Persistence with antiepileptic drugs in epilepsy patients treated in neurological practices in Germany

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ABSTRACT

Objective: The goal of this study was to analyze the persistence with antiepileptic drugs (AED) and associated factors in patients followed in neurological practices in Germany.
Methods: This study included patients aged 18 years or over who received two initial diagnoses of epilepsy and a first prescription of AED between 2007 and 2015 in a neurological practice (index date). The main outcome measure was the rate of AED persistence within five years of the index date. Kaplan–Meier analyses were performed to study treatment persistence as a function of age. A Cox proportional hazards regression model was used to estimate the relationship between non-persistence and demographic/clinical variables.
Results: A total of 8192 patients followed in neurological practices were included. After five years of follow-up, 41.1% (≤40 years), 45.2%, (41–60 years) and 50.1% (>60 years) of patients followed in neurological practices were persistent (log-rank p-value < 0.001). A negative association was found between discontinuation and age (≤40 years vs. >60 years: OR = 1.19, 95% CI: 1.09–1.31; 41–60 years vs. >60 years: OR = 1.10, 95% CI: 1.01–1.19). Furthermore, patients receiving old AED (OR = 1.16, 95% CI: 1.01–1.34) or gabapentin (OR = 1.46, 95% CI: 1.16–1.83) and those diagnosed with depression (OR = 1.12, 95% CI: 1.03–1.21) were at a higher risk of non-persistence, whereas those receiving levetiracetam (OR = 0.69, 95% CI: 0.60–0.80) or lamotrigine (OR = 0.88, 95% CI: 0.79–0.97) and those with dementia (OR = 0.74, 95% CI: 0.65–0.83) were at a lower risk.
Conclusions: The rate of epilepsy patients persistent with AED was low after five years of treatment. Age, gender, co-morbidities, and drug characteristics were associated with this persistence.

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1. Introduction

Epilepsy is a chronic neurological disorder affecting around 50 million people in the world [1]. Approximately 2.4 million new cases are diagnosed each year worldwide. In Germany, the annual cost of antiepileptic drugs (AED) exceeds €285 million, underlying the major socio-economic impact of this chronic condition [2].

To be effective, AED, which are prescribed to decrease the frequency of epileptic seizures, need to be taken on a long-term basis [3,4]. Several studies have underlined the fact that adherence remains suboptimal, indirectly leading to an increased risk of seizures [5–7]. Despite these studies focusing on treatment adherence, little is known about the persistence of such therapy. In 2014, Divino et al. showed in around 25,200 patients that approximately one third of them were persistent during the first year of AED treatment [8]. One year later, a study including 6793 U.S. veterans diagnosed with epilepsy discovered that individuals receiving gamma-aminobutyric acid analogs or compounds with multiple mechanisms of action were more likely to discontinue their treatment compared to those receiving sodium channel blockers [9]. More recently, Lai and colleagues found that AED persistence ranged from 219 days (gabapentin) to 276 days (oxcarbazepine) during the first year of treatment [18]. Although these three studies are of great interest, none of them was conducted in Europe or focused on identifying potential risk factors associated with such non-persistence.

Therefore, the goal of this study was to analyze the persistence with AED and associated factors in patients followed in neurological practices in Germany.

2. Methods

2.1. Database

The Disease Analyzer database (QuintilesIMS) compiles drug prescriptions, diagnoses, and basic medical and demographic data obtained directly and in anonymous format from computer systems used in physicians' practices [10]. Diagnoses (ICD-10), prescriptions (Anatomical Therapeutic Chemical [ATC] Classification System), and the quality of reported data are monitored by QuintilesIMS based on a number of criteria

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(e.g., completeness of documentation, linkage between diagnoses and prescriptions).

In Germany, the sampling methods used for the selection of physicians' practices were appropriate for obtaining a representative database of physicians [10]. Finally, the database has already been used in several studies focusing on epilepsy [2,7,11].

2.2. Study population

This study included patients aged 18 years or over who received two initial diagnoses of epilepsy (ICD-10: G40) and a first prescription of AED (ATC Classification System: N03A) between January 2007 and December 2015 in 137 neurological practices (index date). Follow-up lasted for up to 1800 days and ended in December 2016. Individuals were excluded if they had been prescribed AED prior to the index date.

2.3. Study outcome measure

The main outcome measure of the study was the rate of AED persistence within five years of the index date. Persistence was estimated as therapy time without treatment discontinuation, which was defined as at least 180 days without any AED therapy. The persistence referred not only to the initial AED prescription but also to any subsequent AED prescriptions. A longitudinal dataset of medication supply was created for each individual patient. Hereby, the number of days of drug supply was calculated based on the quantity and dosage information associated with each prescription record. Initial AED drugs included valproate, levetiracetam, carbamazepine, gabapentin, lamotrigine, and other substances. Substances were divided into old AED, which began being marketed before 1980, and new AED. Drugs were further classified as branded, if marketed initially under patent protection, and generic versions sold by other companies after the expiration of patent protection.

2.4. Co-variables

Demographic data included age, gender, type of health insurance (private or statutory), and practice region (Eastern versus Western Germany). Co-occurring disorders were determined based on diagnosis (ICD-10 codes) for depression (F32–F33), anxiety disorder (F41), schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders (F20–29), disorders of adult personality and behavior (F60–F69), intellectual disabilities (F70–F79), dementia (F01, F03, G30), Parkinson's disease (G20–G21), headache (G43–G44), and alcohol abuse (F10).

2.5. Statistical analysis

Kaplan–Meier analyses were performed to study treatment persistence as a function of age in neurological practices. Individuals were censored at the time of loss to follow-up or treatment discontinuation, whichever occurred first. A Cox proportional hazards regression model was used to estimate the relationship between non-persistence and the demographic and clinical variables previously described. A p-value < 0.05 was considered statistically significant. All analyses were carried out using SAS 9.3 (SAS Institute, Cary, USA).

3. Results

Patient characteristics are shown in Table 1. A total of 8192 patients followed in neurological practices were included in the present study. The mean duration of therapy was 813 days (SD 682 days). After one year of follow-up, 62.4%, 64.4%, and 70.9% of patients aged ≤40, 41–60, and >60 years, respectively, were persistent (log-rank p-value < 0.001). After five years of follow-up, 41.1%, 45.2%, and 50.1% of patients aged ≤40, 41–60, and >60 years, respectively, were persistent (log-rank

Table 1
Characteristics of epilepsy patients prescribed antiepileptic drugs in neurological practices in Germany.

Variable	Patients
N	8192
Demographic characteristics	
Age (mean, SD)	57.7 (18.9)
≤40 years (N, %)	1707 (20.8)
41–60 years (N, %)	2697 (32.9)
>60 years (N, %)	3788 (46.2)
Female (N, %)	4350 (53.1)
Male (N, %)	3842 (46.9)
Place of residence - Western Germany (N, %)	6382 (77.9)
Place of residence - Eastern Germany (N, %)	1810 (22.1)
Private health insurance coverage (N, %)	383 (4.7)
Statutory health insurance coverage (N, %)	7809 (95.2)
Comorbidity (N, %)	
Depression (ICD-10: F32–F33)	1842 (22.5)
Anxiety disorder (ICD-10: F41)	1131 (13.8)
Schizophrenia, schizotypal, delusional psychotic disorders (ICD-10: F20–29)	461 (5.6)
Disorders of adult personality and behavior (ICD-10: F60–F69)	371 (4.5)
Intellectual disabilities (ICD-10: F70–F79)	518 (6.3)
Dementia (ICD-10: F01, F03, G30)	1098 (13.4)
Parkinson's disease (ICD-10: G20, G21)	535 (6.5)
Headache (ICD-10: G43–G44)	649 (7.9)
Alcohol abuse (ICD-10: F10)	444 (5.4)
Drug characteristics (last prescription prior to discontinuation) (N, %)	
Old AED	3429 (41.9)
New AED	4763 (58.1)
Branded AED	1831 (22.4)
Generic AED	6361 (77.6)
Most frequently prescribed substances (last prescription prior to discontinuation)	
Levetiracetam	2221 (27.1)
Valproate	1657 (20.2)
Lamotrigine	1158 (14.1)
Carbamazepine	1043 (12.7)
Gabapentin	472 (5.8)
Other substances	1641 (20.0)

AED: antiepileptic drug; ICD10: International Classification of Diseases, 10th edition; SD: standard deviation.

p-value < 0.001, Fig. 1). Table 2 displays the results of the Cox proportional hazard regression model. Patients aged ≤40 (OR = 1.19) and 41–60 years (OR = 1.10) were at a higher risk of discontinuation than those aged >60 years in both practices. This risk was not significantly higher in women than in men (OR = 1.05). Individuals receiving old AED displayed a higher likelihood of discontinuation than those receiving new AED (OR = 1.16). Gabapentin was associated with a higher risk of discontinuation compared to valproate (OR = 1.46),
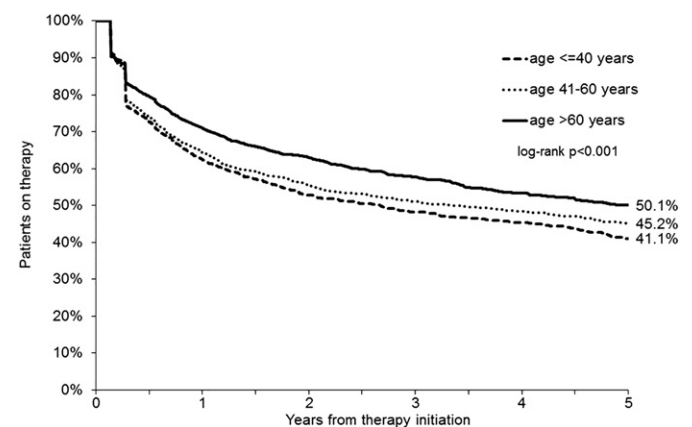

Fig. 1. Kaplan–Meier curves for persistence with antiepileptic drugs in epilepsy patients by age group after five years of follow-up in neurological practices in Germany.