WHITEPAPER

Migraine Treatment and Calcitonin Gene-Related Peptide Inhibitors: A Real-World Electronic Health Record Case Study

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EXECUTIVE SUMMARY

Migraine, a primary headache disorder with significant physical, social, and occupational disability, is estimated to affect 36 million Americans. For patients aged 25 to 49 years, migraine is the third-leading global cause of years lived with disability. In the nearly 1 in 4 US households affected by migraine, family members reported migraine adversely affected family life as well as social or leisure activities. One in three employed respondents to a pharmaceutical survey indicated they turned down work opportunities, including promotions, owing to migraine. Costs of care and lost productivity associated with migraine are measured in tens of billions of dollars. Despite lifestyle modifications and the availability of acute and preventive pharmacotherapies that may mitigate pain and other symptoms and reduce the frequency of attacks, migraine remains inadequately treated in a significant number of patients.

This paper summarizes current knowledge regarding migraine and describes calcitonin gene-related peptide (CGRP) inhibitors, a new therapeutic category of migraine-specific preventive treatment. The paper next considers how streamlining the path to safe and effective management of migraine might be facilitated through analysis of electronic health records (EHRs). Real-world evidence (RWE) derived from longitudinal, de-identified patient information contained on EHR platforms can provide insight regarding provider behavior, patient behavior, and reimbursement; additionally, it can inform medical innovation and product development and help estimate a medical product's economic impact. With a focus on a new CGRP inhibitor, a case study using real-world data from the Practice Fusion EHR ambulatory platform suggests how RWE from patients with migraine may provide insights into the impact of episodic and chronic forms of migraine, management of migraine-related disease burden, and prevention of migraine disease progression.

INTRODUCTION

Migraine, an underdiagnosed and undertreated primary headache disorder characterized by recurrent, painful attacks, affects an estimated 36 million Americans (Lipton and Silberstein, 2015; Lipton et al, 2007; American Migraine Foundation (a), 2018). Gender differences exist, as migraine occurs up to three times more commonly in women than in men (Vetvik et al, 2017). The disorder tends to run in families (Migraine Research Foundation, 2018); genetics may account for 50% of the risk for migraine (Lipton and Silberstein, 2015).

Migraine causes significant physical, social, and occupational disability.

- Worldwide, migraine has consistently been ranked among the top ten causes of disability, affecting more than 10% of the population (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016). For patients aged 25 to 49 years, migraine is the third-leading global cause of years lived with disability (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016).
- Nearly 1 in 4 households in the US includes a family member with migraine (Migraine Research

Foundation, 2018). In one web-based study, cohabitating family members reported migraine adversely affected family life and social/leisure activities (MacGregor et al., 2004). In another study, illness severity was shown to correlate directly with impact on family activities and relationships (Buse et al, 2016).

- More than 90% of Americans with migraine are unable to work or function normally during an attack (Migraine Research Foundation, 2018). One in three employed respondents to a pharmaceutical survey indicated they turned down work opportunities owing to migraine, including promotions (Migraine Impact Report, 2018).

The economic burden imposed by migraine is substantial.

- In the US, total annual costs (direct and indirect) associated with migraine have been estimated at $36 billion (Migraine Research Foundation, 2018).
- A study that examined healthcare resource utilization and costs reported both direct and indirect costs of migraine had increased compared to costs from a study conducted a decade earlier (Bonafede et al, 2018).
- As a result of lost work days due to migraine, more than $13 billion is lost to US employers on an annual basis (Migraine Research Foundation, 2018).
- For families of patients with migraine, healthcare costs are 70% higher than for families unaffected by migraine (Migraine Research Foundation, 2018).

EPISODIC VS CHRONIC MIGRAINE

Migraine is classified based on the frequency of headache-days. Patients who experience headache, with or without aura, on fewer than 15 days per month are considered to have episodic migraine. Chronic migraine is characterized by the presence of headache on 15 or more days per month for at least 3 months, with at least eight headaches per month exhibiting features of migraine headache (Headache Classification Subcommittee of the International Headache Society (a), 3rd edition).

In a population sample of migraine patients who were followed annually for five years, patients with low- or high-frequency episodic migraine progressed to chronic migraine at a rate of 2.5% per year (Bigal et al, 2008). Compared with episodic migraine, chronic migraine is associated with greater disease burden, both personal and societal (Lipton and Silberstein, 2015). Patients with chronic migraine also experience higher rates of medical comorbidity (e.g., depression, anxiety, chronic pain) (Buse et al, 2010) as well as significantly greater headache-related direct, indirect, and total costs (US) than patients with episodic migraine (Messali et al, 2016).

In a cross-sectional study of disease burden and treatment patterns in migraine, a significantly greater percentage of patients with chronic migraine reported medication-overuse headaches (Headache Classification Subcommittee of the International Headache Society (b), 3rd edition) than patients with episodic migraine (24.1% vs 7.3%) (Ford et al, 2017). Avoiding or eliminating medication overuse together with preventing and treating headache and managing comorbidities

may halt progression to chronic migraine (Lipton and Silberstein, 2015). Preventing progression to chronic migraine is a major goal of therapy.

CLINICAL MANAGEMENT OF MIGRAINE

Effective clinical management of migraine requires accurate diagnosis, establishment of a treatment plan for acute symptoms, and a determination of whether preventive treatment is needed (Charles, 2017). Treatment of migraine is multi-pronged and includes patient education, lifestyle modification, and trigger management, as well as use of acute and preventive pharmacotherapies (Lipton and Silberstein, 2015).

Acute Therapy

A stratified approach based on headache severity uses nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen as first-line, acute treatments for mild-to-moderate headaches; moderate-to-severe headaches are initially treated with triptans (e.g., sumitriptan, zolmitriptan) (Mayans and Walling, 2018). For patients with inconsistent symptom patterns or prolonged migraine episodes, a "step care within attack" approach uses a simple analgesic initially, followed by more potent medications for subsequent attacks or later in the same attack if initial treatment is unsuccessful (Mayans and Walling, 2018). When use of triptans is precluded, Food and Drug Administration (FDA)-approved dihydroergotamine nasal sprays or injections may be used (Lipton and Silberstein, 2015). Noninvasive neuromodulation devices (Miller and Matharu, 2017) have been approved by the FDA (American Migraine Foundation (b), 2018) and may serve as useful adjuncts to more conventional therapies (Schwedt and Vargas, 2015).

Preventive Therapy

Preventive therapy is especially important in patients prone to frequent headache; however, nearly half of patients with episodic or chronic migraine who might benefit do not receive preventive therapies (Blumenfeld et al, 2013). Retrospective analyses of US claims data indicate preventive therapy is a cost-effective intervention compared with no preventive therapy, lowering healthcare costs through decreased use of healthcare resources (Devine et al, 2007; Lainez, 2009; Wertz et al, 2009).

> "ALLEVIATING SYMPTOMS, REDUCING DISEASE BURDEN, AND HALTING DISEASE PROGRESSION ARE MAJOR GOALS OF MIGRAINE THERAPY."

A wide variety of pharmacotherapies (40+), both on- and off-label, have been used for migraine prevention, with variable rates of response and severity of adverse events reported across patients (Lipton and Silberstein, 2015). First-line preventive therapies approved by the FDA include propranolol, metoprolol, timolol, divalproex sodium or sodium valproate, topiramate, and botulinum neurotoxin type A (onabotulinumtoxin A) (Lipton and Silberstein, 2015). The use of preventive treatments has been mostly serendipitous, as these preventive therapies have other uses and

indications and were originally developed for the treatment of disorders other than migraine (Bigal et al, 2015).

There is a considerable need for migraine-specific preventive therapies. A recent, cross-sectional study demonstrated more than a quarter of patients with episodic migraine and over one-half of patients with chronic migraine who were receiving preventive treatment discontinued or switched at least once, with 70% indicating they did so owing to lack of efficacy and tolerability/safety (Ford et al, 2017).

MIGRAINE-SPECIFIC PREVENTIVE THERAPY

Recently, a new category of migraine-specific preventive treatment has become available in the US market. Calcitonin gene-related peptide (CGRP) is a 37-amino acid neuropeptide with pro-inflammatory and vasodilatory properties. Localized throughout the trigeminovascular system, CGRP has been implicated in the regulation of brain blood flow and in pain transmission (Walker and Hay, 2013). Evidence of a role for CGRP in the pathogenesis of migraine was provided in early studies that demonstrated its release during acute migraine attacks (Goadsby et al, 1990; Goadsby et al, 1993) as well as its ability to trigger migraine-like symptoms when administered to patients with a history of migraine (Lassen et al, 2002; Hansen et al, 2010). Unlike other preventive medications, CGRP-based therapies target migraine, as they act to inhibit the trigeminovascular pain pathway.

Small-Molecule CGRP Receptor Antagonists

Small-molecule CGRP receptor antagonists, which compete with CGRP for a binding pocket produced by its co-receptors, have shown efficacy as acute agents (Bigal et al, 2015). However, clinical development of one small-molecule receptor antagonist has been discontinued, likely owing to concerns with liver toxicity (Ho et al, 2014). Other small-molecule CGRP receptor antagonists administered orally for acute treatment or prevention of migraine in adults are currently in the drug discovery pipeline and may be available for US launch in 2020 or 2021.

Antibodies Against CGRP or its Receptor

To avoid issues of hepatotoxicity and first-pass metabolism, inhibitory monoclonal antibodies selective for CGRP or its receptor have been developed and evaluated for safety and efficacy as preventive migraine therapies in randomized clinical trials (RCTs) (see text box).

It is estimated that the use of CGRP inhibitors (i.e., peptide antagonists and receptor antagonists) in patients not currently receiving preventive therapy would save $396 billion in indirect costs over a ten-year period. Moreover, the use of CGRP inhibitors may reduce total migraine days by 374 million annually (Soltoff et al, 2018).

Erenumab, a fully human, monoclonal antibody that selectively binds to the CGRP receptor, has been approved by the FDA (May 2018) for the preventive treatment of migraine in adults. Erenumab significantly reduced mean monthly migraine days compared with placebo in patients with episodic migraine during a six-month, Phase 3 RCT (Goadsby et al, 2017) and in patients with chronic migraine during a 12-week, Phase 3 RCT (Tepper et al, 2017). Erenumab is self-administered via subcutaneous injection once monthly.

Fremanezumab, a humanized monoclonal antibody targeting CGRP, received FDA approval (September 2018) for migraine prevention in adults. Fremanezumab significantly reduced mean monthly headache days compared with placebo in patients with chronic migraine in a 12-week, Phase 3 RCT (Silberstein et al, 2017) and significantly reduced the mean number of monthly migraine days in patients with episodic migraine in whom multiple medication classes had not previously failed during a 12-week, Phase 3 RCT (Dodick et al 2018). Fremanezumab is self-administered via subcutaneous injection on a monthly or quarterly basis.

Galcanezumab, a humanized monoclonal antibody that binds CGRP, has been approved by the FDA (September 2018) for the preventive treatment of migraine in adults. Galcanezumab significantly reduced the number of migraine headache days compared with placebo in patients with episodic migraine during a 3-month, Phase 3 RCT (Skljarevski et al, 2018). In another Phase 3 RCT of 6 months' duration, galcanezumab significantly reduced monthly migraine headache days compared with placebo in patients with episodic migraine (Stauffer et al, 2018). Galcanezumab is self-administered via subcutaneous injection once monthly.

Eptinezumab is a humanized monoclonal antibody that targets CGRP; its biologics license application (BLA) is expected to be submitted to the FDA in 2019. Eptinezumab significantly reduced the mean number of migraine headache days in weeks 5 to 8 compared with baseline in patients with frequent episodic migraine in a 12-week, exploratory, Phase 2 RCT, without safety concerns (Dodick et al, 2014). Phase 3 RCTs are currently underway. Eptinezumab is administered intravenously on a quarterly basis.

ELECTRONIC HEALTH RECORDS, REAL-WORLD DATA, AND REAL-WORLD EVIDENCE

In the US, most outpatient healthcare providers (HCPs) have transitioned from paper records to electronic records to document point-of-care interactions (Health IT Dashboard), as encouraged by the Medicare and Medicaid EHR Incentive Program (EHR Incentive Programs, 2018). Medical records can be readily de-identified in compliance with the Health Insurance Portability and Accountability Act and related provisions for patient anonymity and analyzed to identify healthcare trends, to help manage costs, and to facilitate patient care including real-world outcomes. Computerized information systems that are used to collect and store these records can communicate with HCPs and between HCPs and their patients when interfaced with email systems or mobile applications (Chow et al, 2015).

EHR platforms are designed to enhance the uniformity, searchability, transferability, accessibility, and security of patient health information and are excellent sources of real-world data (RWD) (Jarow et al, 2017). RWD may supplement randomized clinical trials (RCTs), increasing efficiency and reducing costs of medical product development. For example, RWD may assist in selecting sites more likely to enroll study participants, provide a basis for power (statistical) calculations in clinical study design, and act as an external control for rare disorders in regulatory submissions (Jarow et al, 2017).

Real-world evidence (RWE) refers to information on health care that is derived from RWD that are routinely generated or collected during healthcare delivery (Sherman et al, 2016; Jarow et al, 2017). Within the healthcare community, RWE may help to address gaps in care associated with

patient and provider behavior; it may be used to develop treatment guidelines, to expand tools for clinical support, and to inform the coverage decision process for medications and procedures (FDA, 2018). Within the FDA, RWE is used to track post-marketing safety and adverse events, as well as to support regulatory decision-making and to develop drugs for rare diseases (FDA, 2018; Salzman, 2018). Increasingly, RWE contributes to medical innovation and product development from the research community, including the design, execution, and analysis of RCTs (Corrigan-Curay et al 2018). Post-approval, medical product manufacturers may use RWE to estimate the economic impact of their products on healthcare and to convince regulatory authorities that additional product uses are safe and effective as new indications for an approved product (Sherman et al, 2016).

In addition to its utility in interventional studies (i.e., RCTs and pragmatic trials), RWE has value in observational settings (Sherman et al, 2016). Its use can give rise to hypothesis generation for testing in prospective trials, assessment of the generalizability (external validity) of findings from RCTs, and surveillance of the safety of medical products (Sherman et al, 2016). RWE can be used to track patterns of drug and device use and to enact changes in healthcare delivery (Sherman et al, 2016).

REAL-WORLD CASE STUDY

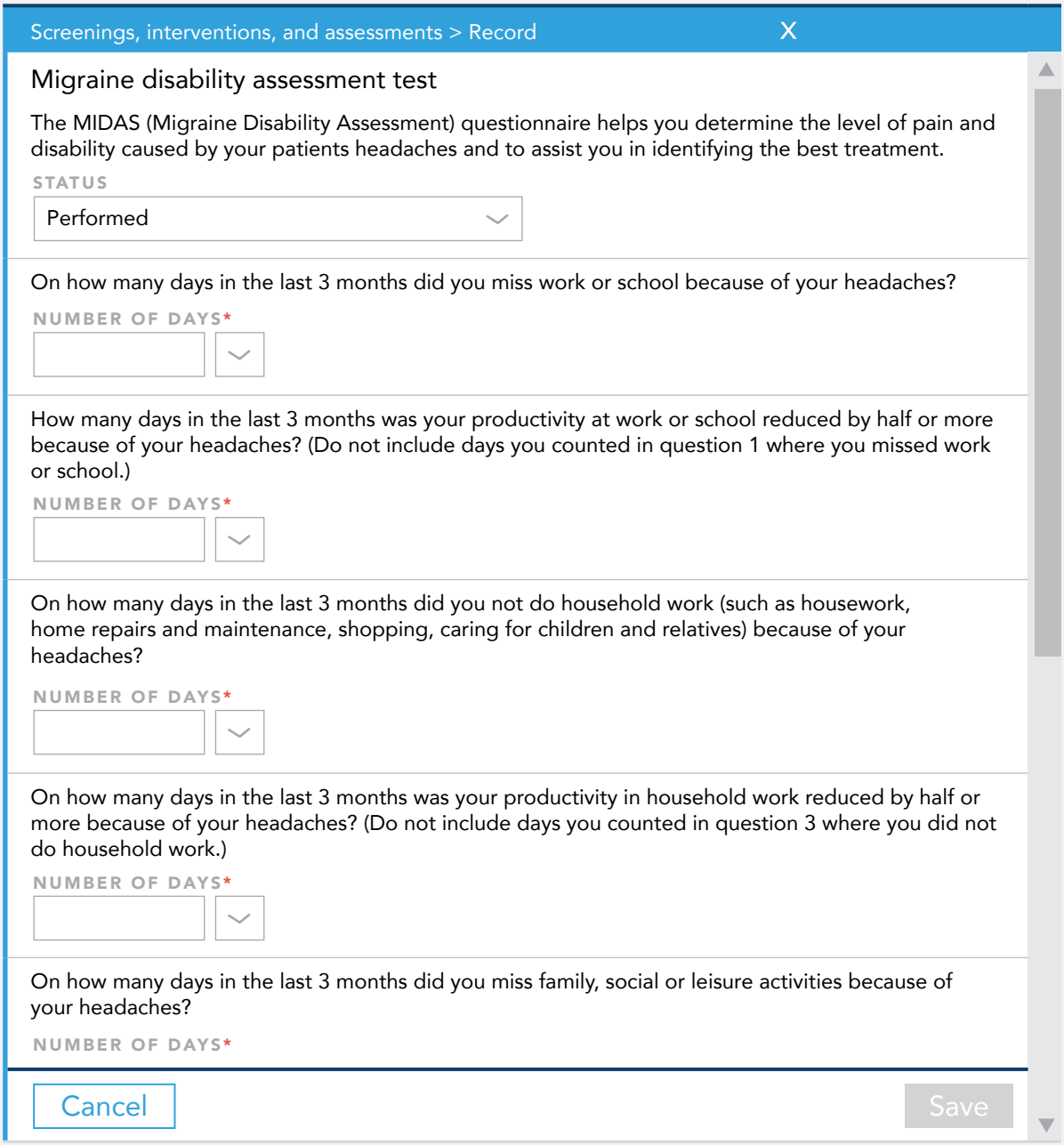
To explore how real-world observations for an FDA-approved CGRP inhibitor might provide insights into managing migraine, an analysis was performed on de-identified RWD of ambulatory patients with migraine using the EHR platform of Practice Fusion, a Veradigm™ company. The Practice Fusion platform contains electronic ambulatory patient medical records sourced from more than 6% of independent physician and small group practices in the US (IQVIA, 2018). The platform is cloud-based, enabling secure, bi-directional communication between Practice Fusion and healthcare providers (HCPs). Since March 2018, HCPs using the Practice Fusion platform have been able to record the results of the Migraine Disability Assessment (MIDAS) questionnaire, a patient-reported outcome of migraine-related disease burden (Stewart et al, 2000). A validated, seven-item assessment, the MIDAS questionnaire is regularly used as a clinical research instrument in RCTs and real-world studies. To an HCP working on the Practice Fusion platform, the MIDAS questionnaire appears as shown in **Figure 1**.

Study Design

This retrospective, observational study evaluated de-identified data (demographics, outpatient prescription treatment, and a clinical indicator of headache-related disability) for patients who received a CGRP inhibitor compared with patients naïve to inhibitor. To be included in the study, patients had to

- Have a documented diagnosis of migraine in their de-identified records
- Have at least one written prescription for a medication recognized as an acute or preventive treatment for migraine, including a CGRP inhibitor, during study intake between June 1, 2018 and September 30, 2018 (the index date)

FIGURE 1 | The MIDAS Questionnaire on the Practice Fusion Platform



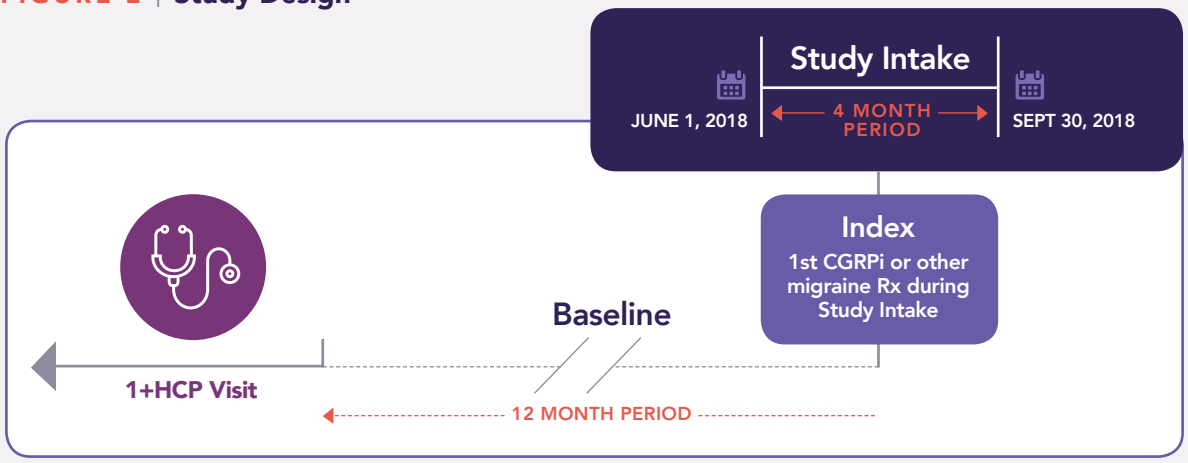
A point-of-care message to the HCP is triggered by the patient's clinical profile, which communicates an opportunity for the provider to complete the assessment. Results are saved as part of the patient's medical record where they form a longitudinal record of the patient's condition.

MIDAS score, 0–5, little to no disability; 6–10, mild disability; 11–20, moderate disability; ≥21, severe disability.

- Be 18 years of age or older on June 1, 2018
- Have one or more ambulatory visits to HCP more than 12 months prior to their index date, with the 12 months prior to index considered to be the baseline period (**Figure 2**).

Prescriptions for all eligible medications were written in the first four months following CGRP inhibitor product launch. MIDAS assessments were conducted prior to index.

FIGURE 2 | Study Design



Patients eligible for study intake were grouped according to migraine medication history in the 12-month baseline period (no medications, acute medications, preventive medications, and mixed [acute and preventive] medications), with or without the CGRP inhibitor (total, 8 cohorts). Based on the pool of de-identified records, 84,470 patients previously diagnosed with migraine had at least one written prescription for eligible medication during study intake. From this initial pool of patient candidates, 59,280 patients additionally met age and prior HCP visit criteria as of their index date.

RESULTS

Demographics

Patient demographics are shown in **Table 1**.

Except for age, the key demographics were comparable to those of migraine patients in recent RWE survey studies (Blumenfeld et al, 2011; Rothrock et al, 2014; Adams et al, 2015; Ford et al, 2017). The mean age for the eight cohorts ranged from 46.9 to 53.7 years, generally older than mean ages (range, 39.2–42.0 years) reported for patients with migraine in real-world survey studies. Most patients in each cohort were female (range of means, 81.4%–89.1%), as were most patients (range, 73.3%–88.3%) in real-world survey studies. The mean BMI for the eight cohorts ranged

TABLE 1 | Patient demographics

CHARACTERISTICS	No Prior Medication N=9,403		Acute Medication N=11,623		Preventive Medication N=14,819		Mixed Medication N=23,435	
	CGRPi	CGRPi Naïve	CGRPi	CGRPi Naïve	CGRPi	CGRPi Naïve	CGRPi	CGRPi Naïve
	n=50	n=9353	n=97	n=11,526	n=114	n=14,705	n=341	n=23,094
Age, mean (SD)	49.2 (13.0)	47.8 (15.1)	52.1 (11.8)	49.8 (13.6)	46.9 (14.3)	53.7 (14.7)	48.5 (12.7)	52.0 (13.1)
Female, n (% of cohort)	44 (88.0%)	7,725 (82.6%)	79 (81.4%)	9,457 (82.0%)	99 (86.8%)	12,105 (82.3%)	304 (89.1%)	19,308 (83.6%)
BMI, mean (SD)	28.2 (6.9)	29.5 (7.3)	27.6 (7.1)	29.2 (7.2)	28.3 (7.8)	30.8 (7.7)	27.9 (6.9)	30.8 (7.9)

CGRPi = calcitonin gene-related peptide inhibitor; SD = standard deviation.

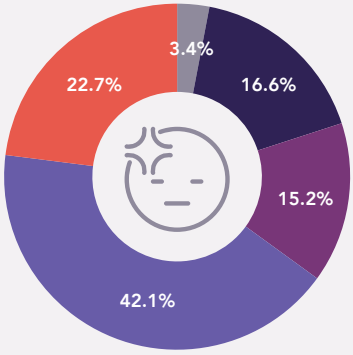


FIGURE 3 | US Regional Distribution of Patients with Migraine at Study Intake

The pie chart shows percentages by region for the 8 cohorts collapsed together (no medications, acute medications, preventive medications, and mixed [acute and preventive] medications, with or without the CGRP inhibitor).

Northeast Midwest South West Undetermined

from 27.6 to 30.8, consistent with mean BMIs (range, 27.4–41.6) reported in two real-world survey studies (Adams et al, 2015; Ford et al, 2017).

Regarding the geographic distribution of eligible patients (**Figure 3**), 42.1% live in the South, 22.7% in the West, 15.2% in the Midwest, and 16.6% in the Northeast, in keeping with regional distributions (for chronic migraine) reported in The Headache and Migraine Policy Forum (Thorpe, 2018).

Likewise, other than age, patient demographics resembled those of patients with migraine in the CGRP inhibitor pivotal RCTs (Tepper et al 2017; Goadsby et al 2017; Silberstein et al 2017; Dodick et al 2018; Skljarevski et al 2018; Stauffer et al, 2018). The mean age for the eight cohorts ranged from 46.9 to 53.7 years, older than the mean ages (range, 39.1–42.9 years) reported for patients

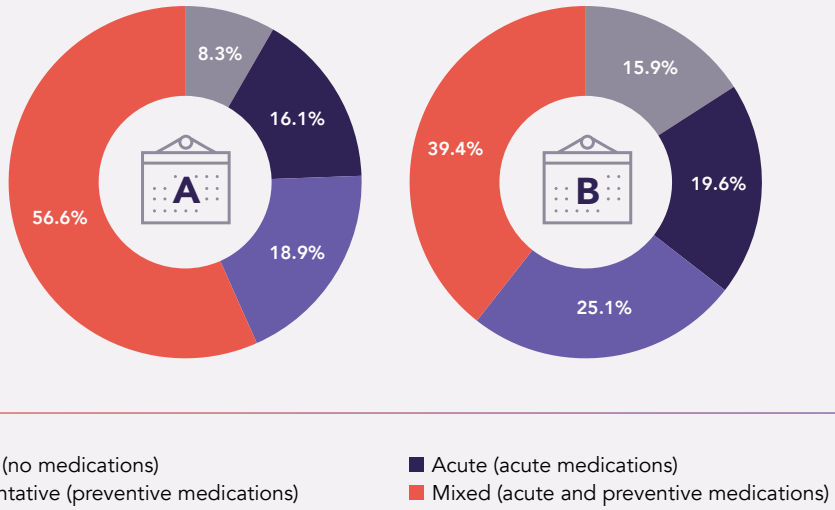
in the RCTs. Patient gender was predominantly female in the eight cohorts (range, 81.4%–89.1%) and in the RCTs (range, 79%–88%). The mean BMIs for the eight cohorts (range, 27.6–30.8) were similar to mean BMIs (range, 26.0–28.6) reported in the RCTs for CGRP inhibitors.

Outpatient CGRP Inhibitor Treatment

Of 59,280 study-eligible patients, 602 (1.0%) had at least one written prescription for or were documented to have taken the CGRP inhibitor. **Figure 4** shows the medication history for patients with CGRP inhibitor prescriptions or for CGRP inhibitor-naïve patients. During the baseline period, 91.7% of patients in the CGRP inhibitor group had prescriptions for or a history of acute, preventive, or a mix of acute and preventive medications (**panel A**). In the CGRP inhibitor-naïve group, 84.1% of patients had prescriptions for or a history of these eligible medications (**panel B**). A total of 56.6% of patients in the CGRP inhibitor group had written prescriptions for or a history of both acute and preventive medications (**panel A**) whereas in the CGRP inhibitor-naïve prescription group, 39.4% of migraine patients had prescriptions for or history of acute and preventive medications (**panel B**).

Study-eligible patients who had at least one written prescription for or were documented to have taken the CGRP inhibitor were generally those who had the most office visits (>3) prior to baseline.

FIGURE 4 | Medication history for CGRP inhibitor treated (A) (n = 602) and CGRP inhibitor-naïve (B) patients (n = 58,678) during the 12-month baseline period.



Although prescribing of the CGRP inhibitor was not restricted to specialists by study design, 76% of inhibitor prescriptions were written by neurologists or pain specialists, yet practices with these specialists accounted for only 22.5% of study-eligible patients. Primary care practices managed nearly three-quarters of study-eligible patients.

MIDAS Questionnaire

A total of 1,666 MIDAS assessments were completed by 2.8% of study-eligible patients. Patients naïve to CGRP inhibitor completed more than 97% of MIDAS assessments, with a mean (SD) MIDAS score of 17.6 (31.0), indicative of moderate disability in the baseline period. For patients in the CGRP inhibitor group, the corresponding baseline mean (SD) score of 50.2 (58.0) indicates severe disability. The number of patients assessed using MIDAS scores in this case study was less than that reported in two migraine surveys, the International Burden of Migraine survey (Blumenfeld et al, 2011) and the US longitudinal CaMEO survey (Adams et al, 2015). There were more participants in this study than in two other US surveys (Ford et al, 2017; Rothrock et al 2014).

Number of headache days over 3 months is assessed as an optional part of the MIDAS questionnaire. More than half (55.3%) of patients reported 0 to 5 headache days per month; (13.6%) reported 6 to 10 headache days per month, (25.8%) reported 11 to 23 headache days per month, and (4.8%) reported 24 or more headache days per month. Because the MIDAS questionnaire evaluates 3 months of patient reported outcomes, the last group of patients may qualify as patients with chronic migraine.

DISCUSSION

Migraine remains inadequately treated in a significant number of patients. Effective clinical management frequently entails the use of both acute and preventive therapies to mitigate symptoms and disability. Alleviating symptoms, reducing disease burden, and halting disease progression are major goals of migraine therapy.

The use of actionable and meaningful RWE in everyday ambulatory clinical settings and healthcare decision-making is rapidly expanding. EHR platforms provide an opportunity to generate RWE to guide migraine treatment in real-world settings. Examples include enablement of automated data interchange among providers, payers, and manufacturers, as well as direct integration of information on medication safety, patient benefits, and patient assistance programs, all existing in the user workflow to enhance clinical practice. EHRs may also be leveraged to inform coverage decisions for drugs and procedures and as input for care management programs.

As primary sources of de-identified patient data, large, cloud-based, digital health information systems enable bidirectional communication between EHR platforms and providers. Given its size, its cloud-based capacity to electronically document point-of-care interactions, and the inclusion of the MIDAS questionnaire, the Practice Fusion EHR is positioned to provide insights regarding the impact of migraine, management of migraine-related disease burden, and prevention of migraine disease progression.

The case study provides an example of how an EHR platform can be leveraged to assess the demographics, treatment patterns, and headache-related disability of ambulatory patients with migraine who had at least one written prescription for a CGRP inhibitor or other migraine treatments in real-world settings. For the overall study population, patient demographics such as gender, body mass

index, and geographic location were shown to align with those reported in previous real-world studies in migraine, as well as with patient demographics (gender, BMI) in RCTs that evaluated CGRP inhibitors. Patients were consistently older than those observed in other real-world studies of migraine, likely due to the older patient population served on the Practice Fusion platform. There was a higher percentage of patients in the CGRP inhibitor group who had written prescriptions for or a history of both acute and preventive medications compared with patients in the CGRP inhibitor-naïve group (56.6% vs 39.4%). This finding suggests patients in the former group may have had more difficulty managing their migraines than patients in the latter group. In terms of headache-related disability, all cohorts in which patients received prescriptions for the CGRP inhibitor were, on average, severely disabled according to MIDAS assessments. These headache-related disability data suggest there continues to be an unmet need for effective therapies in a notable number of patients with migraine.

"THE USE OF ACTIONABLE AND MEANINGFUL RWE IN EVERYDAY AMBULATORY CLINICAL SETTINGS AND HEALTHCARE DECISION-MAKING IS RAPIDLY EXPANDING."

The use of interactive EHR platforms might be expected to support patient care and therapeutic outcomes in a wide variety of real-world scenarios. Such platforms provide tools for clinical support to HCPs whose patients reach a threshold of headache-related disability that is triggered, for example, by the number of switches or discontinuations of acute or preventive medications. HCPs may be prompted to respond to surveys through digital health platforms to administer MIDAS questionnaires to patients not meeting treatment goals. Medication use may be tracked, providing insight into continued disease progression and gaps in preventive therapy. Proactive communication to both provider and patient might then be initiated to directly communicate safety and efficacy guidelines to optimize the potential for better outcomes. Health plans may similarly be advised regarding at-risk members who might benefit from participation in a care management program or other health plan-directed intervention.

Insights generated regarding migraine management may prove useful in designing real-world, observational studies (Booth and Tannock, 2013). HCPs and patients who participate in post-marketing studies within the context of routine medical care may be more willing to be recruited to participate in RCTs. The potential to gather, analyze, and proactively respond to clinical insights will be a significant factor shaping the next generation of integrated clinical data solutions.

Likewise, EHR data capture could be used to drive hypothesis generation and testing in support of medical innovation and product development. Analyses of linked EHR and claims data could also reveal direct costs of treatment and areas for targeted quality improvement. For example, if CGRP inhibitory agents were found to significantly reduce patient visits to urgent care centers or emergency rooms (including hospitalizations), migraine-related cost of care might be estimated, as done previously for the preventive therapy onabotulinumtoxin A (Rothrock et al, 2014), for reasons of cost control and HEDIS assessment.

Recognition of RWE's potential to extend the findings of RCTs, which are internally valid but may not generalize to broader populations in real-world settings, is central to an understanding of its usefulness (Sherman et al, 2016). The use of digital health platforms may facilitate design of less-restrictive, more-inclusive pragmatic studies that focus on healthcare utilization or the relative effectiveness and tolerability among migraine-specific preventive therapies to inform clinical practice. Pragmatic studies and non-interventional, observational studies provide an opportunity to assess heterogeneity of response among patients with migraine in routine healthcare settings. Comparisons may be more feasible with longitudinal observational studies, including registries, than with RCTs. Retrospective data analyses could be combined with observational studies to provide robust views of drug or procedure impact and use in the real world.

CONCLUSION

There has been burgeoning interest in how EHRs may facilitate efficient and cost-effective drug research and development and healthcare decision-making. EHRs contain de-identified patient information from which RWE may be derived. A case study using such RWE from the Practice Fusion EHR demonstrates how RWE from patients with migraine aligns with previous real-world analyses of disease burden, as well as findings from clinical trials. Future studies that leverage RWE may provide insights into the impact of new approaches to episodic and chronic forms of migraine, management of migraine-related disease burden, and prevention of migraine disease progression.

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