Epilepsy & Behavior 99 (2019) 106483

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Association between adherence to sodium channel blockers and patient-reported outcomes: Analysis of US survey data among patients with epilepsy

Krithika Rajagopalan [a], Lulu K. Lee [b,*]

[a] Sunovion Pharmaceuticals Inc., Marlborough, MA, USA
[b] Health Outcomes Practice, Kantar, San Mateo, CA, USA

ARTICLE INFO

Article history:
Received 11 April 2019
Revised 25 June 2019
Accepted 4 August 2019
Available online 31 August 2019

Keywords:
Epilepsy
Sodium channel blockers
Health-related quality of life
Healthcare resource utilization

ABSTRACT

Objective: The objective of this study was to examine the relationship between adherence to treatment with sodium channel blockers (SCBs) and health-related quality of life (HRQoL), work productivity and activity impairment (WPAI), healthcare resource utilization (HRU), and associated costs among patients with epilepsy.
Methods: This retrospective cross-sectional study used data from the 2017 US National Health and Wellness Survey (NHWS; N = 75,004). Health-related quality of life (Study Short-Form 36-Item Health Survey version 2 [SF-36v2]), WPAI (Work Productivity and Activity Impairment—General Health [WPAI-GH] questionnaire), HRU, and annual costs were compared among respondents with epilepsy using SCBs categorized as low/medium adherence (n = 120) and high adherence (n = 80) using generalized linear models, controlling for patient characteristics.
Results: Mental component score, Short-Form 6-Dimension (SF-6D) health utility index, bodily pain, mental health, physical functioning, role emotional, social functioning, and vitality scores were significantly lower in low/medium adherence respondents than in high adherence respondents (for all, $p < 0.05$). Only activity impairment was significantly higher in low/medium adherence respondents compared with the high adherence group ($p < 0.001$). Healthcare resource utilization did not differ significantly between the two groups; however, the number of emergency room (ER) visits and total costs were lower in the high adherence group ($p = 0.038$) compared with the low/medium adherence group ($p = 0.040$).
Conclusion: High adherence to SCBs was associated with improved HRQoL, lower WPAI, and lower HRU and associated costs among patients with epilepsy. Therefore, adherence to SCBs may be an important factor in improving the abovementioned patient-reported outcomes. Findings from this study can help provide further impetus to healthcare policymakers and clinicians for addressing the low antiepileptic drug (AED) adherence levels in adult patients with epilepsy.

1. Introduction

Epilepsy is a disorder of the brain characterized by seizures that may be caused by a host of factors including developmental abnormalities, genetic disorders, fever, infections, severe head trauma, brain tumors, stroke, neurologic or metabolic disorders, alcohol withdrawal, illicit drug use, and even pharmacotherapeutic substances [1]. In the US, the prevalence of active epilepsy among adults has increased from 1.0% (2.3 million cases) in 2010 [2] to 1.2% (3 million cases) in 2015 [3], with men and women being affected equally [4]. The age-adjusted mortality rate for epilepsy as any-listed cause of death from 2005 to 2014 increased from 0.58 to 0.85 per 100,000, which is a 47% increase during this period in the US [5].

Apart from impacting mortality rates, epilepsy is also associated with a significant debilitating effect of morbidity resulting in reduced health-related quality of life (HRQoL) [6]. Additionally, epilepsy adversely affects work productivity and activity impairment (WPAI) [7]. Furthermore, patients with epilepsy face a high economic burden due to increased healthcare resource utilization (HRU) and associated costs [7]. Treatment adherence is known to be a significant predictor of long-term outcomes related to seizure frequency reduction, morbidity, and HRQoL. Nonadherence to antiepileptic drugs (AEDs) among patients with epilepsy ranges from 26% to 79% [8], and the impact of nonadherence is not inconsequential. Poor adherence to AEDs results

* Corresponding author at: Kantar Health, 1810 Gateway Drive, Suite 120, San Mateo, CA 94404, USA.
E-mail address: Lulu.Lee@kantar.com (L.K. Lee).

https://doi.org/10.1016/j.yebeh.2019.106483
1525-5050/

in lower quality of life (QoL), increased mortality, emergency department visits, hospitalizations, fractures, head injuries, and costs as reported in claims-based studies and survey research [9,10,11].

Sodium channel blockers (SCBs) have been used to treat epilepsy since 1938 [12] and are commonly used as a first-line therapy for epilepsy in the US [13]. Moreover, new third-generation SCB AEDs with potentially unique or different mechanisms of action and with fewer or no known pharmacokinetic drug interactions have been introduced recently [12,14]. Although AED class and treatment aspects (e.g., tolerability and dosage) and their association with nonadherence have been studied, little is known about the variation in SCB adherence levels.

As SCBs have a well-defined dose-related set of adverse events, it is important to understand whether good adherence with SCBs is associated with better HRQoL, suggesting that any adverse events related to SCBs did not override the benefits of better seizure control with better adherence. Therefore, the objective of this study was to examine the relationship between adherence to treatment with SCBs and HRQoL, WPAI, HRU, and associated costs among patients with epilepsy.

2. Methods

2.1. Sample

This retrospective cross-sectional study was conducted using data from the 2017 US National Health and Wellness Survey (NHWS; N = 75,004), a survey designed to examine health in the general adult population (age ≥18 years). Potential NHWS respondents were identified from an Internet-based panel maintained by Lightspeed Research and recruited using a stratified random sampling to mirror the age and gender distribution of the general US adult population (based on data from the most recent US Census). Participants were considered to be eligible for the study if they were (1) able to read and understand English, (2) able to operate a computer to access the online survey, (3) located in the US, (4) aged 18 years or older, and (5) willing to provide informed consent to participate in the study. Respondents who self-reported an epilepsy diagnosis from a healthcare provider (n = 774) were categorized into those currently using monotherapy (i.e., only a single prescription medication was used) SCBs or other medications (Fig. 1). The final analyses were conducted only among patients receiving SCBs.

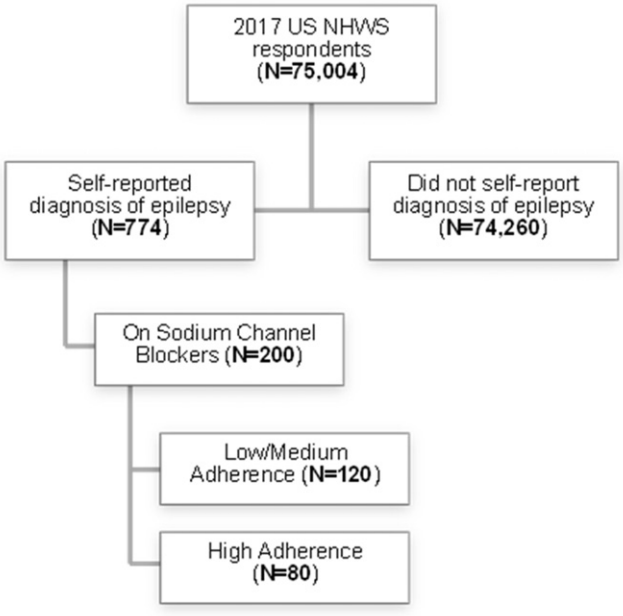

Fig. 1. Study sample flow chart.

The study was found to be exempt from review by the Pearl Institutional Review Board (Indianapolis, IN, USA). Informed consent was provided by all the respondents.

2.2. Measures

2.2.1. Adherence status

Respondents on SCBs were categorized into two groups based on their adherence status using the Morisky Medication Adherence Scale (©MMAS-8) [15] as low/medium adherence (©MMAS-8 score <8; n = 120) and high adherence (©MMAS-8 score 8; n = 80).[1]

2.2.2. Demographics and health characteristics

Demographic measures included age (continuous), gender (male or female), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or other ethnicity), education (<4-year college degree or ≥4-year college degree), marital status (single/married/living with partner/divorced/separated/widowed/decline to answer), annual household income (<$25,000, $25,000–$50,000, $50,000–$75,000, ≥$75,000, or declined to answer), labor force participation (yes or no), and health insurance status (yes or no).

Health characteristics data included smoking status (current smoker, former smoker, or never smoked), exercise for more than 20 min in the past month (zero times or more than once time), alcohol use (yes or no), body mass index (BMI) category (using the World Health Organization's recommendation for US populations: underweight [<18.5 kg/m^2], normal weight [18.5–24.9 kg/m^2], overweight [25–29.9 kg/m^2], and obese [>30 kg/m^2]) [16], and the Charlson Comorbidity Index (CCI) [17].

2.2.3. Epilepsy characteristics

Data on the epilepsy type (idiopathic generalized epilepsy, idiopathic partial epilepsy, symptomatic generalized epilepsy, symptomatic partial epilepsy, or unknown), frequency of seizures (more than once a week, once a week, two to three times a month, once a month, every three months, every six months, once a year, less than once a year), years diagnosed with epilepsy, and number of seizures in the past six months and past 30 days were collected.

2.2.4. Health-related quality of life

Physical component summary (PCS), mental component summary (MCS), and Short-Form 6-Dimension (SF-6D) health utility index scores, as well as scores for eight health subdomains from the Medical Outcomes Study Short-Form 36-Item Health Survey (SF-36) version 2 (SF-36v2) were used to assess the HRQoL [18,19]. The MCS and PCS are normed to the US general population (mean = 50.00, standard deviation [SD] = 10.00) and range from 0 to 100 whereas the SF-6D health utility index scores range from zero to one. Higher scores signify better HRQoL for all these measures. Minimally important differences (MIDs) for the MCS/PCS and SF-6D health utility index scores were represented by three and 0.041 points, respectively [18,20].

2.2.5. Work productivity and activity impairment

Work productivity loss and activity impairment were assessed using the Work Productivity and Activity Impairment—General Health (WPAI-GH) questionnaire, a six-item instrument consisting of four domains (absenteeism, presenteeism, overall work impairment, and activity impairment) [21]. The scores are represented as percentages, with higher values indicating greater impairment in the patient's health for

[1] Note that the original ©MMAS-8 scoring has 3 categories: high adherence (scores = 8), medium adherence (scores = 6 < 8), and low adherence (scores = <6). Here, we combined the low and medium adherence categories.
The use of the ©MMAS-8 is protected by US copyright laws. Permission for use is required. A license agreement is available from: Donald E. Morisky, MMAS Research (MORISKY) 16636 159th Place SE, Renton, WA 98058.

the past seven days. While only currently employed respondents (full-time, part-time, or self-employed) provided the data on absenteeism, presenteeism, and overall work impairment, the data on activity impairment were provided by all the respondents.

2.2.6. Healthcare resource utilization

Self-reported number of all-cause traditional provider visits, emergency room (ER) visits, and hospitalizations in the past six months were used to measure the HRU.

2.2.7. Costs

Indirect and direct costs were estimated from the available NHWS data. The estimated annual direct costs included all-cause HRU costs and were extrapolated from the Medical Expenditure Panel Survey [22] by applying 2014 age-specific unit cost to each HRU event of the NHWS respondents. Similarly, the annual indirect costs were determined by extrapolation, where 2014-specific wages from the Bureau of Labor Statistics [23] were applied to work hours lost with presenteeism and absenteeism from the WPAI-GH. Estimated total costs were calculated as a sum of direct and indirect costs. For respondents who were unemployed, their estimated total costs did not include indirect costs.

2.3. Statistical analyses

2.3.1. Bivariate analyses

Descriptive statistics (means and SD for continuous variables and frequencies and percentages for categorical variables) were reported for all the study outcomes differentiated by adherence levels (low/medium vs high adherence) to SCBs. Chi-square and one-way analysis of variance tests (ANOVAs) were used to determine the significant differences ($p < 0.05$, two-tailed) for categorical and continuous variables, respectively. These results served to characterize differences between those with low/medium adherence and high adherence and advised the selection of the covariates for multivariable analyses.

2.3.2. Multivariable analyses

Generalized linear models (GLMs) that specify a normal distribution and identity function were used for normally distributed outcome variables (e.g., HRQoL) whereas GLMs that specify a negative binomial distribution and a log-link function were used for highly positively skewed outcome variables (e.g., WPAI, HRU, and costs) to test whether any statistically significant ($p < 0.05$, two-tailed) differences existed between the two adherence groups on the outcomes of interest, controlling for covariates. Covariates utilized in this study included age, gender, ethnicity, years diagnosed with epilepsy, and number of seizures in the past six months. Estimated means, standard errors, confidence intervals, and p-values were reported by adherence groups (low/medium adherence vs high adherence).

3. Results

3.1. Demographics and disease characteristics by adherence levels among SCB users (unadjusted results)

Of the 200 respondents included in the study analyses, average age was reported to be 49 years, with 55% being female and 69% non-Hispanic white. The most common type of epilepsy reported by them was idiopathic generalized epilepsy (46.5%), followed by symptomatic partial epilepsy (focal epilepsy, temporal lobe epilepsy, frontal lobe epilepsy; 19.0%), and the patients on SCBs had an average CCI score of 0.82 (Table 1).

Patients in the high adherence group tended to be older and had been diagnosed with epilepsy for a longer period of time than those with low/medium adherence ($p < 0.001$, for both). A higher proportion of non-Hispanic whites were observed among the high adherence group compared with the low/medium adherence group ($p = 0.048$). In addition, the high adherence group was less likely to be in the labor force and consumed alcohol ($p = 0.025$ and $p = 0.020$, respectively; Table 1). The number of seizures in the past six months and in the past 30 days did not differ by adherence levels. However, the percentage of patients experiencing less than one seizure per year was 66.3% in the high adherence group vs 50% in the low adherence group (Table 2).

3.2. HRQoL, WPAI, HRU, and costs by adherence levels among SCB users (unadjusted results)

High adherence levels were associated with significantly greater MCS, SF-6D health utility index, mental health, role emotional, social functioning, vitality ($p < 0.001$ for all); bodily pain ($p = 0.010$); general health ($p = 0.007$); physical functioning ($p = 0.039$); and role physical ($p = 0.040$), and the differences reached MIDs, except for PCS. Presenteeism and activity impairment scores were higher among those with low/medium adherence compared with those who had high adherence ($p = 0.041$ and $p < 0.001$, respectively). The number of ER visits differed significantly by adherence, with patients with low/medium adherence having three times the number of ER visits compared with those with high adherence ($p = 0.008$). Consequently, ER costs among those with low/medium adherence were three times as high as those with high adherence ($p = 0.009$). No other costs were significantly different between the two adherence groups (Table 3).

3.3. HRQoL, WPAI, HRU, and costs by adherence levels among SCB users (adjusted results)

After adjusting for covariates (age, gender, ethnicity, years diagnosed with epilepsy, and number of seizures in the past six months), the results were consistent with unadjusted results. Patients with high adherence showed higher scores for all the SF-36v2 indices (MCS, mental health, and role emotional; $p < 0.001$, for all), SF-6D health utility index ($p = 0.004$), bodily pain ($p = 0.016$), physical functioning ($p = 0.003$), social functioning ($p = 0.002$), and vitality ($p = 0.001$) compared with those with low/medium adherence (Fig. 2). While absenteeism, presenteeism, and overall work impairment did not differ significantly, activity impairment in the low/medium adherence group was two times higher than in the high adherence group ($p < 0.001$; Fig. 3). Although HRU did not differ significantly between the groups (Fig. 4), the ER costs ($801 vs $2366) and the total costs ($19,535 vs $36,151) were significantly lower in the high adherence group than in the low/medium adherence group ($p = 0.038$ and $p = 0.040$, respectively; Fig. 5).

4. Discussion

Epilepsy can be adequately treated with medication in approximately 70% of patients [24]. However, studies have revealed that nonadherence to AEDs is highly prevalent among American adults (26%–46.40%) [10,11,25]. Nonadherent patients with epilepsy report more difficulty in attaining seizure control than adherent patients. In addition, uncontrolled seizures result in major morbidity and mortality [26]. While SCB AEDs were shown to have greater adherence rates compared with non-SCB AEDs [27], this study evaluated the association between varying SCB adherence levels and patient-reported outcomes such as HRQoL, WPAI, HRU, and costs among patients with epilepsy.

In this study, older, non-Hispanic whites, employed respondents, and patients who did not consume alcohol were highly adherent to SCBs compared with their counterparts, indicating that these characteristics may be related to better treatment access and continuity of care. Indeed, an earlier study reported that Caucasians showed better adherence to AEDs compared with African-Americans [28]. Furthermore, in concordance with Sweileh et al. [29], this study found that older

Table 1
Comparison of demographics and health characteristics based on adherence levels among SCB users.

Characteristics		©MMAS-8 adherence categories		p-Value
		Low/medium adherence: 0 < 8 (n = 120)	High adherence: 8 (n = 80)	
Age (mean ± SD)		45.25 ± 16.92	55.14 ± 15.91	<0.001
Gender (count [%])	Female	69 (57.5)	41 (51.2)	0.384
	Male	51 (42.5)	39 (48.8)	
Race/ethnicity (count [%])	Non-Hispanic white	75 (62.5)	63 (78.8)	0.048
	Non-Hispanic black	17 (14.2)	5 (6.3)	
	Hispanic	16 (13.3)	4 (5)	
	Other ethnicities	12 (10)	8 (10)	
Education (count [%])	<4-year college degree	83 (69.2)	51 (63.7)	0.425
	4-year college degree or higher	37 (30.8)	29 (36.3)	
Married/living with partner (count [%])	Single/divorced/separated/widowed/declined to answer	61 (50.8)	33 (41.3)	0.183
	Married/living with partner	59 (49.2)	47 (58.8)	
Labor force participation (count [%])	Yes	55 (45.8)	24 (30)	0.025
Annual household income (count [%])	<$25,000	30 (25)	20 (25)	0.929
	$25,000–$50,000	30 (25)	21 (26.3)	
	$50,000–$75,000	26 (21.7)	17 (21.3)	
	$75,000 or more	26 (21.7)	19 (23.8)	
	Declined to answer	8 (6.7)	3 (3.8)	
Do you currently have any health insurance? (count [%])	Yes	112 (93.3)	78 (97.5)	0.185
BMI category (count [%])	Underweight (<18.5 kg/m^2)	3 (2.5)	2 (2.5)	0.484
	Normal weight (18.5–24.9 kg/m^2)	34 (28.3)	23 (28.7)	
	Overweight (25–29.9 kg/m^2)	29 (24.2)	26 (32.5)	
	Obese (>30 kg/m^2)	48 (40)	28 (35)	
	Unknown	6 (5)	1 (1.3)	
Smoking status (count [%])	Current smoker	18 (15)	11 (13.8)	0.768
	Former smoker	29 (24.2)	23 (28.7)	
	Never smoker	73 (60.8)	46 (57.5)	
Drink alcohol (count [%])	No	46 (38.3)	44 (55)	0.02
Exercise 20+ min 1+ times in the past month [count (%)]	Exercise: 0 times	53 (44.2)	31 (38.8)	0.447
	Exercise: 1+ times	67 (55.8)	49 (61.3)	
CCI (mean ± SD)		0.83 ± 2.06	0.80 ± 1.45	0.925

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; ©MMAS-8, Morisky Medication Adherence Scale; SCB, sodium channel blocker; SD, standard deviation.

patients and patients with longer duration of epilepsy showed higher adherence to AEDs, possibly due to the patients' realization of the benefits of adherence to their medications through time.

Epilepsy is a neurologic condition that results in significant health consequences, economic burden, and decreased productivity of patients worldwide [30]. Previous research in the US has shown that patients

Table 2
Comparison of disease characteristics based on adherence levels among SCB users.

Characteristics		©MMAS-8 adherence categories		p-Value
		Low/medium adherence: 0 < 8,(n = 120)	High adherence: 8, (n = 80)	
Type of epilepsy (count [%])	Idiopathic generalized epilepsy (myoclonic seizures, absence seizures, grand mal seizures)	54 (45)	39 (48.8)	0.318
	Symptomatic partial epilepsy (focal epilepsy, temporal lobe epilepsy, frontal lobe epilepsy)	28 (23.3)	10 (12.5)	
	Idiopathic partial epilepsy (BFEC)	3 (2.5)	3 (3.8)	
	Symptomatic generalized epilepsy (West syndrome, Lennox–Gastaut syndrome)	1 (0.8)	0 (0.0)	
	Do not know	34 (28.3)	28 (35)	
Frequency of experiencing a seizure (count [%])	More than once a week	10 (8.3)	2 (2.5)	0.053
	Once a week	4 (3.3)	2 (2.5)	
	2–3 times a month	16 (13.3)	4 (5)	
	Once a month	8 (6.7)	2 (2.5)	
	Every 3 months	10 (8.3)	3 (3.8)	
	Every 6 months	5 (4.2)	7 (8.8)	
	Once a year	7 (5.8)	7 (8.8)	
	Less than once a year	60 (50)	53 (66.3)	
Years diagnosed with epilepsy (mean ± SD)		22.65 ± 17.35	32.67 ± 16.63	<0.001
Number of seizures in the past 6 months (mean ± SD)		7.44 ± 24.27	9.89 ± 67.67	0.717
Number of seizures in the past 30 days (mean ± SD)		1.58 ± 4.69	1.31 ± 7.08	0.753

Abbreviations: BFEC, benign focal epilepsy of childhood; ©MMAS-8, Morisky Medication Adherence Scale; SCB, sodium channel blocker; SD, standard deviation.

Table 3
Health-related quality of life, work productivity and activity impairment, healthcare resource utilization, and costs by adherence levels among SCB users.

Parameters	©MMAS-8 adherence categories		p-Value
	Low/medium adherence: 0 < 8 (n = 120)	High adherence: 8 (n = 80)	
MCS (mean ± SD)	41 ± 13.39	50 ± 9.52	<0.001
PCS (mean ± SD)	45.68 ± 10.32	47.47 ± 11.07	0.243
SF-6D health utility index scores (mean ± SD)	0.65 ± 0.14	0.72 ± 0.14	<0.001
Bodily pain (mean ± SD)	44.79 ± 10.50	48.75 ± 10.62	0.010
General health (mean ± SD)	42.34 ± 11.42	46.82 ± 11.24	0.007
Mental health (mean ± SD)	41.8 ± 12.53	49.89 ± 9.55	<0.001
Physical functioning (mean ± SD)	45.44 ± 11.60	48.74 ± 10.02	0.039
Role emotional (mean ± SD)	41.11 ± 14.73	49.07 ± 9.06	<0.001
Role physical (mean ± SD)	43.70 ± 12.2	47.16 ± 10.67	0.04
Social functioning (mean ± SD)	42.22 ± 11.98	49.07 ± 10.03	<0.001
Vitality (mean ± SD)	43.54 ± 11.8	49.55 ± 10.5	<0.001
Absenteeism[a] (mean ± SD)	9.53 ± 18.47	9.29 ± 27.52	0.964
Presenteeism[b] (mean ± SD)	37.31 ± 29.65	21.90 ± 25.62	0.041
Overall work impairment[a] (mean ± SD)	39.97 ± 30.73	27.03 ± 32.64	0.109
Activity impairment (mean ± SD)	42.17 ± 30.10	24.50 ± 27.14	<0.001
Number of traditional provider visits (mean ± SD)	8.00 ± 14.53	5.58 ± 6.42	0.162
Number of ER visits (mean ± SD)	0.78 ± 1.64	0.26 ± 0.59	0.008
Number of hospitalizations (mean ± SD)	0.34 ± 0.93	0.18 ± 0.50	0.144
Direct costs (mean ± SD)	31,821 ± 53,875	22,948 ± 32,567	0.188
ER visits cost (mean ± SD)	2791 ± 6224	890 ± 2164	0.009
Hospitalizations cost (mean ± SD)	11,316 ± 30,297	6583 ± 19,658	0.219
Traditional provider visits cost (mean ± SD)	17,715 ± 29,093	15,476 ± 19,562	0.547
Indirect costs (mean ± SD)	10,677 ± 11,033	8295 ± 11,855	0.393
Absenteeism cost (mean ± SD)	2299 ± 4651	3139 ± 10,227	0.618
Presenteeism cost (mean ± SD)	8378 ± 8971	5156 ± 7116	0.124
Total cost (mean ± SD)	36,625 ± 57,189	25,437 ± 34,468	0.118

Abbreviations: ER, emergency room; MCS, mental component summary; ©MMAS-8, Morisky Medication Adherence Scale; PCS, physical component summary; SCB, sodium channel blocker; SD, standard deviation; SF-6D, Short-Form 6-Dimension.
[a] Employed only; Low/medium adherence N = 51, High adherence N = 22.
[b] Employed only; Low/medium adherence N = 52, High adherence N = 21.

with epilepsy had significantly lower HRQoL compared with the general population [31]. In the current study, HRQoL was lower in patients with low/medium adherence to SCBs and with decreased scores for most of the SF-36 components. Consistent with these results, a prior study reported that patients with low/medium adherence showed lower MCS and health utility scores compared with those who had high adherence [32]. Similarly, a cross-sectional study in the US reported reduced HRQoL in nonadherent patients compared with adherent patients [11].

Activity impairment in the current study was higher in respondents with low/medium adherence than those with high adherence. A recent study by Gupta et al. [7] reported that greater seizure frequency is directly correlated with an increase in absenteeism, presenteeism, and WPAI in the US and other countries. The same study reported that patients with lower seizure frequency showed less activity impairment compared with respondents having higher seizure frequency [7].

A retrospective study conducted in the US population reported that nonadherence was associated with an increased incidence of hospitalizations and emergency department visits [10]. Although not statistically significant, the number of traditional provider and ER visits in this study was higher in the low/medium adherence group than the high adherence group.

It has been shown that patients with epilepsy have more chronic comorbid conditions, which in turn results in significantly higher number of medical provider visits and prescription medications and higher

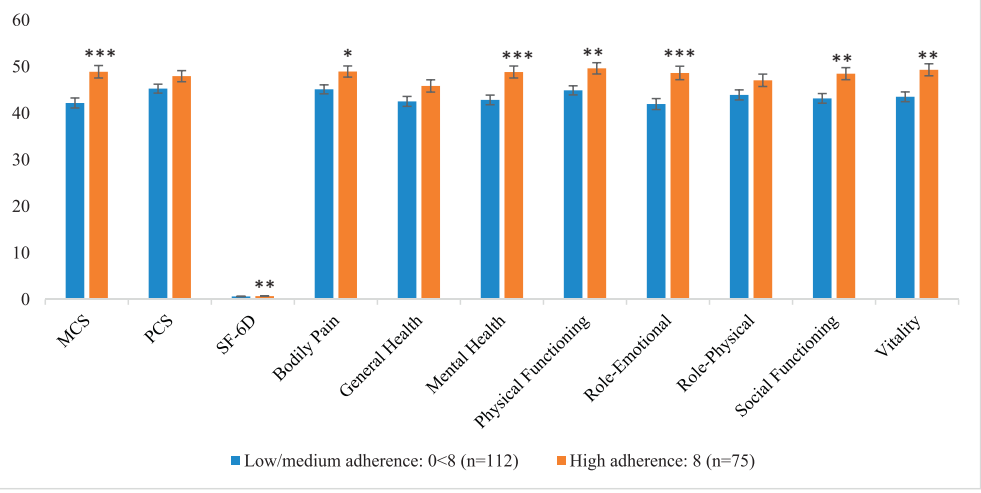

Fig. 2. Health-related quality of life by SCB adherence level, adjusted for covariates. Note: Covariates analyzed in this study included age, gender (male vs female), race/ethnicity (others vs white), years diagnosed with epilepsy, and number of seizures in the past 6 months. p-Values represent post hoc pairwise comparisons of adjusted means. p-Values for the low/medium adherence group versus the high adherence group: *p < 0.05, **p < 0.01, ***p ≤ 0.001. Abbreviations: MCS, mental component summary; PCS, physical component summary; SF-6D, Short-Form 6-Dimension.

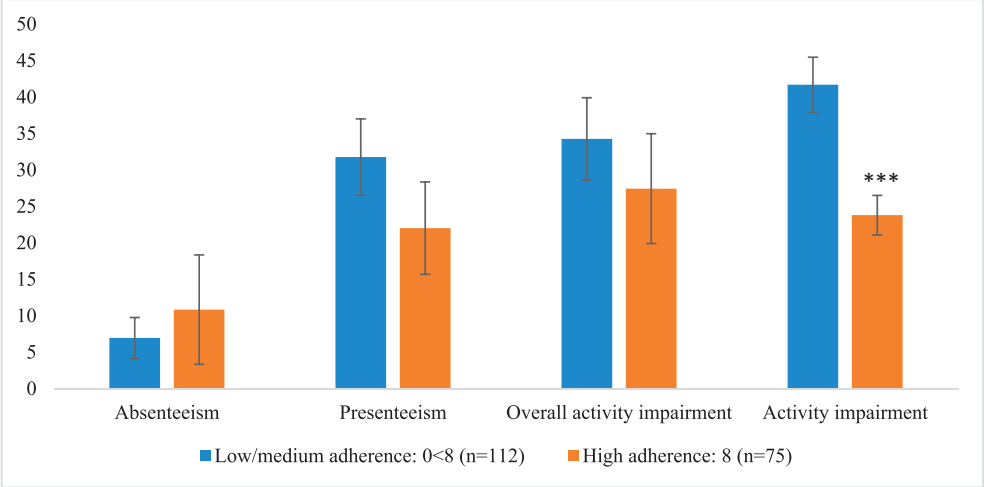

Fig. 3. Work productivity and activity impairment by SCB adherence level, adjusted for covariates. Note: Covariates analyzed in this study included age, gender (male vs female), race/ethnicity (others vs white), years diagnosed with epilepsy, and number of seizures in the past 6 months. p-Values represent post hoc pairwise comparisons of adjusted means. p-Values for the low/medium adherence group versus the high adherence group: ***p ≤ 0.001.

unadjusted average healthcare expenditures (direct costs of illness) [33]. A systematic review of the economic impact of epilepsy stated that studies that evaluated both direct and indirect costs concluded the latter to often be a greater burden than the former [10]. Consistent with the increased HRU, the findings of this study reported an increase in direct costs in the low/medium adherence group compared with high adherence group. Similarly, Ip et al. [34] reported that total direct healthcare costs for AED-adherent elderly patients having Medicare benefits in the US was 13.2% less than those of nonadherent individuals.

In sum, study findings are in line with the larger set of research examining the benefits of high adherence to treatments. However, research on the effect of adherence on patient-reported outcomes by specific classes of AEDs is limited. Thus, the contribution of the current study is the specific examination of whether patient-reported outcomes differ by adherence levels to SCBs among patients with epilepsy.

5. Limitations

The present study has a few limitations. The NHWS is an observational cross-sectional study, preventing causal conclusions from being drawn. However, a cross-sectional study design allows for capturing a specific point in time and the examination of a multitude of patient-reported outcomes in an expedient manner. As is with any research, study findings may be biased because of unknown factors, and therefore, caution needs to be taken while interpreting the data. However, the present analyses adjust for many confounders that may adversely impact the strength of the findings. The use of self-reported measures may lead to inaccurate recall of information. However, the panel took adequate measures to minimize false reporting. Furthermore, the survey was relatively low-stakes and benign, as questionnaire were simple and not designed to be intrusive or offensive. Notwithstanding its limitations, self-reported measures are critical for understanding the impact of treatments and adherence to treatments among patients as only patients themselves can report on their QoL or work productivity loss. In addition, more than one-third of all patients with epilepsy had idiopathic generalized epilepsy. The use of SCBs among this type of epilepsy may exacerbate certain types of primary generalized seizures, and therefore, these patients may be skewed towards the use of only one or two SCBs like lamotrigine. It should be noted that the reliability of the reported epilepsy characteristics of this study might be low as the respondents might have failed to understand

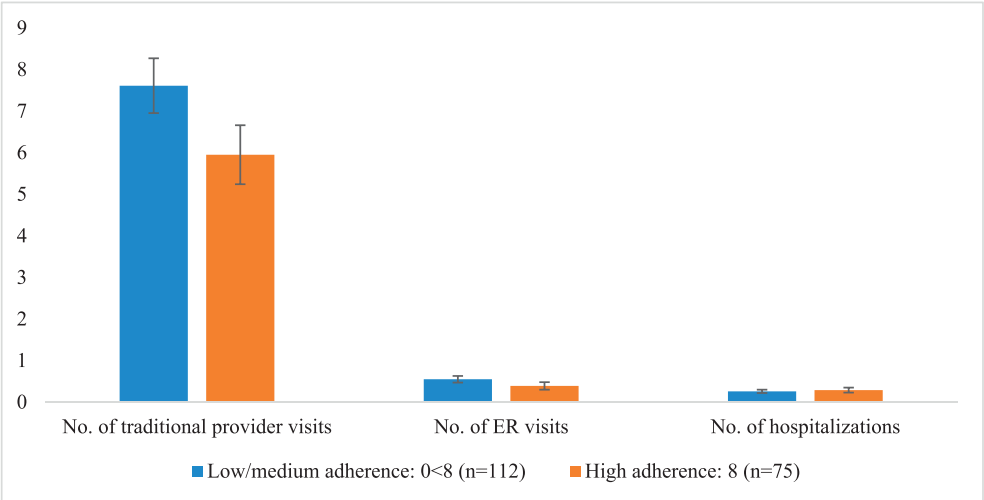

Fig. 4. Healthcare resource utilization by SCB adherence level, adjusted for covariates. Note: Covariates analyzed in this study included age, gender (male vs female), race/ethnicity (others vs white), years diagnosed with epilepsy, and number of seizures in the past 6 months. p-Values represent post hoc pairwise comparisons of adjusted means. Abbreviation: ER, emergency room.

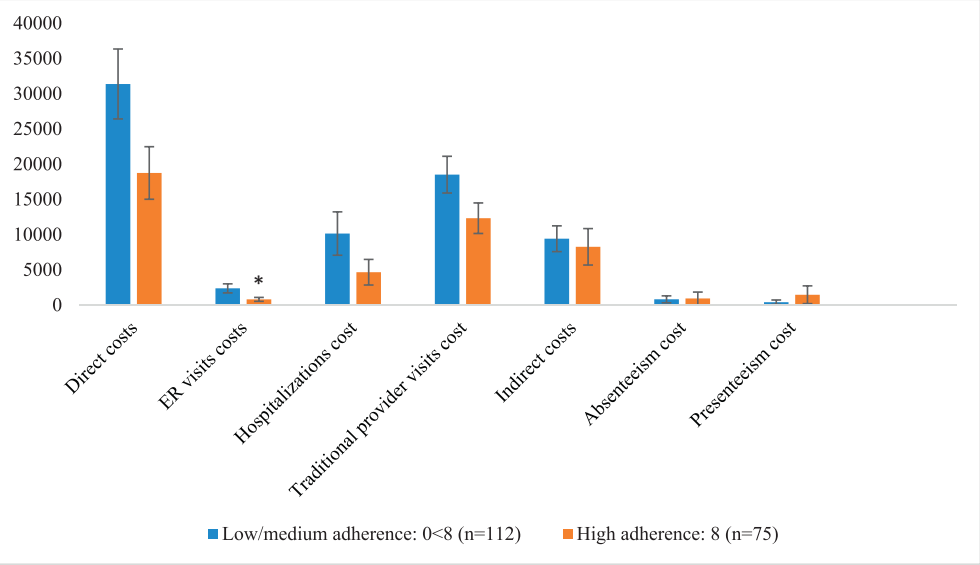

Fig. 5. Costs by SCB adherence level, adjusted for covariates. Note: Covariates analyzed in this study included age, gender (male vs female), race/ethnicity (others vs white), years diagnosed with epilepsy, and number of seizures in the past 6 months. p-Values represent post hoc pairwise comparisons of adjusted means. p-Values for the low/medium adherence group versus the high adherence group: *$p < 0.05$. Abbreviation: ER, emergency room.

their seizure types and could have incorrectly reported them. In future research, this analysis should be repeated with patients with epilepsy who do not have idiopathic generalized epilepsy. In the current study, SCBs were examined as a class; further research could examine how the type of SCBs, dosage, and therapeutic complexities may impact adherence and outcomes. Lastly, the current study focused only on SCB adherence levels and its association with outcomes as the research was scarce on this topic. Further research is needed to examine the variation in adherence levels among other classes of AEDs and its association with patient-reported outcomes.

6. Conclusion

This study demonstrated that high adherence to SCBs was associated with clinically meaningful HRQoL improvement, decrease in activity impairment, and lower HRU and related costs. Therefore, adherence to SCBs may be an important factor in improving the abovementioned patient-reported outcomes. Findings from this study can help provide further impetus to healthcare policymakers and clinicians for addressing the low AED adherence levels in adult patients with epilepsy. Further efforts can be concentrated on breaking down barriers such as dosing schedule (e.g., monotherapy or once-daily regimens), titration, and economic burden on the patients. Future research could consider how to improve the adherence among patients with epilepsy who have been prescribed SCBs.

Ethical statement

We confirm that we have read the journal's position on ethical publication and confirm that this publication is consistent with those guidelines.

Acknowledgments

We would like to thank Gowthami Vullapadu and Ramu Periyasamy, Indegene Pvt. Ltd., for providing medical writing assistance.

Declaration of competing interest

Sunovion sponsored the conduct of this study and the medical writing of this manuscript. Dr. Rajagopalan was an employee of Sunovion Pharmaceuticals Inc. at the time of conducting analyses. Dr. Lulu is an employee of Kantar Health, hired by Sunovion to consult on the analyses.

Funding

The conduct of this study and medical writing of this manuscript was funded by Sunovion Pharmaceuticals Inc., Marlborough, MA, USA.

References

[1] Lowenstein DH. Seizures and epilepsy. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson LJ, Loscalzo J, editors. Harrison's principles of internal medicine. 19th ed. New York, NY: McGraw Hill Education; 2015. p. 2542–674.
[2] Centers for Disease Control and Prevention (CDC). Comorbidity in adults with epilepsy—United States, 2010. MMWR Morb Mortal Wkly Rep 2013;62:849–53.
[3] Zack MM, Kobau R. National and state estimates of the numbers of adults and children with active epilepsy — United States, 2015. MMWR Morb Mortal Wkly Rep 2017;66:821–5.
[4] Tian N, Boring M, Kobau R, Zack MM, Croft JB. Active epilepsy and seizure control in adults — United States, 2013 and 2015. MMWR Morb Mortal Wkly Rep 2018;67:437–42.
[5] Greenlund SF, Croft JB, Kobau R. Epilepsy by the numbers: epilepsy deaths by age, race/ethnicity, and gender in the United States significantly increased from 2005 to 2014. Epilepsy Behav 2017;69:28–30.
[6] Riechmann J, Willems LM, Boor R, Kieslich M, Knake S, Langner C, et al. Quality of life and correlating factors in children, adolescents with epilepsy, and their caregivers: a cross-sectional multicenter study from Germany. Seizure 2019;69:92–8.
[7] Gupta S, Kwan P, Faught E, Tsong W, Forsythe A, Ryvlin P. Understanding the burden of idiopathic generalized epilepsy in the United States, Europe, and Brazil: an analysis from the National Health and Wellness Survey. Epilepsy Behav 2016;55:146–56.
[8] Malek N, Heath CA, Greene J. A review of medication adherence in people with epilepsy. Acta Neurol Scand 2017;135:507–15.
[9] Faught E, Duh MS, Weiner JR, Guérin A, Cunnington MC. Nonadherence to antiepileptic drugs and increased mortality: findings from the RANSOM Study. Neurology 2008;71:1572–8.
[10] Faught RE, Weiner JR, Guérin A, Cunnington MC, Duh MS. Impact of nonadherence to antiepileptic drugs on health care utilization and costs: findings from the RANSOM study. Epilepsia 2009;50:501–9.
[11] Hovinga CA, Asato MR, Manjunath R, Wheless JW, Phelps SJ, Sheth RD, et al. Association of non-adherence to antiepileptic drugs and seizures, quality of life, and productivity: survey of patients with epilepsy and physicians. Epilepsy Behav 2008;13:316–22.
[12] Brodie MJ. Sodium channel blockers in the treatment of epilepsy. CNS Drugs 2017;31:527–34.
[13] Goldenberg MM. Overview of drugs used for epilepsy and seizures: etiology, diagnosis, and treatment. P T 2010;35:392–415.
[14] Lee SK. Old versus new: why do we need new antiepileptic drugs? J Epilepsy Res 2014;4:39–44.

[15] Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. J Clin Hypertens (Greenwich) 2008; 10:348–54.
[16] Obesity: preventing and managing the global epidemic. Report of a WHO consultation, World Health Organ Tech Rep Ser 2000;894(i-xii):1–253.
[17] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
[18] Maruish ME. User's manual for the SF-36v2 Health Survey. 3rd ed. Lincoln, RI: Quality Metric Incorporated; 2011.
[19] Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ 2002;21:271–92.
[20] Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. Qual Life Res 2005;14:1523–32.
[21] Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993;4:353–65.
[22] Agency for Healthcare Research and Quality. Mean expenditure per event by age groups and event type, United States. Web site https://meps.ahrq.gov/data_stats/quick_tables_results.jsp?component=1&subcomponent=0&tableSeries=9&year=-1&SearchMethod=1&Action=Search; 2014, Accessed date: 13 July 2018.
[23] US Bureau of Labor Statistics. Highlights of women's earnings in 2014. Web site. https://www.bls.gov/opub/reports/womens-earnings/archive/highlights-of-womens-earnings-in-2014.pdf. Accessed July 13, 2018.
[24] Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000; 342:314–9.
[25] Khanna R, Pace PF, Mahabaleshwarkar R, Basak RS, Datar M, Banahan BF. Medication adherence among recipients with chronic diseases enrolled in a state Medicaid program. Popul Health Manag 2012;15:253–60.
[26] Brown C. Pharmacological management of epilepsy. Prog Neurol Psychiatry 2016;20:27.
[27] Velez FF, Baser O, Xie L. Adherence and persistence to anti-epileptic drugs among U.S. veterans diagnosed with epilepsy. Value Health 2015;18:A285.
[28] Bautista RE, Graham C, Mukardamwala S. Health disparities in medication adherence between African-Americans and Caucasians with epilepsy. Epilepsy Behav 2011;22:495–8.
[29] Sweileh WM, Ihbesheh MS, Jarar IS, Taha AS, Sawalha AF, Zyoud SH, et al. Self-reported medication adherence and treatment satisfaction in patients with epilepsy. Epilepsy Behav 2011;21:301–5.
[30] de Boer HM, Mula M, Sander JW. The global burden and stigma of epilepsy. Epilepsy Behav 2008;12:540–6.
[31] Wagner AK, Bungay KM, Kosinski M, Bromfield EB, Ehrenberg BL. The health status of adults with epilepsy compared with that of people without chronic conditions. Pharmacotherapy 1996;16:1–9.
[32] Lee L, Velez FF. The association of adherence with health-related quality of life by age group among patients with epilepsy. Neurology 2016;86:P4.205.
[33] Libby AM, Ghushchyan V, McQueen RB, Slejko JF, Bainbridge JL, Campbell JD. Economic differences in direct and indirect costs between people with epilepsy and without epilepsy. Med Care 2012;50:928–33.
[34] Ip Q, Malone DC, Chong J, Harris RB, Labiner DM. Economic impact of epilepsy and the cost of nonadherence to antiepileptic drugs in older Medicare beneficiaries. Epilepsy Behav 2018;80:208–14.