The Effect of Weather Conditions on Demand Forecasting of Migraine Medications in a Specialty Pharmacy Applying ARIMA and VARMA Models

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Received: 06-Apr-2023, Manuscript No. HEOR-23-94422; **Editor assigned:** 10-Apr-2023, Pre-QC No. HEOR-23-94422 (PQ); **Reviewed**: 14-Apr-2023, QC No. HEOR-23-94422 (Q); **Revised**: 19-Apr-2023, Manuscript No. HEOR-23-94422 (R); **Published**: 25-Apr-2023, DOI: 10.35248/2471- 268X.23.9.3.1

Abstract

Background: Demand forecasting in a specialty pharmacy is a challenge that requires a data-driven decision-making process to improve its procedures. Patients with migraine are sensitive to weather conditions, but it is still unclear how it can affect the demand for migraine medications in pharmacies. The objective of the study is to apply ARIMA (Autoregressive Integrated Moving Average) and VARMA (Vector Autoregressive Moving Average) analytical methods to the demand forecasting of four most-prescribed migraine medications in a specialty pharmacy and to assess the impact of weather conditions in the demand forecasting of those medications.

Methods and Findings: This study was a collaboration between the University Of Cincinnati Medical Center, LLC (UC Health Specialty Pharmacy) and the James L. Winkle College of Pharmacy, both located in Cincinnati, Ohio. The pharmacy provided 26 months of pre-recorded actual sales data of Aimovig, Ajovy, Emgality, and Nurtec ODT, representing a total of 1,043 patients ordering migraine medications from the UC Health Specialty Pharmacy. After preprocessing the data, two variables were considered for the forecasting model: demand for each day and the date of each purchase by the pharmacy. For each medication, an approximate total of 800 data points were used to develop the forecast model. Weather conditions variables were added to each medication model to assess its effect on their demand. Then, a comparison was performed between the forecasting models with and without weather conditions as potential factors that could influence the demand for each medication. For the ARIMA models, only the demand was considered as the response variable while for the VARMA models, both demand and weather conditions variables were considered as factors. For MAPE and RMSE accuracy metrics, the lower the value, the more accurate the model. The ARIMA was determined to be the best forecast model for Emgality, Aimovig, and Nurtec ODT. However, VARMA was the best forecast model for Ajovy, indicating that weather conditions may affect the demand forecasting of this medication. Both models (ARIMA and VARMA) for all four medications in this study were considered either very accurate (MAPE<10) or a good predictor (MAPE<20). This is especially true for the ARIMA models for Aimovig, Emgality, and Nurtec ODT and VARMA models for Emgality and Nurtec ODT (MAPE less than 6).

Conclusions: The study showed that weather conditions had a significant effect on Ajovy's demand during the 26-month period. When forecasting its demand, the model had higher accuracy when compared to forecasting its demand without weather conditions as a factor. On the other hand, weather conditions had no significant effect on the demand forecasting models for Aimovig, Emgality, and Nurtec ODT. Those models had higher accuracy when their demands were forecasted without weather conditions as factors.

Keywords: Migraine • Specialty Pharmacy • ARIMA • VARMA • Demand Forecasting

Introduction

Demand Forecasting

Demand forecasting is a challenge that requires relevant data and advanced analytical procedures to address new growth and other opportunities. For instance, fast-growing Taiwan's semiconductor industry heavily relies on demand forecasting techniques [1]. Wang CC used analytical methods such as ARIMA to develop demand forecasting models through historical data and showed improved results when compared to the traditional manufacturer's model. Moreover, according to Gartner, Inc., a research and consulting firm, applying demand forecasting analysis can reduce inventory costs by 15 to 30% [2]. Companies that employ data-driven decision-making add value to their demand forecasting and pharmacies are no different.

From the pharmacy perspective, if the inventory is high, patients will always have their medication in stock, but it will increase the inventory holding and storage costs of medications as well as increase the chance of a medication reaching its expiration date. Even though low inventory may generate savings on inventory holding cost and storage costs, it may also increase the chances of stock-outs, when a medication is not available to patients. Having stock-outs in a specialty pharmacy is not efficient since patients with complex medical conditions such as migraine cannot afford to skip days of treatment. Financial and logistic limitations require the best inventory management possible [3, 4]. Current pharmacy inventory management relies on pharmacists' experiences in the absence of reasonable analytical approaches. Thus, this may create a misalignment between the pharmacist's judgment and the actual inventory needed. This could result in overstocking some medications while leaving others under-supplied. The creation of an analytical approach and data to support decisions is paramount to improving the current demand forecasting model of the UC Health Specialty Pharmacy.

The need to better understand the demand for information requires advanced analytical approaches based on credible data. Some analytical techniques can correctly predict pre-recorded data to create predictive models such as ARIMA (Autoregressive Integrated Moving Average) and VARMA (Vector Autoregressive Moving Average) [5-7]. For instance, ARIMA has shown an improved demand forecast process in a semiconductor company in Taiwan when compared to the manufacturer's empirical model forecast system [8]. A previous study showed that the VARMA model was the best model to forecast the daily mean temperature in a busy seaport in Indonesia [9]. In 2019, Sidy Fall, also found the VARMA model as the most accurate model when forecasting the wage bill of the French Personal

Services sector [10]. Thus, both methods were expected to successfully make predictions based on time series data.

Migraine

Migraines and severe headaches are significant public health problems, with women of reproductive age and people from lower socioeconomic backgrounds being most affected in the United States [11]. According to the National Health Interview Survey (NHIS), employment, poverty, insurance status, and education play an important role in migraine prevalence. Another factor that has been reported as a possible trigger factor for headaches and migraine is weather conditions [12-14]. Although migraineurs frequently attribute certain meteorological conditions or their variations over short periods of time as a triggering component of their attacks in clinical settings there is no definitive causal link established [12, 15, 16]. Previous studies suggested that between 7% to 61% of migraineurs are sensitive to weather conditions, but it is still unclear how it can affect the demand for migraine medications in pharmacies [12, 14, 17-19].

The objective of the study is to apply ARIMA and VARMA analytical methods to the demand forecasting of the four most-prescribed migraine medications in a specialty pharmacy and to assess the impact of weather conditions on their demand. The selected migraine medications are in the top 10 most-prescribed drugs in the UC Health Specialty Pharmacy. The purpose of the study is to improve the pharmacy's demand forecasting by applying analytical methods instead of relying upon the pharmacist's experience alone. The study demonstrates its originality by data-driven assessment of the weather effect on migraine medication demand for the first time.

MATERIALS AND METHODS

Sampling and Study Design

The data for this study was obtained from the Specialty Pharmacy at UCMC, located in Cincinnati, Ohio. The Specialty Pharmacy is URAC (Utilization Review Accreditation Commission) accredited, meeting nationals' standards for quality, accountability, and consumer protection. Specialty pharmacies offer services and medications to treat rare and complex medical conditions like migraine, cancer, hepatitis C, HIV/ AIDS, rheumatoid arthritis, and multiple sclerosis. Specialty medications are usually expensive and required special handling, storage, and consultation. The UC Health Specialty Pharmacy dispenses and distributes medications to Ohio, Indiana, and Kentucky.

The four most-prescribed migraine medications by the UC Health Specialty Pharmacy were selected for the study. The pharmacy provided 26 months of pre-recorded actual dispensing data of Emgality, Aimovig, Nurtec ODT, and Ajovy. All medications were recently approved by the Food and Drug Administration (FDA) [20-23]. There are in total 1,043 patients ordering migraine medications from the pharmacy. The brand and generic names, unit and treatment prices, manufacturer, and FDA approval dates for all medications can be seen in Table 1 [24].

Table 1: Medication name (brand and generic), unit and treatment prices in US dollars, manufacturer, and the Food and Drug Administration (FDA) approval dates.

Medication					
Brand Name	**Generic Name**	**Unit Price ($)**	**Treatment Price ($)**	**Manufacturer**	**FDA Approval Date**
Aimovig	erenumab-aooe	743.18	743.18	Amgen Inc.	May, 2018
Ajovy	freman-ezumab-vfrm	473.17	709.75	Teva Pharmaceuticals USA, Inc.	September, 2018
Emgality	galcan-ezumab-gnlm	696.9	1,728.00	Eli Lilly and Company	September, 2018
Nurtec-ODT	rimege-pant	122.19	977.51	Pfizer Inc.	February, 2020

The selected migraine medications have different characteristics, which may also play a role in their demand forecasting models. For instance, Aimovig, Ajovy, and Emgality are administered subcutaneously by a syringe while Nurtec ODT is an orally administered tablet. Furthermore, syringe medications have different storage requirements since they must be refrigerated. This fact increases the costs of storage and shows the importance of improving the demand forecasting for those medications.

Historical UC Health Specialty Pharmacy Epic dispensing data was used to identify the typical inventory demand [25]. The variables included in the raw data were medication name, NDC number, package size, ordered quantity, invoiced quantity, invoiced price, invoiced price/invoiced quantity (price per package), and order date. The pre-recorded data of each medication were added into a forecasting model to generate a prediction of future demand levels needed in the specialty pharmacy.

3 steps were performed to create the model including weather conditions to forecast the demand forecasting of the four selected medications. First, the raw data needed to be pre-processed (cleaned). The 26-month raw data provided by the pharmacy had several variables not applicable to the model as well as missing data from Epic Systems. The data was pre-processed using Microsoft Excel as well as two advanced statistical software: Minitab® and Python. Both ARIMA and VARMA models were deployed in Python® using JupyterLab, a web-based notebook interface [26]. Pre-processing the data involves spotting and resolving potential data inconsistencies, gaps, and/or errors to improve data quality. After pre-processing the data, two variables were considered for the forecasting model: demand for each day and the date of each purchase by the pharmacy.

For each medication, an approximate total of 800 data points were used to develop the forecasting model. The data was first pre-processed and then divided into developing (first section of data) and validating (later section of data) models. Ninety percent (e.g., the first 720 data points out of 800) and ten percent of the total data were used in developing and validation models, respectively. The next step was to introduce weather conditions variables into each medication model to assess its effect on their demand. For weather conditions, the averages for temperature, dew point, barometric pressure, and 24h precipitation were used. A comparison was performed between the forecasting models with and without weather conditions as potential factors that could influence the demand for each medication. The proposed models were based on a time series analysis with 26 months of historical medication monthly demand values. The study design is shown in Figure 1.

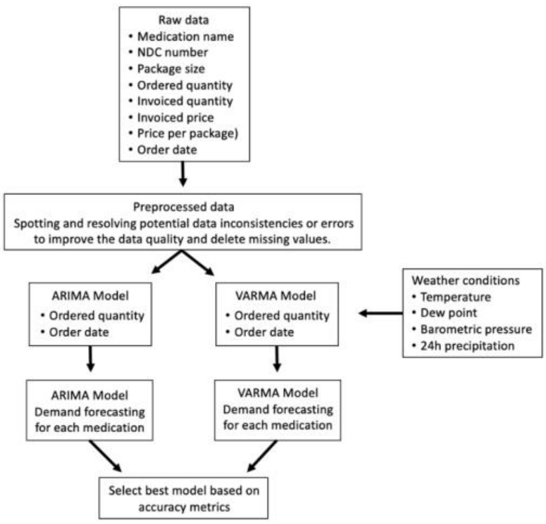

Figure 1: Study design/forecast framework with pre-processing steps and ARIMA and VARMA modeling rationale. The raw data of each medication was pre-processed before deployment into both models. The ARIMA is a

univariate model that considered the demand as the response variable, while VARMA is a multivariate model that considered the daily average of different weather conditions in the model and kept the demand as the response variable.

Weather data was collected from the National Centers for Environmental Information "Climate Data Online" system, using the National Oceanic and Atmospheric Administration's (NOAA) weather stations KCLE for Cleveland, KCMH for Columbus, and KCVG for Cincinnati [27]. Historical data by date for the Midwest region (Ohio, Indiana, and Kentucky) was collected. (Figure 2 shows the heat map to the locations where migraine medications were shipped to).

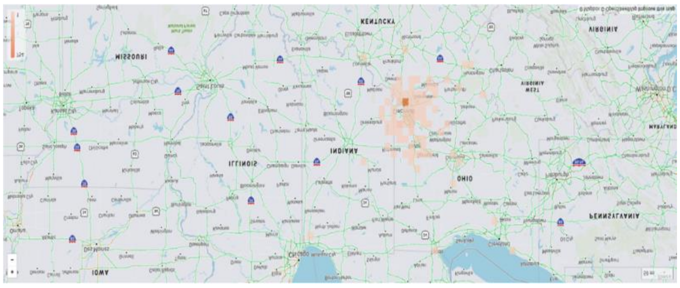

Figure 2: Heat map of areas where the UC Health Specialty Pharmacy distributes the selected-four migraine medications in the Midwest region.

The Box-Jenkins model, often known as ARIMA, is a univariate time-series forecasting technique that was suggested by Box and Jenkins.5 To identify, estimate, and diagnose the three-stage model construction process (p, d, q), fit the best model, and perform the model prediction, ARIMA primarily analyzes past and present data [28]. ARIMA also assesses its autocorrelation (ACF) and partial autocorrelation (PACF) functions, as well as the correlation between residuals. The ARIMA model was used to forecast the demand for each medication without the weather effect. The VARMA model, which is a multivariant time series forecasting model, considers the effect of different variables and was used to forecast the demand for each medication including weather conditions variables (Figure 1). In summary, the ARIMA and VARMA models aim to improve decision-making in demand forecasting situations.

In the ARIMA model, the date of each medication purchase was the independent variable, and the dependent variable was the demand of the prediction model. In the VARMA model, the date of each medication purchase was also the independent variable, and the dependent variables were the demand of the prediction model and weather condition factors. The predicted data from both ARIMA and VARMA models were then compared to each other. Specific accuracy metrics commonly used to assess predictive models were performed to evaluate the models.

Statistical Analysis

To assess the models' accuracy of the four medications, two accuracy metrics, Root Mean Squared Error (RMSE) and the Mean Absolute Percentage Error (MAPE), were determined. Both metrics assessed model error; thus, a lower value indicated a smaller error, therefore a more accurate model. The parameters for the ARIMA and VARMA models were also based on the best values of RMSE and MAPE.

The RMSE metric is the square root of the sum of the squared errors (differences of the mean forecasted and actual values) divided by the product of the number of items and a number of time points as the formula shows:

$$RMSE = \sqrt{\frac{\sum_{i=1}^{n}(y_i - \hat{y}_{Fi})^2}{n}}$$

The MAPE metric is the percentage error (percentage difference of the mean forecasted and actual value) averaged over all time points. The formula below shows how MAPE is calculated by using random time points. Since the MAPE metric is a percentage error, it is useful for comparing models from different datasets.

$$MAPE = \frac{1}{n}\sum_{i=1}^{n}\left|\frac{\hat{y}_{Fi} - y_i}{y_i} - \times 100\%\right|$$

Usually when analyzing if a forecasting model is accurate, there is a trade-off. No one accuracy metric is perfect and should be used for all datasets i.e., different medications data. The present study aims to analyze RMSE and MAPE to have an aggregate measure showing the accuracy of the models. Combining the results of both metrics to conclude if the model is accurate or not is more reliable than considering one single metric as the one to be used for all four different datasets.

Result

ARIMA and VARMA comparisons

To create the forecasting models for both ARIMA and VARMA, the monthly demand values were considered for each medication. Table 2 shows the forecast accuracy metrics for Emgality, Aimovig, Nurtec ODT, and Ajovy. For the ARIMA models, only the demand was considered as the response variable while for the VARMA models, both demand and weather conditions variables were considered as factors. The ARIMA was determined to be the best forecast model for Emgality, Aimovig, and Nurtec ODT. However, VARMA was the best forecast model for Ajovy, indicating that weather conditions may affect the demand forecasting of this medication. It can also be observed that the best overall model was the ARIMA for Aimovig, indicating the lowest values of accuracy metrics (MAPE = 3.59 and RMSE = 7.78). The model adjustment parameters for both models are shown in Table 3.

Table 2: Accuracy metrics MAPE and RMSE for the best-performing ARIMA and VARMA models for each medication in a monthly demand forecast.

Monthly Demand				
Medication	ARIMA		VARMA	
	MAPE (%)	RMSE	MAPE (%)	RMSE
Aimovig	3.59	7.78	11.78	22.64
Ajovy	19.18	21.1	14.91	19.6
Emgality	5.43	19.37	6.29	22.82
Nurtec ODT	5.95	11.38	6.95	14.07

Table 3: Rationale for the selection of best-performing parameters for the ARIMA and VARMA models based on AIC, RMSE, and MAPE accuracy metrics.

	p	d	q	AIC	RMSE	MAPE (%)
Aimovig						
ARIMA	2	1	4	6,238.48	7.79	3.62
ARIMA	2	1	2	6,281.95	8.08	3.75
ARIMA*	2	1	5	6,239.97	7.78	3.59
VARMA	1		4	10,825.40	25.9	13.48
VARMA	1		1	10,835.80	28.43	14.85
VARMA*	1		2	10,820.75	22.64	11.78
Ajovy						
ARIMA*	1	1	5	5,210.17	21.1	19.18

ARIMA	1	1	4	5,208.32	21.39	19.53
ARIMA	1	1	3	5,214.89	21.65	19.84
VARMA*	3		1	9,747.74	19.6	14.91
VARMA	3		2	9,712.94	19.78	14.98
VARMA	1		3	9,741.50	25.34	19.56
Emgality						
ARIMA*	1	1	5	6,374.76	19.37	5.43
ARIMA	1	1	4	6,379.75	19.29	5.48
ARIMA	1	1	2	6,373.52	19.3	5.47
VARMA	3		1	10,540.32	25.47	6.97
VARMA	3		2	10,503.63	25.62	7.14
VARMA*	1		3	10,529.24	22.82	6.29
Nurtec ODT						
ARIMA*	1	1	5	5,323.56	11.38	5.95
ARIMA	1	1	2	5,324.82	11.69	6.18
ARIMA	1	1	3	5,323.56	12.06	6.45
VARMA	3		1	9,884.57	14.97	7.32
VARMA	3		2	9,848.05	16.11	7.82
VARMA*	1		3	9,877.34	14.07	6.95
*Best-performing parameter selected, d = degree of differencing, p = autoregressive term, q = moving average term, AIC = Akaike information criterion, RMSE = root mean squared error, MAPE = mean absolute percentage error						

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Evaluation of MAPE values

According to Lewis CD, when MAPE is less than 10, the model is very accurate, between 10 and 20, it is a good predictor, between 20 and 50, it is a reasonable predictor, and above 50, it is not accurate [29]. The MAPE values for ARIMA and VARMA models are shown in Figure 3. Both models (ARIMA and VARMA) for all four medications in this study were considered either very accurate (MAPE < 10) or a good predictor (MAPE 10 =< 20). Especially the ARIMA models for Aimovig (MAPE = 4), Emgality (MAPE = 5), and Nurtec ODT (MAPE = 6) and VARMA models for Emgality (MAPE = 6) and Nurtec ODT (MAPE = 7). The ARIMA models for Aimovig, Emgality, and Nurtec ODT were very accurate, while the Ajovy model was considered a good predictor. Ajovy was also the only model in that VARMA (MAPE = 15) performed better than ARIMA (MAPE = 19). Even though the VARMA model for Ajovy was less accurate than the other VARMA models, it is important to note that it is better to consider weather conditions to forecast Ajovy's demand, while this is not true for the other medications.

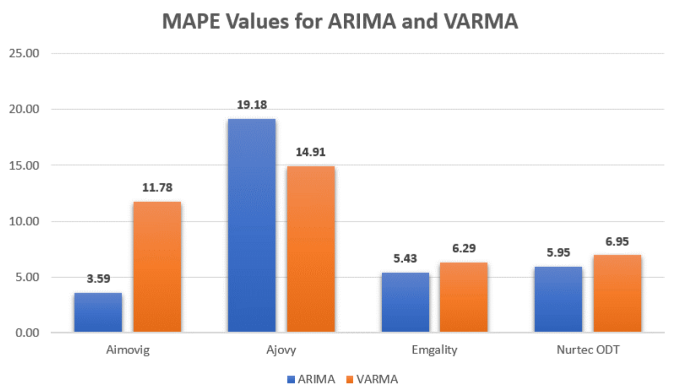

Figure 3: MAPE values for the ARIMA and VARMA models. Both ARIMA and VARMA models for all four medications were considered either very accurate (MAPE < 10) or a good predictor (MAPE 10 =< 20). Ajovy's VARMA model had higher accuracy when considering weather conditions as factors.

Evaluation of RMSE values

Figure 4 shows the RMSE values for ARIMA and VARMA models. The ARIMA models for Aimovig and Nurtec ODT were considered the most accurate models. The Ajovy and Emgality models were less accurate but still presented good accuracy. Similarly, to the MAPE values, the RMSE values for the Ajovy model also showed that VARMA was the most accurate model. Thus, the results suggest that Ajovy demand forecasting may have higher accuracy when considering weather conditions in the model instead of forecasting using its demand values alone.

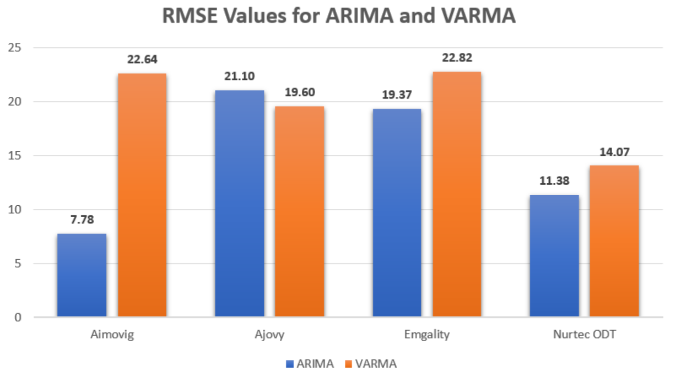

Figure 4: RMSE values for the ARIMA and VARMA models. Ajovy's VARMA model had higher accuracy when considering weather conditions as factors.

Discussion

This study aimed to develop a data-driven and effective forecasting model for the demand of the four most-prescribed migraine medications in a specialty pharmacy and to investigate whether the model is impacted by weather conditions. The findings show that only one medication demand was affected by weather conditions, while the other three drugs are better forecasted without considering weather variables. Although previously published studies suggested a correlation between migraine events and changing weather conditions, the present study found that one out of four medications have demand forecasting correlated to the weather [30-33]. The VARMA model indicated that demand was impacted by weather conditions. Ajovy's model was considered a good predictor of its demand, while the other three studied medications' models were considered of high accuracy. The findings of this study suggest that both ARIMA and VARMA have the potential to be good forecasting models to be used in a specialty pharmacy setting. VARMA is the preferred method to forecast the demand for medications when assessing the effect of weather conditions since it is a multivariate model.

A previous study has shown that even within a weather-sensitive migraineurs population, it is not possible to forecast a migraine event by solely considering weather conditions variables [34]. In the study, Jan Hoffmann aimed to investigate a potential correlation between migraine events and weather conditions variables. The authors conducted a logistic regression analysis in 13 weather-sensitive migraineurs to assess the correlation. The study found that it is not feasible to correlate a migraine prognosis with weather conditions alone. Moreover, the authors concluded that the complexity of the pathophysiology of the disease may suggest that, in most events, migraine is triggered by a combination of factors.

With respect to inventory management, more research is needed to quantify the frequency of stock-outs, i.e., how many times a pharmacy is out-of-stock of certain medication. This fact is important to compare the financial impact and effectiveness of traditional demand forecasting, which usually relies on the pharmacist's experience, with utilizing the demand forecasting models created by analytical methods. The use of ARIMA and VARMA models may provide better economic outcomes since it applies data analysis to support the decision-making process. The present study showed that ARIMA and VARMA generated very accurate or good demand forecasting models for all four migraine medications. Weather is a migraine trigger factor that cannot be avoided, hence the optimization of the demand forecasting for those medications may need special attention within pharmacies.

Although the present study showed intriguing results about the weather effect on the demand forecasting of Ajovy, additional studies are required to verify the findings and its implication in general. The preliminary results may also have several ramifications. First, weather conditions may play a broader role in other migraine medications if the training data is bigger. Second, specialty pharmacies may need to consider different demand forecasting models for migraine medications. Third, longer-duration modeling with weather and environmental allergen data may also add higher precision and accuracy than the current study.

The current study may have some limitations. First, the medications have different dosage forms, which alters the storage requirement and may interfere with their demand. For instance, Nurtec ODT is orally administered as a tablet while Aimovig, Ajovy, and Emgality are administered subcutaneously by a syringe. Second, the UC Health Specialty Pharmacy does not record the number of stock-outs for each medication, which does not allow the forecast models to claim any decrease in the frequency of stock-outs in the pharmacy. Third, all models were created based on 26 months of historical sales data with approximately 800 data points each, after preprocessing. Accessibility and use of more data may potentially improve the accuracy metrics of the models, especially Ajovy's.

The study developed an analytical data-driven and effective forecasting model for the demand of the four most-prescribed migraine medications in a specialty pharmacy and investigated the effect of weather conditions on their demand. The study showed that weather conditions may have a significant effect on Ajovy's demand during the 26-month period. When forecasting its demand, the model had higher accuracy when compared to forecasting its demand without weather conditions as a factor. On the other hand, weather conditions had no significant effect on the demand forecasting models for Aimovig, Emgality, and Nurtec ODT. Those models had higher accuracy when their demands were forecasted without weather conditions as factors. These results can assist pharmacies in making demand-oriented decisions by applying data analysis aiming to improve their financial health as well as increase migraineurs' treatment care quality.

Conclusion

The study showed that weather conditions had a significant effect on Ajovy's demand during the 26-month period. When forecasting its demand, the model had higher accuracy when compared to forecasting its demand without weather conditions as a factor. On the other hand, weather conditions had no significant effect on the demand forecasting models for Aimovig, Emgality, and Nurtec ODT. Those models had higher accuracy when their demands were forecasted without weather conditions as factors.

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Cite this article: Scharf-Costa L. et al. The Effect of Weather Conditions on Demand Forecasting of Migraine Medications in a Specialty Pharmacy Applying ARIMA and VARMA Models. J Health Econ Outcome Res. 2023, 9 (3), 001-006