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ARTICLE

Trends in prescribing patterns of antiepileptic drugs among older adult inpatients in a Brazilian tertiary center

Tendências no padrão de prescrição de drogas antiepilépticas em idosos internados em um centro terciário brasileiro

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ABSTRACT

Background: Data on prescribing patterns of antiepileptic drugs (AEDs) to older adult inpatients are limited. **Objective:** To assess changes in prescribing patterns of AEDs to older adult inpatients with late-onset epilepsy between 2009–2010 and 2015–2019, and to interpret any unexpected patterns over the 2015–2019 period. **Methods:** Patients aged ≥60 years with late-onset epilepsy from a tertiary center were selected. Demographic data, seizure characteristics and etiology, comorbidities, and comedications were analyzed, in addition to prescription regimens of inpatients taking AEDs to treat epilepsy. AED regimens were categorized into two groups: group 1 included appropriate AEDs (carbamazepine, oxcarbazepine, valproic acid, gabapentin, clobazam, lamotrigine, levetiracetam, topiramate, and lacosamide); and group 2 comprised suboptimal AEDs (phenytoin and phenobarbital). Multivariate logistic regression analysis was performed to identify risk factors for prescription of suboptimal AEDs. **Results:** 134 patients were included in the study (mean age: 77.2±9.6 years). A significant reduction in the prescription of suboptimal AEDs (from 73.3 to 51.5%; p<0.001) was found; however, phenytoin remained the most commonly prescribed AED to older adult inpatients. We also found an increase in the prescription of lamotrigine (from 5.5 to 33.6%) and levetiracetam (from 0 to 29.1%) over time. Convulsive status epilepticus (SE) and acute symptomatic seizures associated with remote and progressive etiologies were risk factors for the prescription of suboptimal AEDs. **Conclusions:** Phenytoin was the main suboptimal AED prescribed in our population, and convulsive SE and acute symptomatic seizures associated with some etiologies were independent risk factors for phenytoin prescription. These results suggest ongoing commitment to reducing the prescription of suboptimal AEDs, particularly phenytoin in Brazilian emergence rooms.

Keywords: Aged; Antiepileptic Drugs; Epilepsy; Inpatients; Seizures.

RESUMO

Introdução: Os dados referentes à prescrição de drogas antiepilépticas (DAE) em pacientes idosos hospitalizados são limitados. **Objetivo:** Avaliar as mudanças no padrão de prescrição de DAE em idosos hospitalizados com epilepsia de início tardio, entre 2009–2010 e 2015–2019, e interpretar quaisquer padrões inesperados no período de 2015–2019. **Métodos:** Foram selecionados pacientes com ≥60 anos com epilepsia de início tardio admitidos em um centro terciário. Analisamos os dados demográficos, as características e etiologia das crises, as comorbidades e as comedicações. Foram avaliados os esquemas de prescrição das DAE no tratamento de epilepsia para pacientes internados. Os regimes de DAE foram categorizados em dois grupos: o grupo 1 incluiu as DAE apropriadas (carbamazepina, oxcarbazepina, ácido valproico, gabapentina, clobazam, lamotrigina, levetiracetam, topiramato e lacosamida); e o grupo 2 compreendeu as DAE subótimas (fenitoína e fenobarbital). A análise de regressão logística multivariada foi realizada para identificar fatores de risco para prescrição de DAE subótimas. **Resultados:** Foram incluídos 134 pacientes (idade média: 77,2±9,6 anos). Encontramos uma redução significativa do uso das DAE subótimas (73,3 para 51,5%; p<0.001); entretanto, a fenitoína permaneceu sendo a DAE mais prescrita para os idosos hospitalizados. Também encontramos um aumento na prescrição da lamotrigina (5,5 para 33,6%) e do levetiracetam (0 para 29,1%) no período. O estado de mal epiléptico (EME) convulsivo e as crises agudas sintomáticas que estiveram associadas a etiologias remotas e progressivas foram fatores de risco para prescrição de DAE subótimas. **Conclusões:** A fenitoína foi a principal DAE subótima prescrita em

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Authors' contributions: TA conceived the study idea, designed the methods, collected data, performed statistical analysis, and drafted the manuscript; AB, LC, SS, and GC collected data, examined medical records, and reviewed manuscript drafts; LC also performed the English editing; OJN discussed the study idea, methods, statistical analysis, and results. All authors read, discussed, and approved the final manuscript.

Data availability: The data used to support the findings of this study are available from the corresponding author upon request.

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nossa população, e o EME convulsivo e as crises agudas sintomáticas associadas a algumas etiologias foram fatores independentes de risco para a prescrição da fenitoína. Esses resultados sugerem a necessidade de compromisso contínuo para reduzir a prescrição de DAE subótimas, particularmente a fenitoína nas salas de emergência brasileiras.

Palavras-chave: Idoso; Anticonvulsivantes; Epilepsia; Paciente Internados; Convulsões.

INTRODUCTION

People aged over 60 years represent the fastest-growing population group in the world[1]. The burden of neurological disorders such as stroke, neurodegenerative, and neoplastic disorders, which are the most frequent etiologies of epilepsy in older adults, increases as the population ages[2]. Moreover, 25 to 30% of all new-onset seizures occur in individuals older than 60 years[3,4]. Prescription of antiepileptic drugs (AEDs) has been increasing as epilepsy diagnoses in older people escalate. This demographic shift poses important challenges to prescription safety. Although there is some evidence for prescribing AEDs to older individuals, the inclusion of this population in clinical trials is uncommon[5]. Older people often have multiple comorbidities in addition to other impairments such as altered physiology and pharmacokinetics, polypharmacy, and atypical disease presentations. Furthermore, the simultaneous use of AEDs and other medicines may result in drug-drug interactions, dose-related side effects, and idiosyncratic drug reactions, which hamper the appropriate treatment of epilepsy[6]. Newer AEDs were introduced in the market to increase efficacy and reduce side effects, and epilepsy experts regard several of them as more appropriate options for older people with epilepsy[7,8]. Older AEDs, such as phenobarbital and phenytoin, have similar efficacy compared with the newer ones, but they usually have a less favorable safety profile and are considered suboptimal AEDs for older people with epilepsy (EPWE)[9,10,11].

A prior study was conducted to investigate prescribing patterns of AEDs for older adult inpatients with late-onset epilepsy and found that the most common AED prescribed to that population was phenytoin (53%)[12], which is consistent with several studies also showing phenytoin as the most commonly prescribed AED (50–70%)[9,13]. Notwithstanding guidelines and expert consensus opinions advocating the use of newer AEDs in the treatment of epilepsy among older people, these patients still receive suboptimal treatment in clinical practice. The aim of this study was: first, to assess changes in prescribing patterns of AEDs among older adult inpatients with late-onset epilepsy between 2009–2010 and 2015–2019; and second, to interpret any unexpected patterns of AED prescription over the 2015–2019 period.

METHODS

This prospective, observational, single-center study was conducted on patients aged ≥60 years who were consecutively admitted to Hospital São Rafael, a general tertiary teaching hospital with 356 beds located in Salvador, state of Bahia, Brazil, between November 2015 and May 2019.

The study participants included older adult inpatients with epileptic seizures that either led to their hospital admission or occurred during a period of care in the emergency room or during hospitalization, and who had their first unprovoked seizure at 60 years of age or older. All patients were under the care of a neurology team.

Exclusion criteria were: (1) older adult inpatients who had been admitted with a diagnosis of seizure that was not confirmed or who were later diagnosed with other paroxysmal neurological disorders such as syncope, delirium, or transient ischemic attack; (2) patients with isolated acute symptomatic seizures, including those who had seizures in the setting of an acute traumatic brain injury and were followed up by the neurosurgery team, except those with remote and/or progressive seizures (epilepsy) who also had a seizure due to an acute cause at the time of the study; (3) previously included patients who had been readmitted to the hospital, even if they had had other seizures; and (4) patients on AEDs for conditions other than epilepsy such as neuropathic pain, mood disorders, and migraine.

To investigate trends in prescribing patterns of AEDs, the AEDs prescribed to the study cohort of older adult inpatients with late-onset epilepsy between 2015 and 2019 (Y2) were identified and these data were compared to results of the previous retrospective study on a similar population conducted between 2009 and 2010 (Y1)[12]. Patient characteristics were also analyzed to identify any risk factor for receiving suboptimal therapy.

Diagnostic criteria

The diagnosis of epilepsy followed the recommendations of the International League Against Epilepsy (ILAE) Official Report[14]. The diagnosis of status epilepticus (SE) included the revised concepts, definition, and classification from the ILAE[15].

The characteristics of the seizures were described, according to the latest recommendations, based on the Operational Classification of Seizure Types by the ILAE[16].

An acute symptomatic seizure was diagnosed according to the ILAE recommendations[17].

To ascribe an acute symptomatic seizure to metabolic imbalance, the cutoff values that are most likely to be associated with seizures were used, namely: sodium <115 mg/dL (or >145 mmol/L), calcium <5.0 mg/dL, magnesium <0.8 mg/dL, glucose fasting <36 mg/dL (or >~450 mg/dL,

when associated with ketoacidosis), urea >214 mg/dL, and creatinine >10 mg/dL[17,18].

Seizure etiology was categorized as (1) symptomatic (known cause), including a) acute seizures (e.g., stroke, central nervous system [CNS] infection, metabolic disorder, and autoimmune disease), b) remote seizures (e.g., post-stroke, posttraumatic, and postencephalitic), and c) progressive symptomatic (brain tumor and dementia), and as (2) unknown cause[15,19].

Late-onset epilepsy was conventionally defined as epileptic seizures first occurring in subjects aged 60 years or older[20,21]. An unprovoked seizure was defined as a seizure occurring in the absence of precipitating factors and that may have been caused by static or progressive injury[22].

Patient multimorbidity was defined as the coexistence of two or more chronic conditions[23].

Investigation of seizure etiology included laboratory tests (glucose, urea, magnesium, sodium, calcium, and creatinine). Routine electroencephalogram (EEG), 24-h video-EEG, and brain imaging data (computed tomography [CT], magnetic resonance imaging [MRI], MRI angiography [MRA], and positron emission tomography [PET]) were also collected when necessary. Some patients underwent cerebrospinal fluid analysis. The following EEG results were considered abnormal: diffuse or focal slowing abnormalities and interictal or ictal paroxysms. This definition excluded records with non-specific abnormalities.

Analysis methods

The following data were analyzed: (1) demographic data, including age and sex; (2) hospitalization data, including intensive care unit (ICU) admission and length of stay (LOS); (3) characteristics of the seizure disorders during the index seizure, such as SE, acute symptomatic seizure, single unprovoked seizure, epilepsy, seizure type, and age at onset of the first seizure; (4) prescription of AEDs at the time of the index seizure and/or at discharge; (5) potentially proconvulsant comedications; (6) seizure etiology; and (7) clinical and neurological comorbidities.

AED regimens were classified for this population into two subgroups according to evidence-based clinical recommendations to keep the same categorization of our previous study on a similar population conducted between 2009 and 2010 (Y1): a) group 1 included appropriate AEDs (carbamazepine, oxcarbazepine, valproic acid, gabapentin, clobazam, lamotrigine, levetiracetam, topiramate, and lacosamide); and b) group 2 comprised suboptimal AEDs (phenytoin and phenobarbital)[12]. AED regimens included both monotherapy and polytherapy (combination therapy with two or more AEDs)[12].

Statistics

Descriptive statistics for the cohort of late-onset epilepsy were tabulated. Quantitative variables with normal distribution were expressed as means and standard deviations. Variables with non-normal distribution were expressed as medians and interquartile ranges. Normal variables were identified by the analysis of histograms and box plots and by the Kolmogorov-Smirnov test. Categorical variables were reported as frequencies and percentages.

Chi-square analysis was used to investigate changes in the initial AED treatments that patients received between Y1 (year) (2009–2010) and Y2 (2015–2019). To ensure these bivariate results were not due to changes in patient characteristics over time, logistic regression models were also used to control for patient characteristics (age, sex, and comorbidities).

For bivariate comparisons, Student's *t*-test was used for numerical variables with normal distribution and the Mann-Whitney test for those with non-normal distribution. Categorical variables were compared by Pearson's chi-square or Fisher's exact test when necessary.

A backward stepwise multiple logistic regression was performed for data analysis, which was conducted in three blocks to improve the power of the model, with demographic variables followed by seizure etiologies and comorbidities.

This study considered $p \leq 0.05$ as statistically significant for univariate and multivariate analysis.

SPSSâ Statistics (v. 25, Chicago, IL, USA), R Program (v.3.4.4), and Microsoft Excelâ 2016 were used to perform statistical analyses.

Ethics

The Research Ethics Committee of Hospital São Rafael approved this study on November 24, 2014 (no. 904.379, version 5).

RESULTS

Demographic data

A total of 150 older adult patients met the study inclusion criteria, 16 of whom were excluded because they were later recognized to have isolated acute symptomatic seizures; however, patients with acute symptomatic seizures in combination with another seizure etiology, such as remote or progressive causes, were enrolled in this study. The present cohort comprised 134 patients that were followed up during their hospitalization. Patients were mostly men (53%) and married (62.7%); 91.8% of patients had private health insurance coverage.

The mean age of the cohort was 77.2±96.6 years, with a median age of 78 years (interquartile range [IQR], 62–94 years). Mean age at the first-time seizure was 76.5±9.8 years. A total of 87 (64.9%) patients were admitted to the ICU. The median LOS was 11 days, with an interquartile range of 5–21 days.

Clinical characteristics

The cause of epilepsy was determined for nearly all patients, including: cerebrovascular disorders in 75 (56%)

patients, dementia in 33 (24.6%) patients, and brain tumors in nine (6.7%). Three (2.2%) patients had a combination of two of these conditions (stroke and dementia). Epilepsy of unknown cause was found in 14 (10.5%) patients of this population. Focal onset seizures were the most common type, occurring in 68.6% of patients, while seizures of unknown type occurred in 3%. In addition, we found a great proportion of patients who presented with SE (33.6%), most of whom had convulsive SE (75.5%).

The mean number of comorbidities was high, 5.4±2.1 (95% confidence interval [95%CI] 5.04 to 5.77). The most commonly identified clinical comorbidities were hypertension (83.6%), dyslipidemia (58%), and systemic infections (50%). Data are summarized in Table 1.

Routine EEG was performed in 91.8% of patients, and 77 (57.5%) of them fulfilled the predefined criteria for abnormal records.

Potentially proconvulsant comedications were used by 50% of patients and are shown in Table 2.

Prescribing patterns of antiepileptic drugs

A suboptimal AED regimen was prescribed to 69 patients (51.5%; 95%CI 42.7–60.2), and there were no sex disparities; these patients received phenytoin and/or phenobarbital alone or in combination with any other AED (Figure 1). Patients were preferentially treated with monotherapy (53.7%; 95%CI 44.9–62.3). Polytherapy with two or three AEDs was prescribed to 41.8% and 3.7% of patients (95%CI 33.4 to 50.6%; 95%CI 1.4–8.9), respectively (Figure 2). Phenytoin was the most commonly used AED (51.5%; 95%CI 42.7–60.15). Lamotrigine was the second most frequently prescribed AED in a monotherapy regimen (33.6%; 95%CI 25.8–42.3), followed by levetiracetam (29.1%; 95%CI 21.7–37.7).

When comparing prescribing patterns of AEDs in Y2 (2015–2019) with the results of the previous study in Y1 (2009–2010), a significant change was observed in prescribing patterns of AED regimens over time, with the proportion of patients prescribed a suboptimal regimen in Y1 (73.3%) proving higher than that in Y2 (51.5%) ($p<0.001$). This reduction in the use of suboptimal AEDs was due to a considerable decline in phenobarbital prescription (from 9.2 to 0.75%). In addition, a modest decrease in the use of phenytoin was found (from 64 to 51.5%). Although carbamazepine was not listed as suboptimal, its prescription dropped from 16.5% (Y1) to 9.7% (Y2) in this study.

Figure 3 shows changes in the proportion of prescribed AEDs between Y1 and Y2, including phenytoin, phenobarbital, valproic acid, lamotrigine, oxcarbazepine, carbamazepine, clobazam, gabapentin, and levetiracetam. A trend toward the prescription of lamotrigine (33.6 *versus* 5.5%) and levetiracetam (29.1 *versus* 0%) was observed in Y2 compared with Y1, whereas valproate, oxcarbazepine, carbamazepine, and gabapentin were less often prescribed over time.

Multivariate analysis showed patients who did not present with convulsive SE were seven times more likely to be in the appropriate regimen group than those patients with

Table 1. Most common neurological and clinical comorbidities among 134 older adult inpatients in a tertiary center.

Comorbidities	Frequency
Hypertension	112 (83.6)
Cerebrovascular disorders	84 (62.7)
Ischemic stroke	72 (53.7)
Dyslipidemia	78 (58%)
Systemic infections	67 (50)
Diabetes mellitus	57 (42.5)
Psychiatric disorders	47 (35)
Cardiac arrhythmias	41 (30.6)
Toxic and metabolic disorders	39 (29)
Dementia	35 (26)
Kidney failure	32 (24)
Non-brain tumors	27 (20.2)
Sepsis	24 (18)
Hypothyroidism	24 (18)
Delirium	21 (15.7)
Toxic-metabolic encephalopathy	15 (11.2)
Movement disorders	13 (9.7)
Brain tumors	9 (6.7)

Data are expressed as number of patients, with percentages (%) in brackets.

Table 2. Potentially proconvulsant comedications in addition to antiepileptic drugs among 134 older adult inpatients.

Comedication	Frequency
Cephalosporin 3rd and 4th generation (35)	32 (23.9)
Quetiapine (36)	31 (23.1)
Beta blocker (35)	24 (17.9)
Carbapenem (35)	20 (14.9)
Insulin (35)	19 (14.2)
Diuretic (thiazide) (35)	13 (9.7)
Penicillin derivative (35)	11 (8.2)
Antiarrhythmic (35)	9 (6.7)
Levodopa (35)	8 (5.9)
Olanzapine (36)	8 (5.9)
Opioid pain killer (35)	7 (5.2)
Haloperidol (35)	5 (3.7)
Phenothiazine (35)	4 (2.9)
Risperidone (36)	1 (0.7)
Quinolone (35)	1 (0.7)
TCAs (amitriptyline) (35)	1 (0.7)

TCAs: tricyclic antidepressants. Data are expressed as number of patients, with percentages (%) in brackets.

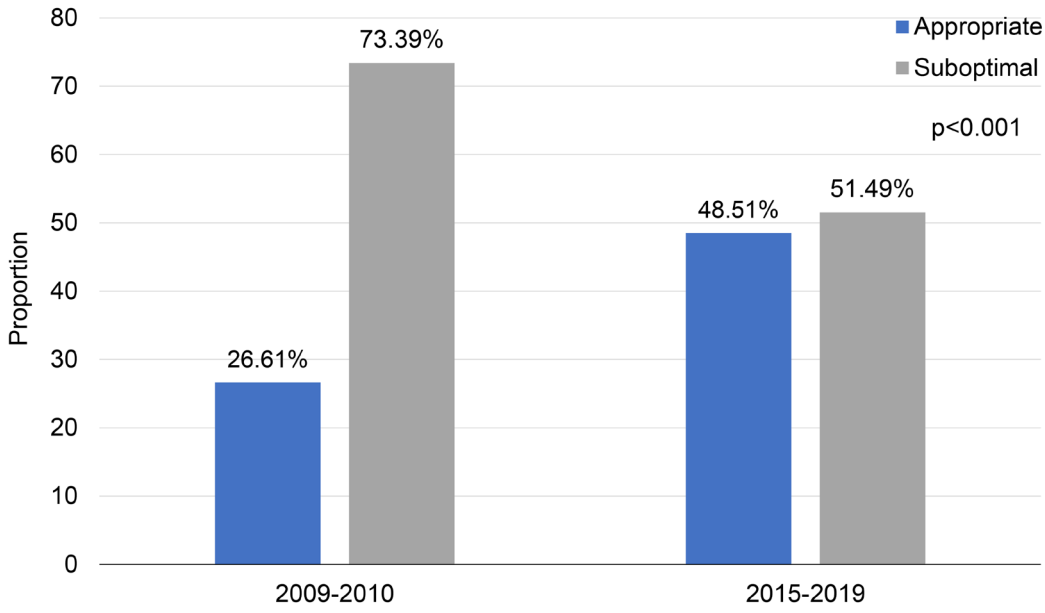
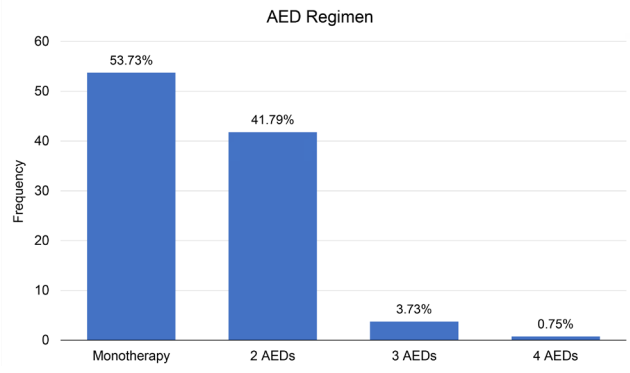


Figure 1. Temporal trend in the proportion of inpatients on appropriate AEDs and suboptimal AEDs between Y1 (2009–2010) and Y2 (2015–2019).



AED: antiepileptic drugs.

Figure 2. AED regimens including monotherapy and polytherapy among 134 older adult inpatients.

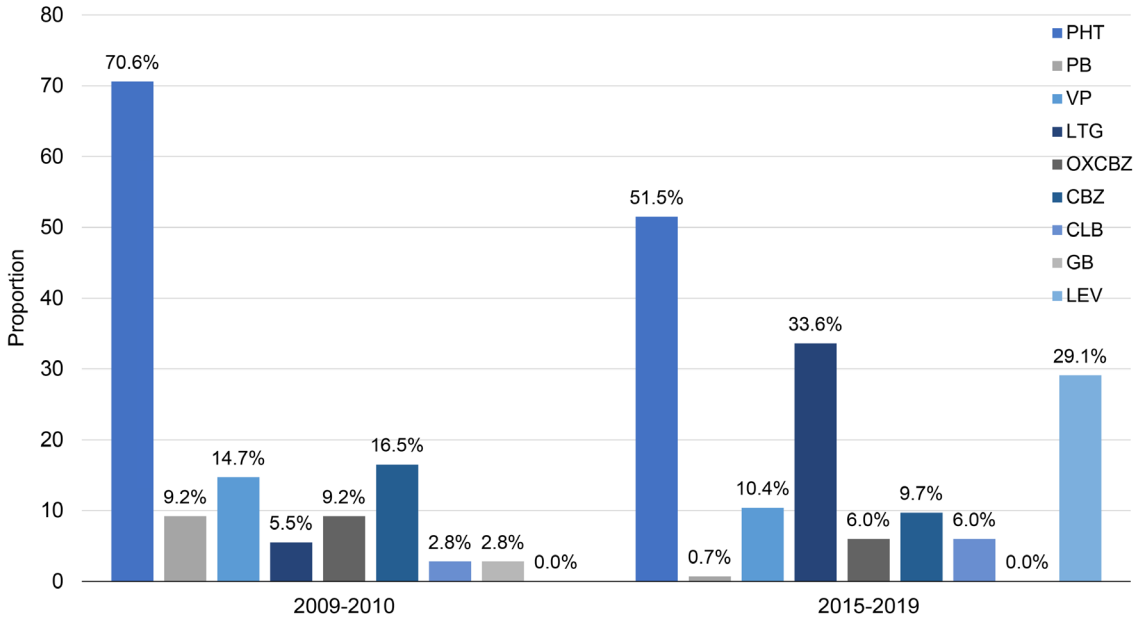
convulsive SE [$1/(e^{-2.0141})$=7.4940] (p<0.001). Patients who did not have remote or progressive etiologies associated with acute symptomatic seizures were four times more likely to be in the appropriate regimen group than those patients who did [$1/(e^{-1.42784})$=4.1697] (p=0.02).

Eight patients who required drug discontinuation due to severe adverse reactions were identified and, in these cases, the culprit drug was replaced by another AED; among patients taking phenytoin, four had idiosyncratic reactions and one of them developed Stevens-Johnson syndrome. One patient had erythema multiforme in the first few days of levetiracetam use; two patients exhibited a rash during lamotrigine dose escalation, and another patient presented with valproic acid-induced hepatotoxicity.

DISCUSSION

There are limited data evaluating prescribing patterns of AEDs in the older adult population, despite published guidelines and expert opinion recommendations regarding the treatment of epilepsy in this population[24]. The present study investigated changes in prescribing patterns of AEDs that occurred from 2009 to 2019 in older adult inpatients. The authors hypothesized there would be a downward trend in the use of phenytoin and phenobarbital, formerly deemed inappropriate in the previous retrospective study on prescribing patterns of AEDs in older adult inpatients[12], and consequently an increase in the use of newer AEDs over time, typifying an improvement in the quality of treatment. The decision to categorize an AED regimen as appropriate or inappropriate (suboptimal) considered the evidence-based clinical recommendations and expert consensus opinions. These guidelines included phenobarbital and phenytoin, both enzyme inducers, in the group of inappropriate drugs, because of their unsuitable safety profile for older adult patients[6,9]. Although carbamazepine is also an enzyme inducer, it is well-tolerated by older adult patients and so it was not included in the inappropriate group[9,11,25].

Significant changes were found in prescribing patterns of AEDs for older adult inpatients with late-onset epilepsy throughout the ten-year study period. Although often utilized, a significant decrease in the prescription of suboptimal AEDs was observed, which was due to a considerable decrease in phenobarbital prescription. This consistent change in the quality of AED prescription coincided with the increasing dissemination of newer AEDs into clinical practice in Brazil. The modest drop in phenytoin



PHT: phenytoin; PB: phenobarbital; VP: valproic acid; LTG: lamotrigine; OXCBZ: oxcarbazepine; CBZ: carbamazepine; CLB: clobazam; GB: gabapentin; LEV: levetiracetam.

Figure 3. Temporal trend in the proportion of inpatients treated with the most commonly used AEDs.

prescription and the fact it remains the most commonly prescribed AED in this study may be explained by the characteristics of these hospitalized older adult patients. One third of the included patients presented with SE, thus requiring treatment with intravenous (IV) AEDs according to the guidelines on the management of SE. Despite the increased availability of other IV AEDs in several countries, IV phenytoin remains the drug of choice for most patients in emergency settings. In the center where this study was conducted (HSR), phenytoin, phenobarbital, valproic acid, and lacosamide are currently available in IV formulation. Levetiracetam is not available in IV formulation in Brazil. Phenytoin was prescribed to 69 patients in initial care, with 27.5% of them requiring replacement for another AED such as lamotrigine or levetiracetam. The present results are in line with a previous study on older adult patients, which found phenytoin to be the most commonly prescribed AED; conversely, a significant reduction in the use of phenobarbital was observed in the present research[11]. Since 1985, data supporting the status of phenobarbital as a suboptimal AED have been widely cited[26]; a subsequent meta-analysis confirmed this notion and recommended against the use of phenobarbital due to adverse drug effects[27]. Despite scientific evidence favoring newer AEDs over older ones, changes in clinical practice face some obstacles related to prescriber profile, higher cost of new drugs, and the circumstances in which the AED is used.

A randomized trial of gabapentin, lamotrigine, and carbamazepine in new-onset geriatric epilepsy has demonstrated these AEDs to have similar efficacy, but has found the discontinuation rate to be the lowest with lamotrigine and the highest with carbamazepine[25]. When compared with lamotrigine and carbamazepine, levetiracetam had the lowest discontinuation rate among older adults with new-onset epilepsy[28]. Moreover, despite similar effectiveness between drugs, levetiracetam had the lowest discontinuation rate when compared with valproate and carbamazepine among older adult patients[29]. A recent systematic review with meta-analysis concluded lamotrigine was better tolerated than carbamazepine among older adults with epilepsy; levetiracetam was seemingly associated with a higher probability of seizure freedom when compared with lamotrigine, although no difference was found in long-term efficacy and tolerability[5]. Levetiracetam and lamotrigine may cause fewer drug-drug interactions than enzyme inducers, such as phenytoin, carbamazepine, and phenobarbital, and therefore the former tend to be prescribed more often with advancing age. A revision of guidelines on the management of epilepsy in England recommends two first-line AEDs (carbamazepine and lamotrigine) and three alternative AEDs in monotherapy (levetiracetam, oxcarbazepine, and valproate); however, notwithstanding the substantial increase in the use of newer AEDs over time, the authors observed persistent widespread use of suboptimal therapy with phenytoin, primidone, and phenobarbital[30].

Multiple comorbidities are common among older adult inpatients, and polypharmacy tends to be the rule[31], which may affect AED choice. Potential drug interactions of statins, antihypertensive agents, warfarin, and chemotherapeutic agents with phenytoin, carbamazepine, phenobarbital, and valproate are reasons for concern[32,33]. Enzyme inducers may interact with many other drugs commonly prescribed to

older people such as tricyclic antidepressants, selective serotonin reuptake inhibitors, antipsychotics, and calcium channel blockers[33].

Post-stroke epilepsy usually occurs after 5-6 months, and no specific AED is recommended, although there has been an attempt to use levetiracetam in this setting[34].

Limitations and strengths

This study was conducted on a relatively small sample of a heterogenous population of older adult patients from a single center who had epilepsy, which is also a heterogenous disease. The patients received specialized care from a neurology team, which could affect the generalizability of the reported findings to some extent. Additionally, the present results may not reflect some categories of individuals such as those residing in nursing homes or other long-term care facilities.

Key strengths of this study include: its prospective design, which allowed the authors to identify acute symptomatic seizures as well as epileptic and nonepileptic events and to determine seizure type and etiology according to the ILAE recommendations; and its focus on the prescription of AEDs to patients who had been diagnosed with epilepsy.

In conclusion, this study showed a downward trend in suboptimal therapy for older adult inpatients over a period of time, notably fewer phenobarbital prescriptions. The use of newer AEDs substantially increased, although phenytoin remains the most commonly prescribed drug to older adult inpatients. Convulsive SE and some acute symptomatic seizures were found to be independent risk factors for suboptimal prescription among this population.

These results suggest ongoing commitment to reducing the prescription of suboptimal AEDs to older adults, particularly phenytoin, in Brazilian emergency rooms.

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References

1. Centers for Disease C, Prevention. Trends in aging--United States and worldwide. MMWR. 2003 Jan;52(6):101-4,6.
2. Liu S, Yu W, Lu Y. The causes of new-onset epilepsy and seizures in the elderly. Neuropsychiatr Dis Treat. 2016 Jun;12:1425-34. https://doi.org/10.2147/NDT.S107905
3. Stephen LJ, Brodie MJ. Epilepsy in elderly people. Lancet. 2000 Apr;355(9213):1441-6. https://doi.org/10.1016/S0140-6736(00)02149-8.
4. Trinka E, Bauer G, Oberaigner W, Ndayisaba JP, Seppi K, Granbichler CA. Cause-specific mortality among patients with epilepsy: Results from a 30-year cohort study. Epilepsia. 2013 Mar;54(3):495-501. https://doi.org/10.1111/epi.12014
5. Lezaic N, Gore G, Josephson CB, Wiebe S, Jette N, Keezer MR. The medical treatment of epilepsy in the elderly: A systematic review and meta-analysis. Epilepsia. 2019 Jul;60(7):1325-40. https://doi.org/10.1111/epi.16068
6. Kaur U, Chauhan I, Gambhir IS, Chakrabarti SS. Antiepileptic drug therapy in the elderly: a clinical pharmacological review. Acta Neurol Belg. 2019 Jun;119(2):163-73. https://doi.org/10.1007/s13760-019-01132-4
7. Brodie MJ, Kwan P. Newer drugs for focal epilepsy in adults. BMJ. 2012 Jan;344:e345. https://doi.org/10.1136/bmj.e345
8. Pugh MJ, Foreman PJ, Berlowitz DR. Prescribing antiepileptics for the elderly: differences between guideline recommendations and clinical practice. Drugs Aging. 2006 Nov;23(11):861-75. https://doi.org/10.2165/00002512-200623110-00002
9. Pugh MJ, Cramer J, Knoefel J, Charbonneau A, Mandell A, Kazis L, et al. Potentially inappropriate antiepileptic drugs for elderly patients with epilepsy. J Am Geriatr Soc. 2004 Mar;52(3):417-22. https://doi.org/10.1111/j.1532-5415.2004.52115.x
10. Karceski S, Morrell MJ, Carpenter D. Treatment of epilepsy in adults: expert opinion, 2005. Epilepsy Behav. 2005 Sep;7 Suppl 1:S1-64; quiz S65-7. https://doi.org/10.1016/j.yebeh.2005.06.001
11. Pugh MJ, Van Cott AC, Cramer JA, Knoefel JE, Amuan ME, Tabares J, et al. Trends in antiepileptic drug prescribing for older patients with new-onset epilepsy: 2000-2004. Neurology. 2008 May;70(22 Pt 2):2171-8. https://doi.org/10.1212/01.wnl.0000313157.15089.e6
12. Assis TR, Nascimento OJ, Costa G, Bacellar A. Antiepileptic drugs patterns in elderly inpatients in a Brazilian tertiary center, Salvador, Brazil. Arq Neuro-Psiquiatr. 2014 Nov;72(11):874-80. https://doi.org/10.1590/0004-282X20140151
13. Ruggles KH, Haessly SM, Berg RL. Prospective study of seizures in the elderly in the Marshfield Epidemiologic Study Area (MESA). Epilepsia. 2001 Dec;42(12):1594-9. https://doi.org/10.1046/j.1528-1157.2001.35900.x
14. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE Official Report: a practical clinical definition of epilepsy. Epilepsia. 2014 Apr;55(4):475-82. https://doi.org/10.1111/epi.12550
15. Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, et al. A definition and classification of status epilepticus--Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia. 2015 Oct;56(10):1515-23. https://doi.org/10.1111/epi.13121
16. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017 Apr;58(4):522-30. https://doi.org/10.1111/epi.13670
17. Beghi E, Carpio A, Forsgren L, Hesdorffer DC, Malmgren K, Sander JW, et al. Recommendation for a definition of acute symptomatic seizure. Epilepsia. 2010 Apr;51(4):671-5. https://doi.org/10.1111/j.1528-1167.2009.02285.x
18. Karceski S. Acute symptomatic seizures and systemic illness. Continuum (Minneap Minn). 2014 Jun;20(3 Neurology of Systemic Disease):614-23. https://doi.org/10.1212/01.CON.0000450969.61204.6f
19. Phabphal K, Geater A, Limapichat K, Sathirapanya P, Setthawatcharawanich S. Risk factors of recurrent seizure, co-morbidities, and mortality in new onset seizure in elderly. Seizure. 2013 Sep;22(7):577-80. https://doi.org/10.1016/j.seizure.2013.04.009

20. No authors listed. Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia. Jul-Aug 1989;30(4):389-99. https://doi.org/10.1111/j.1528-1157.1989.tb05316.x

21. Maxwell H, Hanby M, Parkes LM, Gibson LM, Coutinho C, Emsley HC. Prevalence and subtypes of radiological cerebrovascular disease in late-onset isolated seizures and epilepsy. Clin Neurol Neurosurg. 2013 May;115(5):591-6. https://doi.org/10.1016/j.clineuro.2012.07.009

22. Gavvala JR, Schuele SU. New-onset seizure in adults and adolescents: a review. JAMA. 2016 Dec;316(24):2657-68. https://doi.org/10.1001/jama.2016.18625

23. Prados-Torres A, Calderon-Larranaga A, Hancco-Saavedra J, Poblador-Plou B, van den Akker M. Multimorbidity patterns: a systematic review. J Clin Epidemiol. 2014 Mar;67(3):254-66. https://doi.org/10.1016/j.jclinepi.2013.09.021

24. Watkins L, O'Dwyer M, Shankar R. New anti-seizure medication for elderly epileptic patients. Expert Opin Pharmacother. 2019 Sep;20(13):1601-8. https://doi.org/10.1080/14656566.2019.1618272

25. Rowan AJ, Ramsay RE, Collins JF, Pryor F, Boardman KD, Uthman BM, et al. New onset geriatric epilepsy: a randomized study of gabapentin, lamotrigine, and carbamazepine. Neurology. 2005 Jun;64(11):1868-73. https://doi.org/10.1212/01.WNL.0000167384.68207.3E

26. Mattson RH, Cramer JA, Collins JF, Smith DB, Delgado-Escueta AV, Browne TR, et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. N Engl J Med. 1985 Jul;313(3):145-51. https://doi.org/10.1056/NEJM198507183130303

27. Taylor S, Tudur Smith C, Williamson PR, Marson AG. Phenobarbitone versus phenytoin monotherapy for partial onset seizures and generalized onset tonic-clonic seizures. Cochrane Database Syst Rev. 2003 Apr;(2):CD002217. https://doi.org/10.1002/14651858.CD002217

28. Werhahn KJ, Trinka E, Dobesberger J, Unterberger I, Baum P, Deckert-Schmitz M, et al. A randomized, double-blind comparison of antiepileptic drug treatment in the elderly with new-onset focal epilepsy. Epilepsia. 2015 Mar;56(3):450-9. https://doi.org/10.1111/epi.12926

29. Pohlmann-Eden B, Marson AG, Noack-Rink M, Ramirez F, Tofighy A, Werhahn KJ, et al. Comparative effectiveness of levetiracetam, valproate and carbamazepine among elderly patients with newly diagnosed epilepsy: subgroup analysis of the randomized, unblinded KOMET study. BMC Neurol. 2016 Aug;16(1):149. https://doi.org/10.1186/s12883-016-0663-7

30. Nicholas JM, Ridsdale L, Richardson MP, Ashworth M, Gulliford MC. Trends in antiepileptic drug utilisation in UK primary care 1993-2008: cohort study using the General Practice Research Database. Seizure. 2012 Jul;21(6):466-70. https://doi.org/10.1016/j.seizure.2012.04.014

31. Assis T, Bacellar A, Costa G, Pires E, Nascimento O. Predictors of early seizure recurrence among elderly inpatients admitted to a tertiary center: a prospective cohort study. Epilepsy Behav. 2019 Sep;98(Pt A):145-52. https://doi.org/110.1016/j.yebeh.2019.07.004

32. Savica R, Beghi E, Mazzaglia G, Innocenti F, Brignoli O, Cricelli C, et al. Prescribing patterns of antiepileptic drugs in Italy: a nationwide population-based study in the years 2000-2005. Eur J Neurol. 2007 Dec;14(12):1317-21. https://doi.org/10.1111/j.1468-1331.2007.01970.x

33. Leppik IE, Birnbaum AK. Epilepsy in the elderly. Ann N Y Acad Sci. 2010 Jan;1184:208-24. https://doi.org/10.1111/j.1749-6632.2009.05113.x

34. Bleck TP. Seven questions about stroke and epilepsy. Epilepsy Curr. 2012 Nov-Dec;12(6):225-8. https://doi.org/10.5698/1535-7511-12.6.225