Seizure 41 (2016) 9–15

Contents lists available at ScienceDirect

Seizure

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

Guideline conform initial monotherapy increases in patients with focal epilepsy: A population-based study on German health insurance data

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ARTICLE INFO

Article history:
Received 7 April 2016
Received in revised form 29 June 2016
Accepted 4 July 2016

Keywords:
Clinical practice guideline
Epilepsy
Seizure
Epidemiology

ABSTRACT

Purpose: To examine the implementation of the clinical practice guideline "first epileptic seizure and epilepsy in adulthood" published in 2008 to patients with newly diagnosed epilepsy between 2008 and 2014.

Method: This retrospective, population-based analysis was performed on patient data of 4.1 million insurants from the German statutory health insurance. Prevalent and incident cases in adults were identified based on ICD-10 codes, using a hierarchical diagnosis selection algorithm. The first anticonvulsive agent in a newly diagnosed epilepsy patient was validated against the clinical practice guideline.

Results: We determined an annual crude prevalence rate in adults between 0.946% and 1.090% and incidence rates of at least 156 per 100,000. A significant increase in guideline compliant monotherapy was found in patients with a focal epilepsy syndrome, while, among patients with idiopathic generalised epilepsies, the share of guideline noncompliant monotherapy increased. Both changes are likely due to the overall increase in prescription of levetiracetam from 19.6% in 2008 to 58.9% in 2014 in all newly treated patients. Overall, the proportion of enzyme-inducing anticonvulsants fell significantly from 20.7% in 2008 to 4.3% in 2014 ($p < 0.001$). The likelihood to receive non-enzyme-inducing antiepileptic drugs was 5.82 (95% CI 4.62–7.33) higher in 2014 than in 2008.

Conclusion: Initial monotherapy for focal epilepsy is in line with current clinical practice guidelines and mainly implemented by prescription of levetiracetam. Further evaluations should address the question of whether patients treated in line with the guidelines have a favorable outcome, compared to patients not treated in line with current guidelines.

1. Introduction

Epilepsy is a common and chronic neurological disorder that imposes a substantial burden on individuals and society as a whole. The initial diagnosis of epilepsy is associated with costs of diagnostic procedures, inpatient admission and related loss of income [1,2]. Even after a first seizure or with newly established diagnosis of epilepsy, patients are affected by social stigma, reduced employment opportunities and impaired quality of life for themselves and their caregivers, resulting in increased indirect and intangible costs [3–8].

Antiepileptic drugs (AEDs) are the central and crucial element in the treatment of epilepsy patients. The majority of patients require an anticonvulsant treatment for an extended period of time, and up to 30% of patients remain refractory, despite optimal medical treatment [9,10]. Economic evaluations are particularly important in patients with newly diagnosed and active epilepsy, as these patients account for a high proportion of total costs [11–15].

To allow for the best possible therapy in patients with neurological diseases, the German Neurological Society (Deutsche Gesellschaft für Neurologie [DGN], Berlin) has been regularly publishing clinical practice guidelines since 2002. In general, guidelines are viewed by physicians as helpful in terms of increasing the quality of patient care, education and the presentation of information without bias [16,17]. However, there

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http://dx.doi.org/10.1016/j.seizure.2016.07.001
1059-1311/

Table 1
Epilepsy syndromes with corresponding ICD-10 codes and recommendation for initial anticonvulsant monotherapy according to clinical practice guidelines and authorisation status as of 2008.

Epilepsy syndrome	ICD-10 codes	Anticonvulsants considered as first choice
Idiopathic/genetic	G40.3	LTG, TPM, VPA
Focal/structural-metabolic	G40.1, G40.2	LEV, LTG, OXC
Unknown reason	G40.6, G40.7, G40.8, G40.9	LEV, LTG, TPM, VPA
Lennox-Gastaut-Syndrome	G40.4	VPA

LEV = levetiracetam, LTG = lamotrigine, OXC = oxcarbazepine, TPM = topiramate, VPA = valproate, OXC was assumed as first choice in focal epilepsy as there was non-significant advantage of LTG compared with OXC in the SANAD study [19], furthermore OXC was recommended by the Vademecum Antiepilepticum [23].

is no data on the implementation of clinical practice guidelines regarding anticonvulsive treatment in epilepsy patients.

In 2007, the pivotal SANAD studies [18,19] and a randomised controlled trial comparing carbamazepine extended-release with levetiracetam [20] were published. As a consequence, the German clinical practice guidelines on epilepsy published in 2008 [21,22] named certain drugs as the first choice (i.e. lamotrigine and levetiracetam in focal epilepsy), warned against using strong enzyme-inducing drugs (i.e. carbamazepine, phenytoin or phenobarbital) and warned against use of valproate in women of childbearing age. Table 1 shows anticonvulsive treatment options according to authorisation status of each individual drug for initial monotherapy as of January 1st, 2008 and recommendations from the guidelines. Oxcarbazepine was assumed as first choice in focal epilepsy as there was non-significant advantage of lamotrigine compared with oxcarbazepine in the SANAD study [19], furthermore oxcarbazepine was recommended by the Vademecum Antiepilepticum [23].

The aim of this study is to examine the implementation of the clinical practice guidelines "first epileptic seizure and epilepsy in adulthood" [21] published in 2008 for patients with newly diagnosed epilepsy between 2008 and 2014. This evaluation is performed on the research database of Gesundheitsforen Leipzig that covers more than 4.1 million German insurants in the statutory health insurance (Gesetzliche Krankenversicherung [GKV]). This top-down approach, for the first time, allows for the examination of a high number of patients affected by epilepsy in Germany.

2. Methods

This retrospective analysis was conducted on the research database of Gesundheitsforen Leipzig that provides access to data of statutory health insurance from approximately 4.1 million insurants (i.e. 5.1% of the overall German population). Information related to in- and outpatient diagnoses, medication, costs, procedures and demographics is regularly collected and routinely inspected for outliers, data errors and changes over the years. The research database is continuously evaluated for its representativeness by comparison with the annual publications of the German Federal Social Insurance Office (Bundesversicherungsamt [BVA]) and has already been used for epidemiological studies [24]. This analysis was performed on consecutive insurance years from 2007 to 2014 in adult patients (≥18 years of age).

2.1. Identification of study population with epilepsy

The study population was identified by the presence of ICD-10-GM (10th revision of the International Statistical Classification of Diseases and Related Health Problems, German Modification, www.dimdi.de) codes for epilepsy (G40*). As there are no significant differences in epilepsy codes between the ICD-10 and ICD-10-GM systems at the third or fourth digit level, the term ICD-10 is used throughout this article. To ensure the validity of epilepsy classification, a patient has to meet the requirement of an ensured diagnosis, which is composed of at least one inpatient G40* diagnosis or two confirmed outpatient G40* diagnoses. A similar process of epilepsy case identification was used in Canadian evaluations based on ICD-10 coding and validation showed sensitivity and positive predictive value of up to 98% [25–29]. To avoid bias due to psychiatric comorbidities, patients with organic, including symptomatic, mental disorders (F00–F09), mental and behavioural disorders due to psychoactive substance use (F10–F16, F18–F19), schizophrenia, schizotypal and delusional disorders (F20–F29), manic episodes (F30) and bipolar affective disorder (F31) were excluded from the analysis.

2.2. Identification of newly diagnosed epilepsy

To analyse the implementation of the clinical practice guidelines [21], newly diagnosed epilepsy patients had to be identified. Four different methods, with increasingly stringent inclusion criteria, were applied to identify newly diagnosed patients during the whole observation period from 2008 to 2014. Method 1 assigns a newly diagnosed epilepsy to patients if there has been no ensured epilepsy diagnosis in the previous year of observation (i.e. one-year-incidence). Method 2 attributes a newly diagnosed epilepsy to patients if there is no ensured epilepsy coding in the preceding two years (i.e. two-year-incidence). Method 3 attributes a newly diagnosed epilepsy to patients if neither an ICD-10 diagnosis of epilepsy nor treatment with AEDs is present in the preceding year of identification (i.e. one-year-incidence-noAED). Method 4 accounts for patients where neither an ICD-10 diagnosis of epilepsy nor treatment with AEDs is present for two years (i.e. two-year-incidence-noAED). Thus, the incidence for method 1 and 3 can be provided from 2008 onwards, while, for method 2 and 4, it can be provided from 2009 onwards.

2.3. Determination of epilepsy syndromes

The determination of an epilepsy syndrome based on ICD-10 diagnoses is complicated by the mixture of seizure classification with the classification of syndromes. Furthermore, there is no exact correspondence between ICD-10 codes for epilepsy and the epilepsy syndrome [30] and seizure [31] classification defined by the International League Against Epilepsy (ILAE) in the eighties or with the latest terminology and concepts for organisation of seizures and epilepsies, revised in 2009 [32]. The ICD-10 code was used to determine four main groups with focal or structural-metabolic epilepsy corresponding to ICD-10 G40.1 or G40.2, idiopathic or genetic generalised epilepsy corresponding to ICD-10 G40.3, specific epilepsy syndromes corresponding to ICD-10 G40.0, G40.4 and G40.5, and unknown epilepsy syndromes corresponding to ICD-10 G40.6 to G40.9. The basic assumption is to overrule less specific diagnoses by more specific diagnosis. For this purpose, we developed a hierarchical approach to specify a set of epilepsy diagnoses. The hierarchical diagnosis selection algorithm is represented in Fig. 1. If a patient presented with both G40.1/2 and G40.3 then the patient was assigned to the majority class of diagnoses. An additional group of "unspecific G40.1/2/3" was introduced if the selection was ambiguous. Finally, patients having only ICD-10 diagnoses G40.6 to G40.9 were assigned to the group of "unknown epilepsy syndrome". Patients with ICD-10 G40.0 were not further analysed, as this code for idiopathic focal epilepsies is predominantly present in children and adolescents.