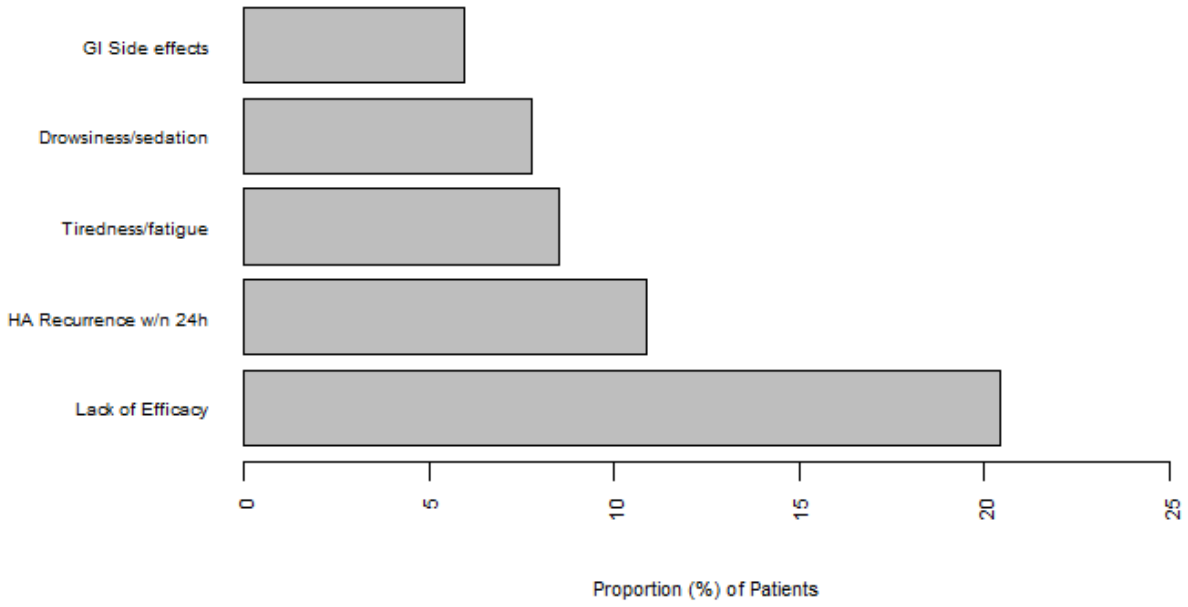
∞ = PRF (Patient Record Form)

Figure 6b: Among patients with CV risk, Physician Reported Proportion of Patients Who Experienced Prior Use of At Least Three Previously Prescribed Acute Medications (N=236) ∞



∞ = PRF (Patient Record Form)

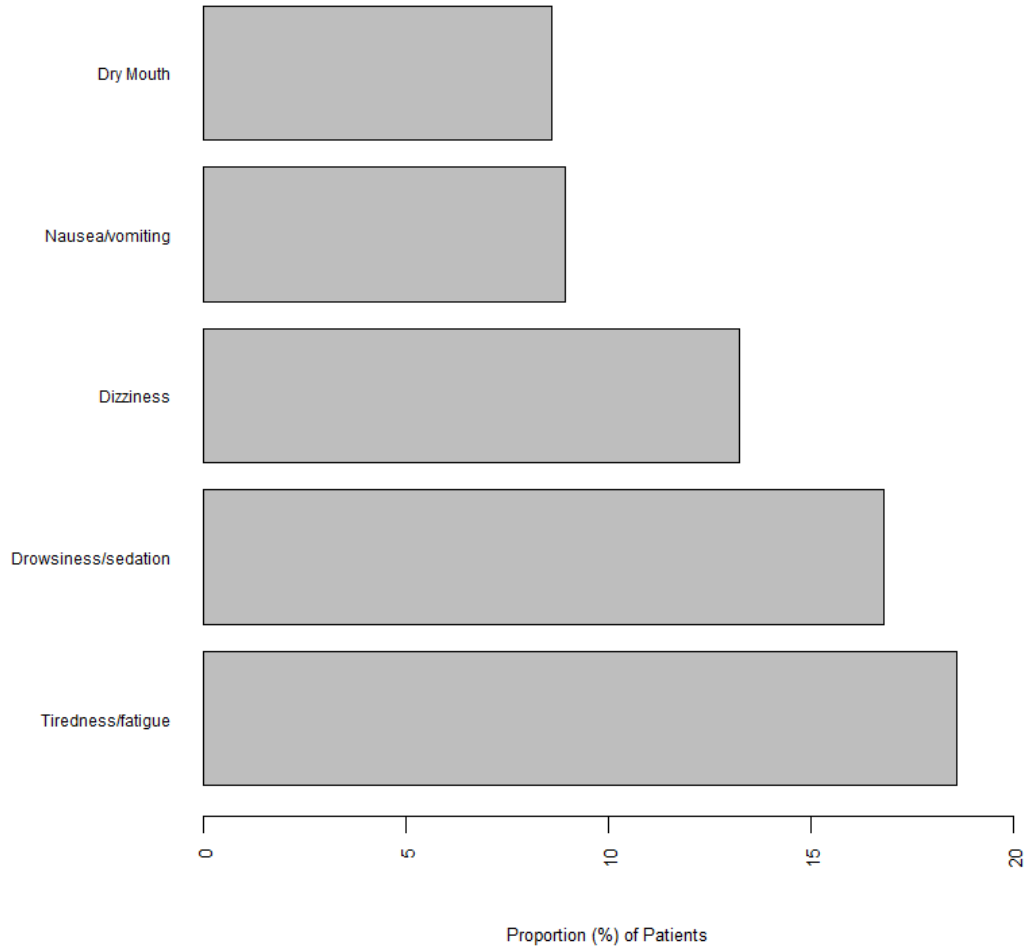
Figure 7a: Among patients with CV Risk, Physician-Reported Current Issues/Reasons for Discontinuation of Acute Medications (top five reasons) (N=387) ∞



∞ = PRF (Patient Record Form)

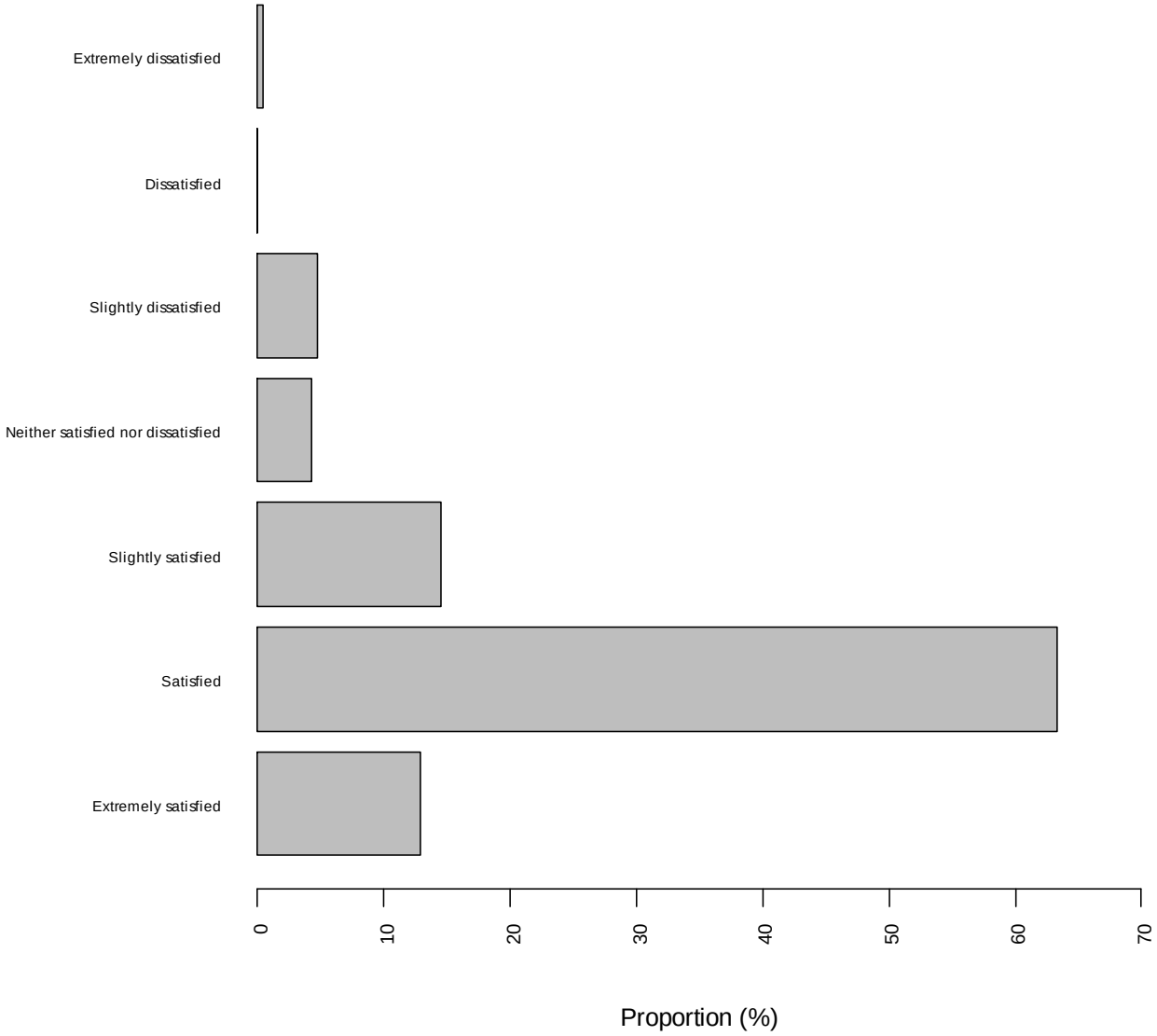
GI = gastrointestinal; HA=headache; w/n = within; 24h = 24 hours

Figure 7b: Among patients with CV risk, Patient-Reported Side Effects Experienced with Current Acute Medications (N=280) 🎗



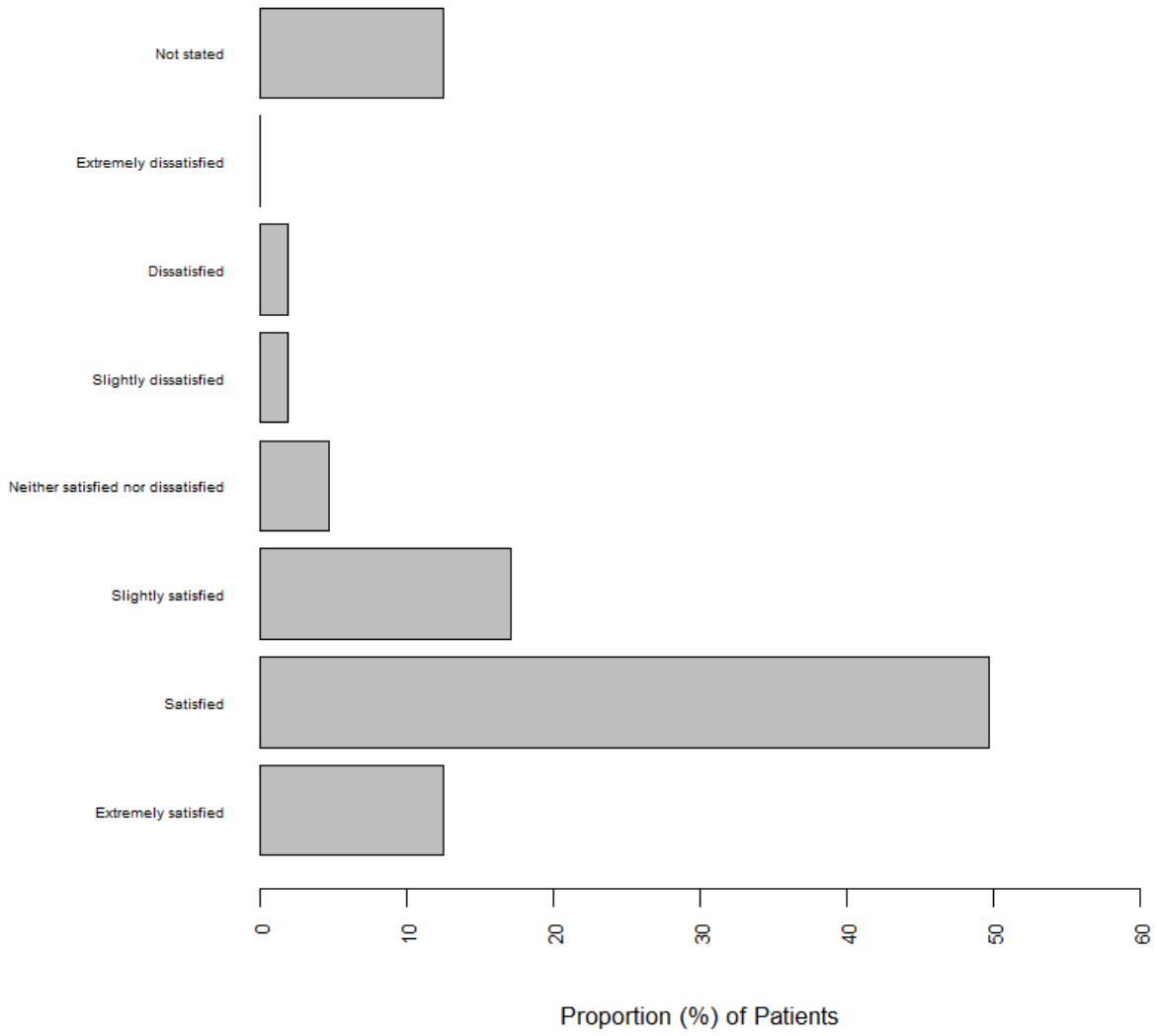
🎗 = PSC (Patient Self-Completed Questionnaire)

Figure 8: Among patients with CV risk, Physician-Reported Satisfaction with Current Acute Medications (N=557) ∞



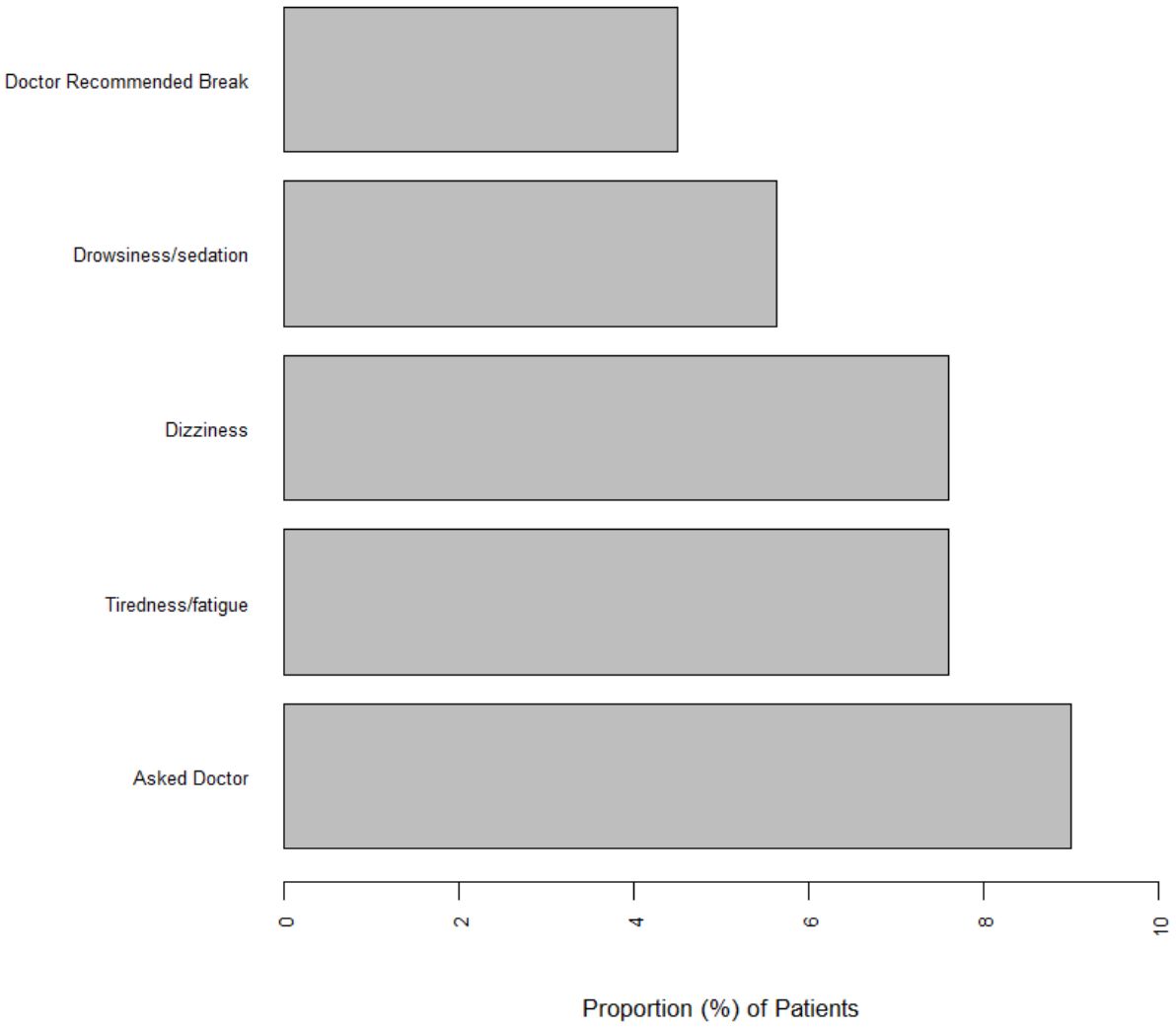
∞ = PRF (Patient Record Form)

Figure 9: Among patients with CV risk, Patient-Reported Satisfaction with Current Acute medications (N=322) 🎗



🎗 = PSC (Patient Self-Completed Questionnaire)

Figure 10: Among patients with CV risk, Patient-Reported Reasons for Discontinuation or Switching Triptan (N=322) 🎗



🎗 = PSC (Patient Self-Completed Questionnaire)

APPENDICES

Appendix 1: Commonly Used Acute Migraine Treatments with FDA Approvals initially identified in Fall 2017 Ð

Drug Class/ Pharmacologic action	Drug	FDA Indication(s)	Initial FDA/ US Approval
Triptans: Serotonin (5-HT1B/1D) receptor agonist	Sumatriptan, Sumatriptan/naproxen, rizatriptan, eletriptan, almotriptan, zolmitriptan, naratriptan, frovatriptan	Acute treatment of migraine with or without aura. Sumatriptan: Adults only Sumatriptan/naproxen: Adults only Rizatriptan: Adults and pediatric patients age 6 to 17 years Eletriptan: Adults only Almotriptan: Adults and adolescents age 12 to 17 years Zolmitriptan: Adults only Naratriptan: Adults only Frovatriptan: Adults only	Sumatriptan: 1992 Zolmitriptan: 1997 Rizatriptan: 1998 Naratriptan: 1998 Almotriptan: 2001 Frovatriptan: 2001 Eletriptan: 2002 Sumatriptan/naproxen: 2008
Opioids: *Tramadol*: Opioid agonist, norepinephrine and serotonin reuptake inhibitor *Codeine/* *acetaminophen:* Centrally acting	Tramadol, tramadol/ acetaminophen, codeine/ acetaminophen, butorphanol	Tramadol: Severe pain management in adults Tramadol/acetaminophen: Severe acute pain in adults Codeine/acetaminophen: Mild to moderately severe pain Butorphanol: Severe pain management	Methadone: 1973 Codeine/acetaminophen: 1977 Tramadol: 1995 Butorphanol: 1997 Tramadol/acetaminophen: 2001

Drug Class/ Pharmacologic action	Drug	FDA Indication(s)	Initial FDA/ US Approval
codeine, peripherally acting acetaminophen			
Non-steroidal Anti-inflammatory Drugs (NSAIDs): Nonselective COX-1/COX-2 inhibitors	Aspirin, ibuprofen, naproxen, diclofenac, ketorolac, ketoprofen, phenazone	Aspirin: Pain reliver/fever reducer Ibuprofen: Pain reliver/fever reducer Naproxen: Pain reliver/fever reducer Diclofenac: Acute or chronic treatment of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis Ketorolac: Acute pain in adults Ketoprofen: Treatment of pain, osteoarthritis, rheumatoid arthritis, and primary dysmenorrhea	Aspirin: ? Ibuprofen: 1984 Ketoprofen: 1992 Naproxen: 1993 Diclofenac: 1995 Ketorolac: 1997
Acetaminophen	Acetaminophen, Acetaminophen/ Aspirin/ Caffeine	Acetaminophen: Pain reliver/fever reducer Acetaminophen/aspirin/caffeine: Treatment of migraine	Acetaminophen: ? Acetaminophen/aspirin/caffeine: 2001
Ergot Alkaloids: Alpha-adrenergic blocking agent	Dihydroergotamine (DHE), ergotamine, ergotamine/caffeine	Dihdroergotamine: Acute treatment of migraine headaches with or without aura. Ergotamine: Abortive or preventative treatment of vascular headache Ergotamine/caffeine: Abortive or preventative treatment of vascular headache	Ergotamine/caffeine: 1948 Ergotamine: 1960 Dihydroergotamine: 1997

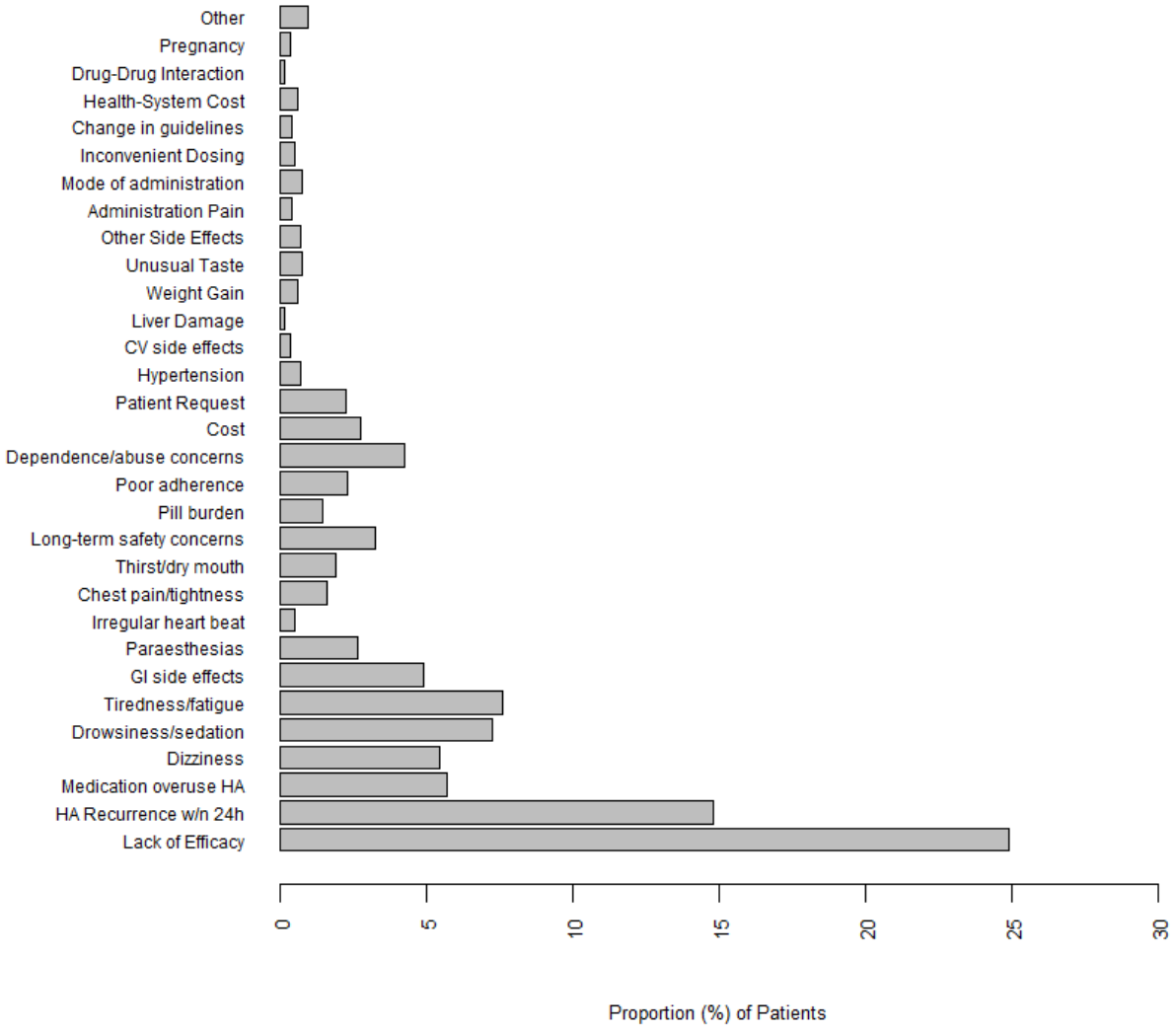
Drug Class/ Pharmacologic action	Drug	FDA Indication(s)	Initial FDA/ US Approval
Antiemetics: Dopamine receptor antagonists	Chlorpromazine, prochlorperazine, metoclopramide, droperidol, haloperidol	Chlorpromazine: Off-label Prochlorperazine: Off-label Metoclopramide: Off-label Droperidol: Off-label Haloperidol: Off-label	Haloperidol: 1967 Droperidol: 1970 Chlorpromazine: 1973 Prochlorperazine: 1996 Metoclopramide: 1985
FDA: US Food and Drug Administration Ð = Working Document (not used in the analysis)			

Appendix 2: Comparison of Package insert, Adelphi Survey and Cardiovascular (CV) Risk Assessment in included in analysis ∞

Triptans Package Insert CV risk (contraindications, warnings/precautions)	**Adelphi Survey CV risk characteristics ∞**	**CV risk operationalization (included in analysis)**
Ischemic coronary artery disease (CAD)	Coronary artery disease	Coronary artery disease
Myocardial infarction	Myocardial infarction	Myocardial infarction
Stroke Transient ischemic attack (TIA) Cerebrovascular Events: Cerebral hemorrhage, subarachnoid hemorrhage, and stroke	Haemorrhagic stroke Cerebrovascular disease Ischaemic stroke Transient Ischaemic Attack (TIA)	Cerebrovascular disease
Uncontrolled hypertension	Hypertension	Hypertension
Angina pectoris	Angina	Angina
Raynaud's syndrome	Reynaud's disease	Reynaud's disease
Peripheral vascular disease	Peripheral vascular disease	Peripheral vascular disease
Arrhythmias Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders	Atrial fibrillation Arrhythmia	Arrhythmias
Myocardial Ischemia Silent ischemia	Ischaemic heart disease	Ischemic Heart Disease
History of hemiplegic or basilar migraine	Congestive heart failure Cardiomyopathy	
Chest/throat/neck/jaw pain, tightness, pressure, or heaviness	Hypotension	
Other Vasospasm Reactions: non-coronary vasospastic reactions, such as peripheral vascular ischemia, gastrointestinal vascular ischemia and infarction (abdominal pain and bloody diarrhea), splenic infarction	Deep vein thrombosis	
Coronary artery vasospasm, including Prinzmetal's angina		
CV = Cardiovascular ∞ = PRF (Patient Record Form)		

Appendix 3: Reasons for discontinuation (physicians) and side effects (patients)

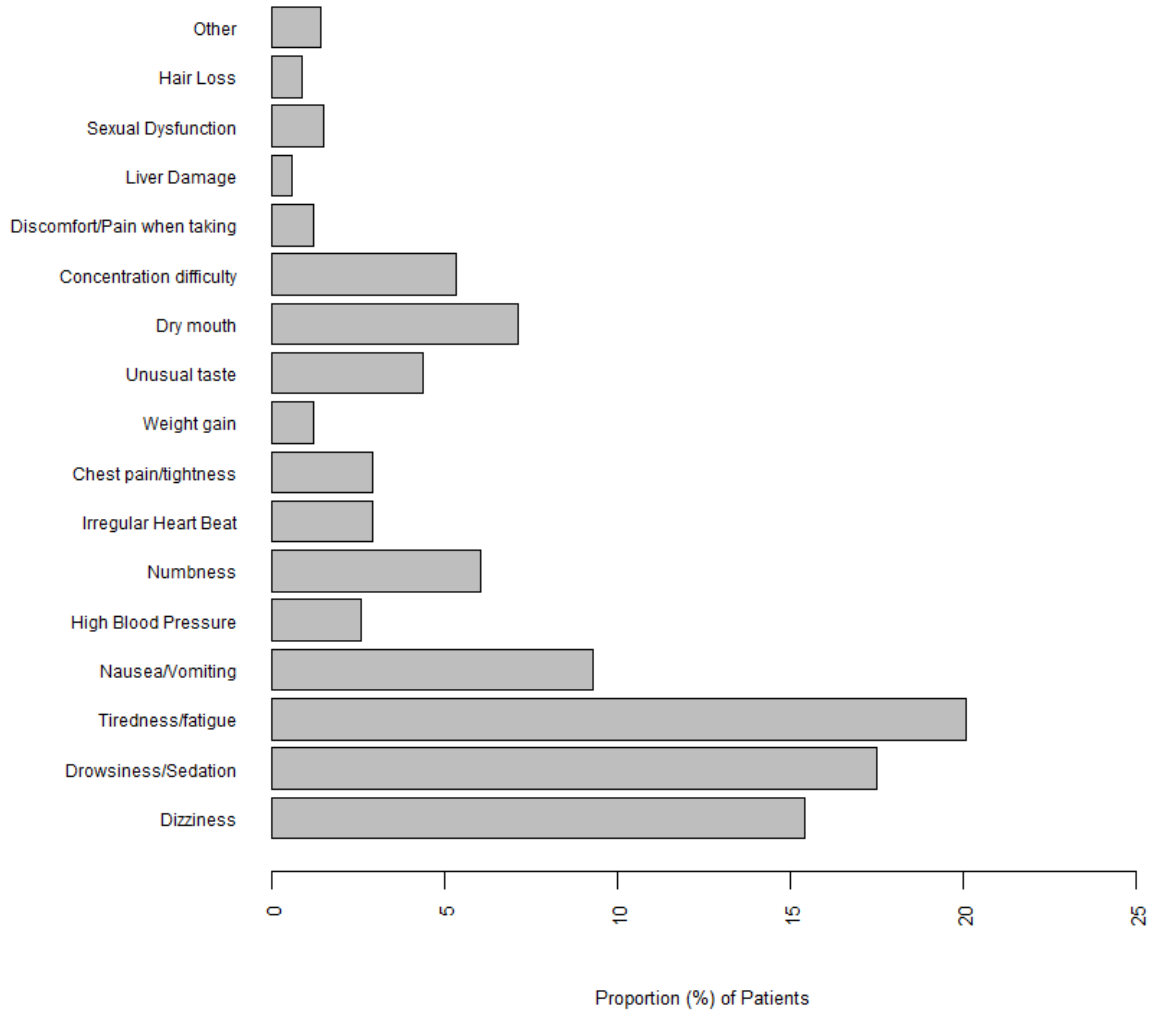
Figure 2bi: Physician-Reported Current Issues/Reasons for Discontinuation of Acute Medications (exhaustive list) (N=1,768) ∞



∞ = PRF (Patient Record Form)

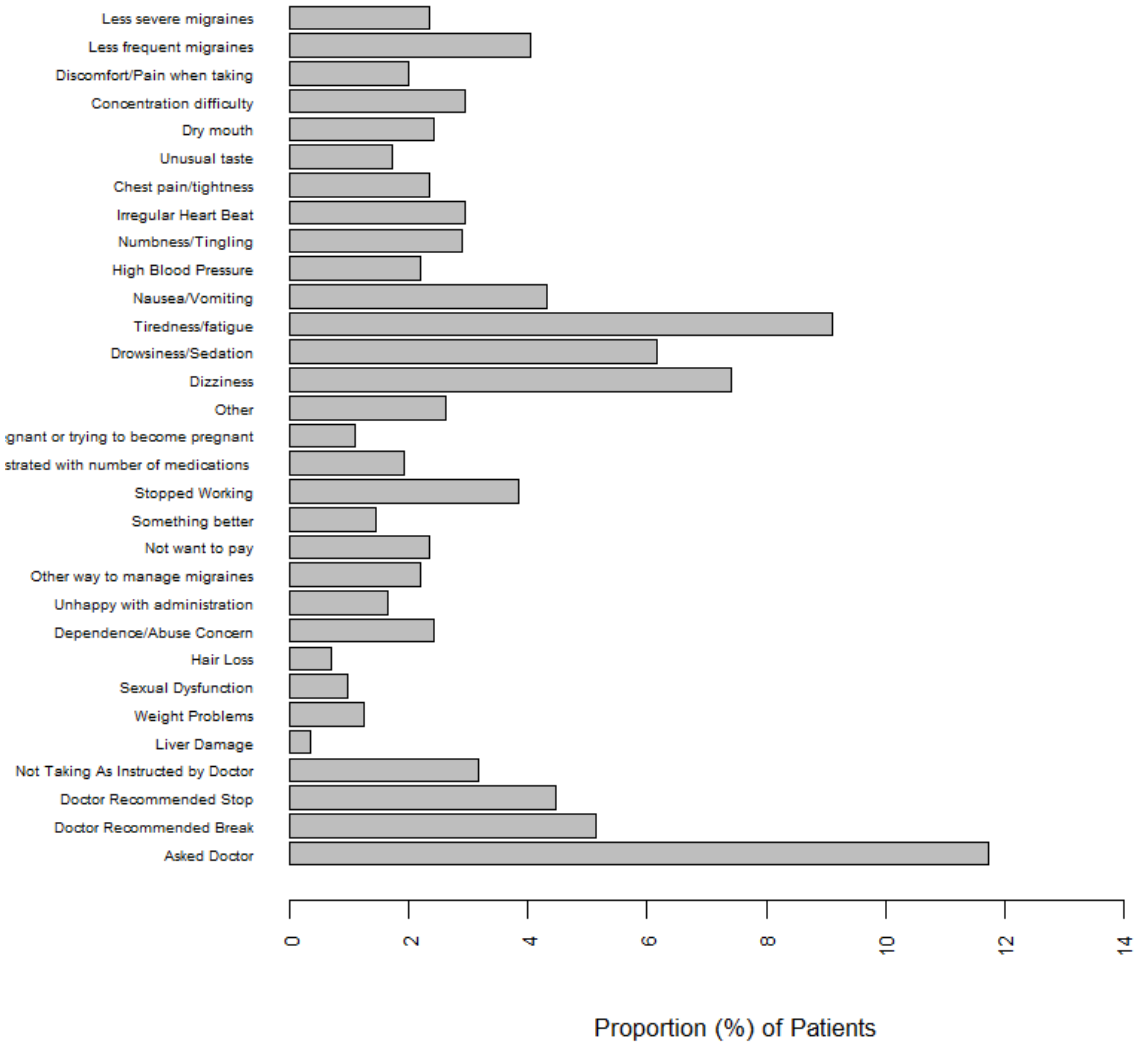
CV = Cardiovascular; GI = Gastrointestinal; HA = Headache; w/n = within; 24h = 24 hours

Figure 2ci: Patient-Reported Side Effects Experienced with Current Acute Medications (exhaustive list) (N=1,281) 🎗



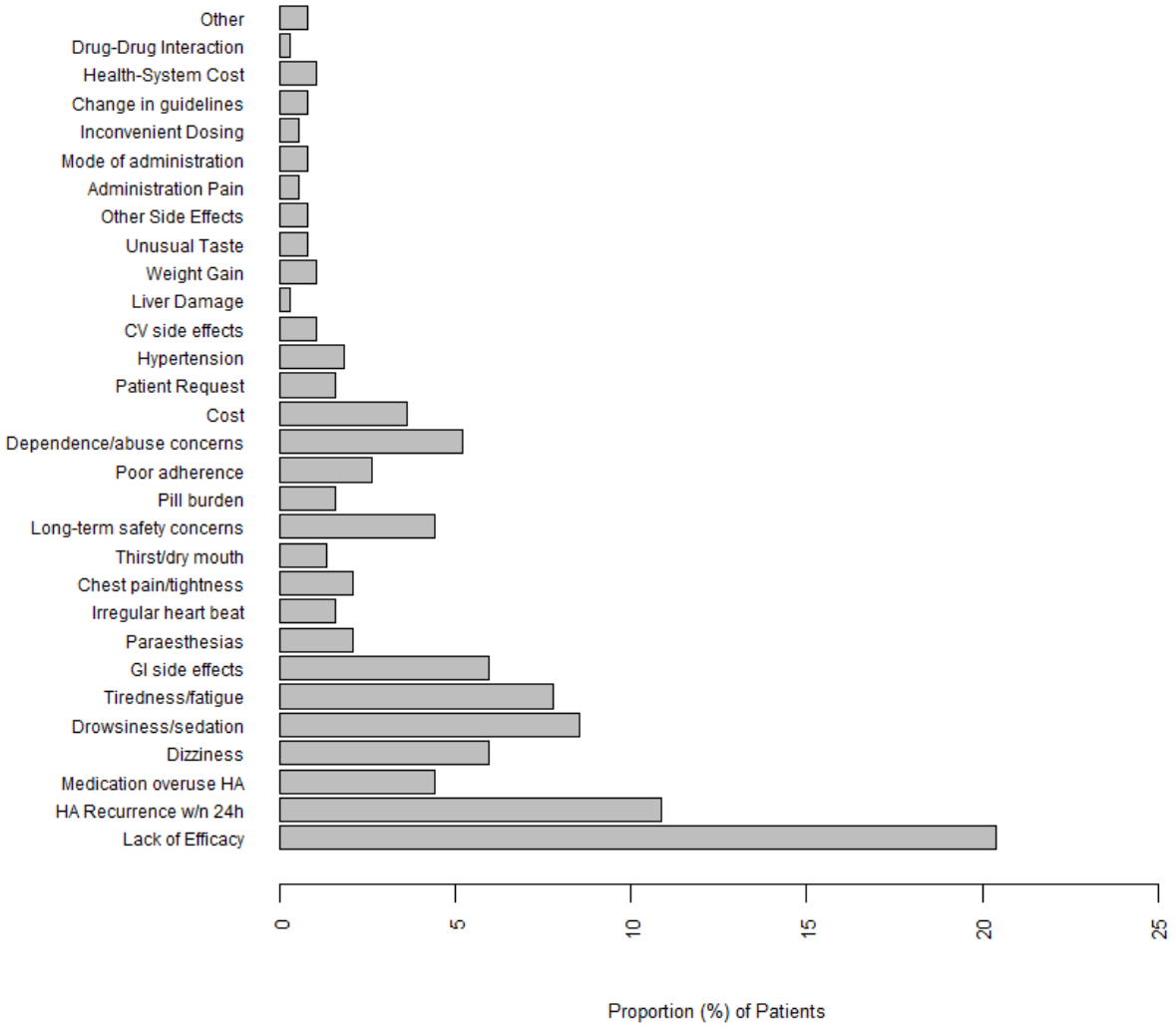
🎗 = PSC (Patient Self-Completed Questionnaire)

Figure 5a: Patient-Reported Reasons for Discontinuation or Switching Triptan (N=1458) 🎗



🎗 = PSC (Patient Self-Completed Questionnaire)

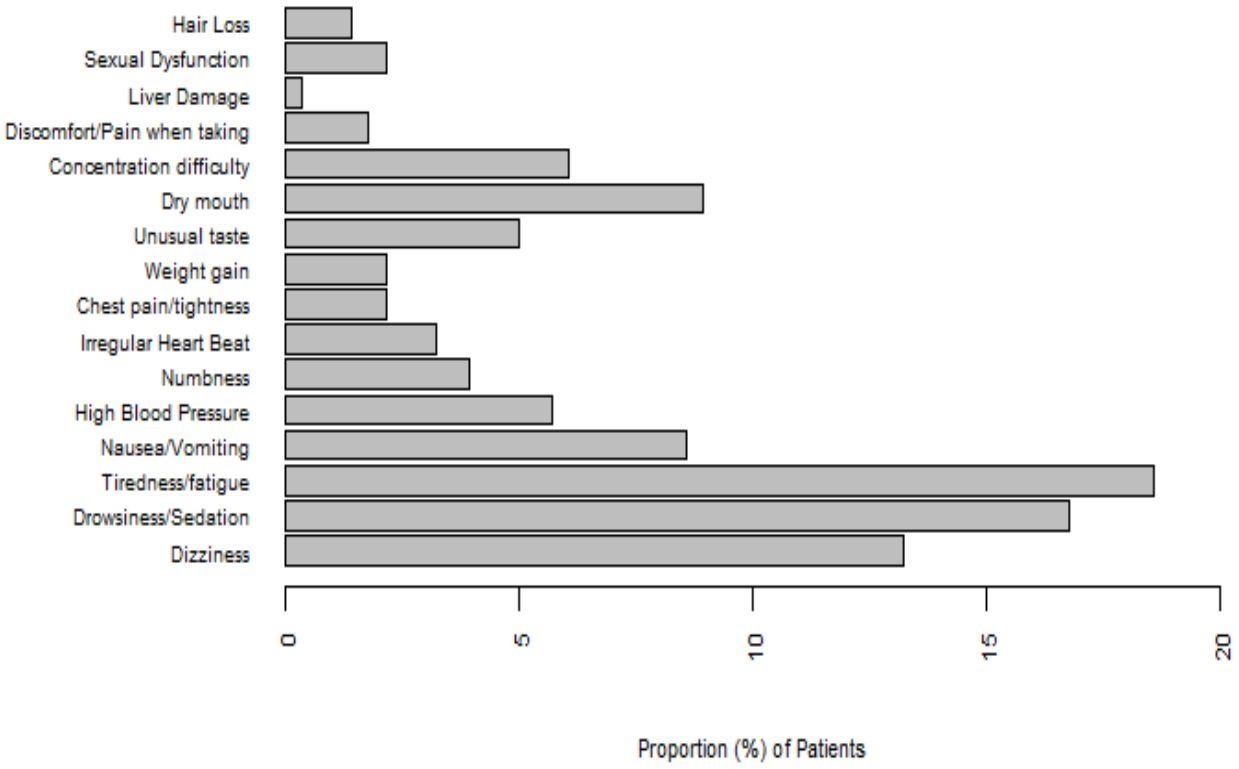
Figure 7ai: Among patients with CV risk, Physician-Reported Current Issues/Reasons for Discontinuation of Acute Medications (exhaustive list) (N=387) ∞



∞= PRF (Patient Record Form)

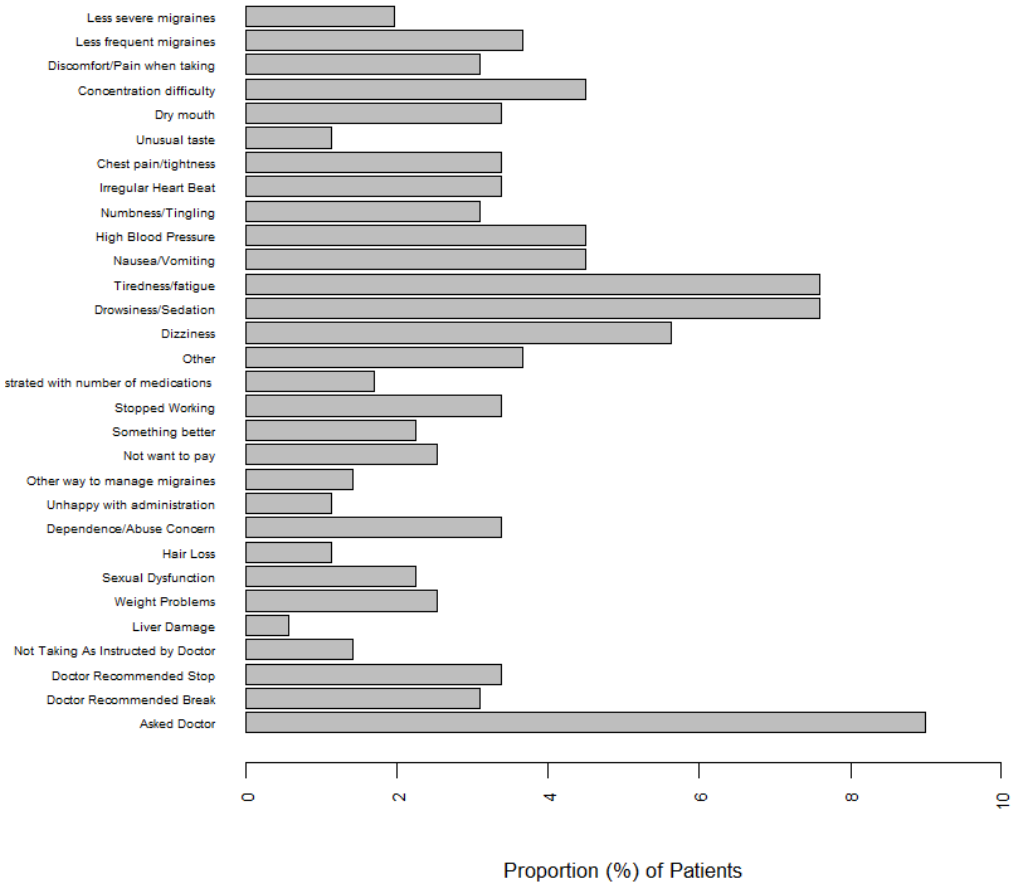
GI = Gastrointestinal; HA=Headache; w/n = within; 24h = 24 hours

Figure 7bi: Among patients with CV risk, Patient-Reported Side Effects Experienced with Current Acute Medications (exhaustive list) (N=280) 🎗



🎗 = PSC (Patient Self-Completed Questionnaire)

Figure 10a: Among patients with CV risk, Patient-Reported Reasons for Discontinuation or Switching Triptan (N=356) 🎗



🎗 = PSC (Patient Self-Completed Questionnaire)