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Costs and cost-drivers of a diagnosis of depression among adults with epilepsy in the United States

Alain Lekoubou [a,*], Kinfe G. Bishu [b,c], Bruce Ovbiagele [d,e]

[a] Department of Neurology, Medical University of South Carolina, Charleston, SC, USA
[b] Department of Medicine, Medical University of South Carolina, Charleston, SC, USA
[c] Section of Health Systems Research and Policy, Medical University of South Carolina, Charleston, SC, USA
[d] University of California, San Francisco, CA, USA
[e] The San Francisco VA Healthcare System, USA

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ABSTRACT

Objective: The objective of this study was to evaluate the amount of direct costs associated with occurrence of depression in people with epilepsy.
Methods: The Medical Expenditure Panel Survey Household Components (MEPS-HC) served as data source to identify adults (≥18 years) with epilepsy from 2003 to 2014, using the Clinical Classification Code CCC-83. Annual unadjusted per person total healthcare expenditures and individual cost components (inpatient, outpatient, prescription, emergency room, and home health) were compared between people with epilepsy and depression vs. without depression. A two-part model estimated the adjusted incremental direct cost of depression (total and individual cost components) among adults with epilepsy. The model was adjusted for sex, race/ethnicity, education, marital status, insurance status, census region, income, Charlson Comorbidities index (CCI), and year trend.
Results: Out of a weighted 1,942,413 US adults with epilepsy, 675,037 (34.7%) had a diagnosis of depression. Annual total unadjusted per person direct cost of depression was $5290 higher in people with epilepsy vs. without [$18,776 (95% confidence interval [CI]: 16,241–21,311) vs. $13,486 (95%CI: 9780–17,191)]. Costs for outpatient and prescriptions were higher among people with epilepsy plus depression vs. without depression, but no differences were observed for inpatient, emergency room, and home health costs. In the adjusted model, total costs [$2523 (95%CI: 62–4984)], incremental annual direct costs per person for outpatient [$1940 (95%CI: 1266–2613)], prescriptions [$1285 (95%CI: 772–1798)], and emergency room [$191 (95%CI: 20–361)] were significantly higher for people with epilepsy plus depression. Unadjusted and adjusted incremental total aggregate annual direct costs of depression for people with epilepsy were $3.5 billion and $1.7 billion respectively.
Conclusion: Costs of epilepsy with presence of depression in the US are high, and primarily driven by outpatient, prescriptions, and emergency room costs.

1. Introduction

Of the estimated 3.4 million Americans living epilepsy, about 25% have depression, the most common psychiatric comorbidities in this population [1]. Epilepsy and depression are closely interrelated. They share neuroanatomical pathways disruption in the temporal, prefrontal, orbitofrontal, and inferior prefrontal regions [2]. Furthermore, they may influence occurrence of each other. For example, in an observational study of >10 million adults aged 18–90 years, incident epilepsy was associated with a twofold hazard of developing depression, and incident depression was associated with a 2.5-fold higher hazard of developing epilepsy (REF 3).

Medical and social impacts of depression in individuals with epilepsy are well-known, spanning from poor seizure control, increased length of stay [4], increased mortality, to poor quality of life [5]. The direct cost of epilepsy is high. For example, using recent estimates from the Medical expenditure panel, the direct total annual incremental economic costs of epilepsy were estimated at $16.7 billion [6]. It stands to reason that depression may contribute to the direct economic cost of epilepsy. Little is known about the magnitude of direct cost attributable to depression among people with epilepsy. In a systematic review of 15 studies totalizing 58,787 people with epilepsy, evaluating the predictors of health-related quality of life and costs, none of the included studies reported on the impact of depression on epilepsy costs [7]. Luoni et al.

* Corresponding author at: Department of Neurology, Medical University of South Carolina, 96 Jonathan Lucas Street, suite 301, Charleston, SC 29425, USA.
E-mail address: lekoubou@musc.edu (A. Lekoubou).

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analyzed the direct medical cost of epilepsy in a cohort of patients with refractory epilepsy in Italy; depressed mood explained about 3% of the variability in cost, but the independent impact of depression on direct cost was not evaluated, as data on mood were available only in a subset of patients [8].

Understanding the impact of depression on healthcare expenditures is of paramount importance as this could facilitate a tailored allocation of resources to depression care in individuals with epilepsy, and possibly contribute to better care and outcomes for patients with epilepsy. Planning and spending resources in patients with a comorbid diagnosis of depression would ideally require data on specific cost components such as inpatient, outpatient, medications, emergency room, and home health costs. Such data would preferably be of national scope and include all payers. To the best of our knowledge, no study has comprehensively evaluated healthcare expenditures associated with depression in people with epilepsy. In this analysis, we cover a 12-year period of national data from the Medical Expenditure Panel with the objective of comprehensively evaluating the direct economic impact (direct costs) of depression among people with epilepsy.

2. Methods

2.1. Data source and study population

The study involves 2450 adults (≥18 years) with epilepsy (representing a weighted population of 1,942,413) from the 2003–2014 Medical Expenditure Panel Survey (MEPS) Household Components (HC). The 12-year pooled MEPS-HC data was merged from each full year consolidated file and the medical condition files. The full year consolidated file contains information such as demographic characteristics, employment status, health status, health-related quality of life, quality of care, healthcare use, and expenditures. Medical condition files contain medical diagnoses and procedures. The MEPS-HC was initiated in 1996; it is a nationally representative survey of the U.S. civilian noninstitutionalized population. It is cosponsored by the Agency for Healthcare Research and Quality (AHRQ), and respondents are selected from the sampling frame of the prior year's National Health Interview Survey (NHIS). The NHIS sampling frame reflects an oversampling of minority populations (Blacks and Hispanics). The NHIS is a complex multistage sample design involving primary sampling unit (PSU), stratification, and clustering insuring representativeness of survey samples. Thus, MEPS data must be weighted to produce national estimates. Each annual MEPS-HC sample size is about 15,000 households, and data can be analyzed at person or event level [9,10].

2.2. Data verification and validity

The MEPS panel design survey includes 5 rounds of interview covering two full calendar years. Data are collected using computer assisted personal interview (CAPI) technology. All data about each household member are collected by interviewing a single household respondent. The survey collects this information from interviews to interviews. After completing the household CAPI interview and obtaining permission from the household survey respondents, a sample of medical providers are contacted by telephone to obtain information, which the household respondents cannot accurately provide [9]. This part of MEPS is contained in the Medical Provider Component (MPC). Information contained in the MPC also includes dates of visits, diagnoses and procedures, charges, and payments. Diagnoses are coded according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). Medical conditions and procedures related to diseases in MEPS-HC are recorded by an interviewer as verbatim text and then converted by professional coders to ICD-9-CM codes. The error rate for any coder did not exceed 2.5% on verification. The AHRQ also validates information in MEPS by comparing MEPS data with other data source numbers like the Census Bureau and NHIS [9–11]. Date collection is designed in such a way that the interview frequency, MPC verification and AHRQ comparison with Census validate MEPS information. Further details on MEPS-HC are available at www.meps.ahrq.gov.

2.3. Population of interest

We included adults with a diagnosis of epilepsy that was based on the CCCs of 83 recorded in the medical condition files [9]. The CCC-83 is collapsed in MEPS and combines ICD-9-CM codes 345.xx (epilepsy) and 780.3x (which include 780.31 = febrile epilepsy, 780.32 = complex febrile epilepsy, two conditions that affect primarily children; 780.33 = posttraumatic epilepsy; and 780.39 = other epilepsy). These two codes have previously been used in epidemiological studies [12–14] and have been validated by the International League Against Epilepsy for epidemiologic studies and surveillance of epilepsy [15].

2.4. Study variables

2.4.1. Dependent variables

The dependent variables were 6 types of healthcare expenditures (total expenditure, inpatient hospital expenditure, outpatient hospital expenditure, prescription medicine expenditure, emergency room expenditure, home healthcare expenditure, and other medical expenditures). Cost estimates from the pooled data are presented per person per year.

2.4.2. Independent variable

The primary independent variable was depression, identified by the ICD-9-CM codes 296, 300, 309, and 311 as entered in the MEPS medical condition files [16].

2.4.3. Covariates

Covariates included in the adjusted model were sex, race/ethnicity, education, marital status, insurance status, census region, income, Charlson Comorbidities index (CCI), and year trend. Sex was categorized as male and female. Race/ethnicity was categorized into: Non-Hispanic White, Non-Hispanic Black, Hispanic, and others. Education was categorized as less than high school (≤grade 11), high school (grade 12), and college or more (grade ≥ 13). Marital status was grouped into married, nonmarried (widowed/divorced/separated), and never married. Health insurance was coded as private, public only, and uninsured at all time in the year. Census region was categorized as Northeast, Midwest, South and West. The income level was defined as a percentage of the poverty level and grouped in to four categories: poor (<125%), low income (125% to less than 200%), middle income (200% to less than 400%) and high income (≥400%). We used D'Hoore et al.'s algorithm to create the Charlson Comorbidities Index (CCI) from a weight score of 17 conditions, and the scores were grouped into three categories: 0, 1, and ≥2 [17]. Calendar years were grouped into 2003/06, 2007/10, and 2011/14.

2.5. Analyses

We used a pooled (2003–2014) cross-sectional panel data to ensure sufficient sample size of patients with epilepsy with depression and increase the precision of our estimates. All costs were converted into 2016 dollar value using the consumer's price index obtained from the Bureau of Labor Statistics (BLS) [18]. STATA 14 was used to analyze the data at a person level [19], and estimates that were statistically significant at the $p < 0.05$ level were discussed in the paper. We used chi-square (χ^2) tests to compare demographic characteristics, and we used 95% confidence interval (CI) to estimate the unadjusted mean expenditure by depression status. We used the two-part model to evaluate; the association between the six cost categories and depression, adjusting for potential confounders. This model was used to account the excess zeros

expenditure data, nonnormal error-terms, and calculation of marginal effects from the first and the second part of the model using *margins* STATA command [20]. The first part of the model was a probit model for the probability of observing a zero vs. greater than zero medical expenditure. The second part was a generalized linear model (GLM) used to estimate the adjusted association of medical expenditures conditional on greater than zero medical expenditures [20,21]. The use of GLM in the second part of the model had an advantage over log Ordinary Least Squares (OLS) as it relaxed the normality and homoscedasticity assumptions and avoided biases associated with retransformation to the dollar value [20]. The model diagnostic test used to assess the model fit, the Modified Park Test (MPT) verified that the use of GLM with gamma distribution and log-link was the best fit for consistent estimation of marginal effects. No evidence of multicollinearity between the covariates of the model was revealed by the Variance inflation factor. The current analysis accounted for the sampling weights, clustering, and stratification design to estimate nationally representative healthcare expenditures in the US population [9].

3. Results

3.1. Population characteristics

The weighted population consisted of 1,942,413 US adults with epilepsy during the 2003–2014 period, including 675,037 (34.7%) with a diagnosis of depression (Table 1). Depression was significantly more frequent in the age group 45–64 years, females, Non-Hispanic Whites, nonmarried (widowed/divorced/separated), publicly insured, individual in the poor income categories, and among those with comorbid conditions.

3.2. Annual unadjusted cost differences of epilepsy by depression status

Unadjusted mean healthcare expenditures of epilepsy by person and by depression status is presented in Table 2. For the pool study period, the total individual unadjusted direct cost of epilepsy was $13,486 (95%CI: 9780–17,191) for adults without depression and $18,776 (95% CI: 16,241–21,311) for those with depression. Unadjusted outpatient expenditures for people with epilepsy and depression were $4582 (95%CI: 3813–5351), vs. $2414 (95%CI: 2062–2767) for those without depression. Unadjusted prescription expenditures for people with epilepsy and depression and those without depression were respectively $5381 (95%CI: 4710–6053) and $2964 (95%CI: 2468–3461). Unadjusted mean total healthcare expenditures difference between people with epilepsy and depression and those without depression was $5290 per person per year. Based on unadjusted mean healthcare expenditures difference, the aggregate total unadjusted direct cost incurred by depression among people with epilepsy in the US was estimated at $3.5 billion.

3.3. Adjusted incremental expenditures of depression

Table 3 summarizes the incremental expenditures of depression among people with epilepsy, after adjustments for demographics, medical comorbidities, and time trends. Relative to people with epilepsy and no depression, the total per person adjusted incremental cost of epilepsy and depression was $2523 (95%CI: 62–4984). Similar figures for outpatient expenditures, prescription expenditures, and emergency room expenditures were $1940 (95%CI: 1266–2613), $1285 (95%CI: 772–1798), and $191 (95%CI: 20–361) respectively. The incremental inpatient expenditures, home healthcare expenditures, and other expenditures were not statistically significant. Extrapolating on the total adjusted incremental expenditures, we estimated the depression burden among US population with epilepsy. The annual average aggregate incremental (after adjustment) expenditures of depression was $1.7 billion among adults with epilepsy in the United States.

Table 1
Weighted population characteristics with and without depression among adults with epilepsy, MEPS 2003–2014.

Variables	All (%)	Depression (%)	No-Depression (%)	p value
N (n)	1,942,413 (2450)	675,037 (856)	1,267,376 (1694)	
Age category				
Age 18–44	39.8	36.8	41.4	<0.001
Age 45–64	38.8	47.0	34.4	
Age 65–85	21.4	16.2	24.2	
Gender				
Male	45.4	37.6	49.5	<0.001
Female	54.6	62.4	50.5	
Race/ethnicity				
Non-Hispanic White	69.8	74.6	67.4	0.016
Non-Hispanic Black	13.8	10.5	15.5	
Hispanic	11.1	9.5	12.0	
Others	5.3	5.4	5.1	
Marital status				
Married	41.1	36.7	43.4	<0.001
Nonmarried	24.8	31.7	21.1	
Never married	34.1	31.6	35.5	
Education category				
<High School	8.6	8.2	8.7	0.541
High School	49.3	51.6	48.1	
College or more	42.1	40.2	43.2	
Insurance				
Private	48.1	40.1	52.3	<0.001
Public	43.4	53.7	37.9	
Uninsured	8.5	6.3	7.8	
Census region				
Northeast	17.0	15.9	17.6	0.833
Midwest	25.0	24.1	25.5	
South	35.5	36.7	34.8	
West	22.5	23.3	22.1	
Income category				
Poor income	29.8	36.9	26.0	<0.001
Low income	17.3	17.5	17.2	
Middle income	28.0	26.5	28.8	
High income	24.9	19.1	28.0	
Charlson Comorbidity Index				
0	60.8	51.8	65.6	<0.001
1	11.5	12.9	10.7	
≥2	27.7	35.3	23.7	
Year category				
Year 2003/06	31.9	33.5	31.1	0.663
Year 2007/10	32.5	30.8	33.3	
Year 2011/14	35.6	35.7	35.6	

N — weighted sample size; n — unweighted sample size; % — weighted percentage.

4. Discussion

This US based cost analyses study revealed that one out of three patients with epilepsy had depression, which was associated with significantly higher direct medical cost after adjusting for potential confounders. The direct cost difference was significant for outpatient visits (adjusted incremental expenditures: $1940), medication prescriptions (adjusted incremental expenditures: $1285), and Emergency department visits (adjusted incremental expenditures: $191).

The prevalence of depression in this study falls in the same prevalence range of lifetime depression from a meta-analysis of 4 studies that reported on 5454 with epilepsy (5.1–33.1%) [1]. Our findings, which relied on administrative data in a large US nationwide representative database, therefore further underscore the high rate of depression in people with epilepsy. The current study has also shown that previously reported high prevalence rates of depression among non-Hispanic Whites [22,23], female [24,25], and elderly [26] in the general population apply to people with epilepsy. Similarly, people with epilepsy and depression had low income and more comorbidities, corroborating previous findings in the general population [27].

Table 2
Unadjusted mean of total healthcare expenditures with and without depression among adults with epilepsy (in 2016 USD), MEPS 2003–2014.

Costs	Depression Mean ($)	95% CI	No-Depression Mean ($)	95%CI	p value
Total costs	18,776	16,241–21,311	13,486	9780–17,191	0.021
Inpatient	5488	4200–6776	4469	3099–5838	0.272
Outpatient	4582	3813–5351	2414	2062–2767	<0.001
Medications	5381	4710–6053	2964	2468–3461	<0.001
Emergency room	654	508–800	509	399–619	0.114
Home health	2143	592–3694	2679	−706–6066	0.776
Others	538	431–645	461	354–567	0.313

To the best of our knowledge, our study is the first of its kind to look at the direct medical costs related to depression in people with epilepsy at a national level in the United States. The direct cost of depression in people with epilepsy is high with an annual average aggregate cost difference of $1.7 billion between people with and those without depression. While most of the burden of direct medical cost of epilepsy is related to inpatient care [6,14], the incremental cost of depression is primarily driven by outpatient visits and medications prescriptions. These findings are of importance as it suggests that outpatient visits could be used to curb direct medical cost in patients with epilepsy. Specific interventions would start with a systematic screening for depression during clinic visits. Although several screening tools have been validated, a recent systematic review suggests that the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), the only epilepsy-specific tool, is the most validated tools with a good performance and translation in multiple languages, thus may be suitable in a wide variety of clinical setting and countries [28]. Unfortunately, despite consensus statement guidelines recommending screening for depression, physicians often fail to diagnose depression in people with epilepsy, and when they do so, they are often undertreated. For example, it was suggested that only 2 out of 5 physicians adhered to the recommendations to screen people with epilepsy for depression and other behavioral health issues [29] despite detrimental effects of depression such as decreased treatment adherence and quality of life [5,30].

In the current study, prescription expenditures were also significantly higher among people with epilepsy and comorbid depression.

Table 3
Two-part regression model: adjusted incremental effects of direct healthcare cost by depression status among adults with epilepsy.

Regression[a]	Variables	Incremental cost	95%CI	p value
	Total cost			
I	No-Depression (Ref.)	–	–	
	Depression	2523*	62–4984	0.045
	Inpatient			
II	No-Depression (Ref.)	–	–	
	Depression	1000	−328–2328	0.140
	Outpatient			
III	No-Depression (Ref.)	–	–	
	Depression	1940***	1266–2613	<0.001
	Medications			
IV	No-Depression (Ref.)	–	–	
	Depression	1285***	772–1798	<0.001
	Emergency Room			
V	No-Depression (Ref.)	–	–	
	Depression	191*	20–361	0.028
	Home Health			
VI	No-Depression (Ref.)	–	–	
	Depression	12	−585–611	0.966
	Others			
VII	No-Depression (Ref.)	–	–	
	Depression	86	−47–221	0.204

*Level of significance $p < 0.05$; **Level of significance $p < 0.01$; ***Level of significance $p < 0.001$.

[a] For regressions I–VII, the primary outcome is total, inpatient, outpatient, medication, emergency room, home health, and other expenditures, respectively. Each regression controls for age, sex, race/ethnicity, marital status, education, health insurance, census region, income, Charlson Comorbidity Index, and time trend.

One possible explanation may be related to the coprescription of antidepressants; however, this would not account for the total excess direct prescription cost as the percentage of patients with epilepsy that is screened for depression and therefore prescribed an antidepressant is rather low [29]. Having a diagnosis of depression, particularly when this is not comprehensively addressed may lead to poor adherence and hence poor seizure control [5], which may ultimately results in more than one antiepileptic drug prescription. Furthermore, patients with refractory epilepsy who often received more than one antiepileptic drug including newest and more expensive ones have a higher rate of depression [31,32]. In this study, significantly more patients with epilepsy and depression were publicly insured. After Medicare Part D prescription went into effect on January 1, 2006, individuals who were eligible to both Medicaid and Medicare were switched from Medicaid to privately own Part D drugs program and as such, the vast majority of publicly insured patients had a Part D drug program [33]. Although, the implementation of Part D drug program has been shown to reduce health expenditures, improved access to drugs particularly via the adoption of generic drugs [34], it is possible that these benefits have not extended to some people living with epilepsy and comorbid depression. This may be particularly true for poor and low income individuals who had a higher rate of depression in this study. There are evidence that Medicare families with income ≥250% below the poverty level and not eligible to income supplement assistance are more likely to have high healthcare related expenditures and less likely to receive information about Part D drug programs [35,36].

Emergency room expenditures were also high among people with epilepsy and depression compared to those with epilepsy only. This excess cost likely results from a combination of several factors. First depression is more frequent among people with refractory epilepsy [31,32] who also utilizes the emergency room at a disproportionally higher rate compare to those with controlled epilepsy [37]. Second, depression is associated with poor adherence [38], another independent factor of excess emergency room utilization. Third, in this study people with epilepsy and depression had a higher rate of comorbidities than those without depression. Having comorbidities has been associated with higher rate of ER utilization [39].

In all, the data presented here suggest that addressing the excess direct medical cost in people with epilepsy and depression could contribute to reducing prescription costs. Besides identifying and directly managing depression, examples of interventions could include increasing competitions among drug manufacturer, promoting the prescription of generic drug, and improving transparence in drug pricing.

5. Strengths and limitations

The strengths of this study include the use of the largest national up-to-date database of healthcare expenditures in the United States, covering a twelve-year period and including patients from all socioeconomic background, racial groups, irrespective of their insurance status. Our analysis accounted for the complex sampling design and our results are therefore generalizable to the entire noninstitutionalized adult population of the United States. Furthermore, the use of a two-part model allowed us to account for the excess zeros expenditures data,

and the observation that distribution of expenditures is heavily right skewed;, two frequent situations in cost estimates. The full model adjusted for covariates including demographic, economic, CCI, and time trend, which are potential cost driving factors. However, there are several limitations that should be taken into account in the interpretation of the results of this study. The database did not allow breaking down costs by the level of depression or seizure control or therapeutic interventions. Misclassification biases were also possible as diagnoses reported relied on claim data and self-reports; however, the conversion of diagnoses by professional coders resulting in only 2.5% error in MEPs suggest that misclassification bias was low. Finally, indirect costs including cost of absenteeism, loss of productivity, and premature death were not evaluated.

6. Conclusion

The direct costs of depression among adults with epilepsy in the US are substantial and driven by three key cost components, outpatient, medication prescriptions, and emergency room expenditures. Furthermore, the aggregate yearly cost of depression among individuals with epilepsy was also high (unadjusted: $3.5 billion, adjusted incremental: $1.7 billion). Future studies should focus on the role of specific therapeutic interventions including, but not limited to epilepsy surgery and neurostimulation, on the economic impact of depression in people with epilepsy.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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