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Factors associated with treatment non-adherence in patients with epilepsy in Brazil

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ABSTRACT

Purpose: To investigate factors associated with treatment non-adherence in Brazilian patients with epilepsy.
Methods: Prospective cross-sectional study. We evaluated 385 epilepsy outpatients in a tertiary referral center, 18 years or older, literate, without cognitive impairment or active psychiatric disorders, who were independent in daily living activities. Data were analyzed with correlation tests and conjoint analysis using multivariate logistic regression.
Results: Non-adherence rate, measured by the Morisky–Green Test, was 66.2%, a moderate-to-low adherence level. Non-adherence was higher in men, in younger patients and in patients with uncontrolled seizures. Increasing treatment complexity was also associated with decreased treatment adherence.
Conclusion: Strategies designed to improve treatment adherence should address peculiarities associated with younger ages and male gender. Physicians should be made aware that prescription of less complex treatment regimens may result in better treatment adherence, and, therefore, better seizure control. The challenge in adjusting AED treatment in this population is to minimize treatment complexity, thus increasing chances for treatment adherence.

1. Introduction

Long-term antiepileptic drugs (AEDs) remain the mainstay of epilepsy treatment. AEDs eliminate or reduce seizure frequency in up to 67% of patients.[1] Medication treatment for chronic diseases, such as epilepsy, requires that patients incorporate complex medication regimens into their daily routines. Managing medication schedules may pose a significant burden in patients' lives.[2] AED choice should therefore be tailored to patients' factors that may limit medication use, such as tolerability, treatment adherence and side effect profile.

Non-adherence to medication treatment regimens is a worldwide health problem. Non-adherence rates among patients with epilepsy range from 30% to 50%.[3] Clinicians treating patients with epilepsy note that non-adherent patients report more difficulty in attaining seizure control compared to adherent patients. Uncontrolled seizures lead to major morbidity and mortality, including not only physical injury, such as head trauma, fractures and burns, but also psychosocial problems, such as depression, anxiety disorders, decreased quality of life, and sudden unexpected death. Even though educating patients to strictly follow medication regimens is key to epilepsy treatment,[3] intentional non-adherence may also interfere with seizure control.[4]

Lack of seizure control is influenced by epilepsy etiology, seizure type, comorbidities, and treatment non-adherence.[5] Treatment adherence is affected by individual patient factors (demographic and socioeconomic features, as well as perception and beliefs about epilepsy), disease features (seizure frequency and severity), medication use (number of daily doses and side effects), and factors related to patient–provider relationship.[6] Seizure control is also affected by the treatment gap, defined as the proportion of people with epilepsy who require treatment but do not receive it. Treatment gap is influenced by access to and quality of medical care, as well as cultural differences and stigma associated with epilepsy.[7]

Non-adherence studies in patients with epilepsy have not systematically accounted for the wide range of variables related to patients, disease, and treatment features. Few studies have been conducted in Brazil on treatment non-adherence in patients with

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epilepsy. Identifying adherence related factors allows development of strategies to improve treatment adherence, with consequent better seizure control.

We studied treatment non-adherence factors in patients with epilepsy and determined its association with patients, disease, treatment features, as well as with social support issues.

2. Methods

The study was approved by the institutional review board (CAPPesq, Process number 210/09), and was performed in accordance with the 1964 Declaration of Helsinki (and succeeding revisions) ethics parameters. Written informed consent was obtained from all patients prior to study inclusion. Anonymity was assured.

This is a prospective, cross-sectional study using descriptive and correlation analyses, conducted in an epilepsy outpatient clinic in a university-affiliated, tertiary referral hospital in São Paulo, Brazil. This clinic receives referrals from other specialty clinics from the Hospital Complex and from neurologists in the public system. Most patients are referred if patients' seizures are not controlled after perceived optimal treatment with antiepileptic drugs. Since January 2002, 4882 new cases have been evaluated, and, as of July 2012, 1851 patients were followed in the clinic. Patients who attain seizure control or are considered optimally controlled are counter-referred to the original service. This clinic population is, therefore, heavily biased toward very refractory epilepsy cases.

Eligibility criteria were: diagnosis of epilepsy according to the International League Against Epilepsy (ILAE) criteria,[8] age $\geq$18 years, independence in daily living activities, and absence of major cognitive impairment or active psychiatric disorders. These inclusion criteria were chosen to ensure that patients would be able to understand and respond to questions from the study instruments, which were read to the patient. Exclusion criteria were: presence of a rapidly progressing neurological or medical disorder, history of psychiatric syndromes that could limit participation, coexisting non-epileptic psychogenic seizures, patients not receiving AEDs, and a history of significant substance abuse within the past year.

Sampling was nonrandom. Patients were invited to participate while waiting for the medical consult on Epilepsy Clinic days. All patients fulfilling eligibility criteria, and who attended the epilepsy clinic after study onset were included in the study, until the estimated enrolment number of patients was reached. All patients who met eligibility criteria and attended the epilepsy clinic between July 2009 and February 2010 (n = 385 patients) were included in the study.

2.1. Sample size calculation

To calculate sample size, non-adherence rate was chosen as the primary endpoint. We calculated a conservative sample size, assuming a 50% non-adherence rate, with a 95% confidence interval and a 5% significance level. This yielded a sample size of 385 patients.[9]

Therapeutic adhesion was considered the dependent variable. Morisky–Green Test was used to assess treatment adherence.[10] This is a simple four-item questionnaire assessing non-adherence behavior. Adherence was classified as high if all four questions were answered as "no", moderate if one or two questions were answered as "yes", and low if more than two questions were answered as "yes". Patients with moderate or low adherence were considered non-adherent.

Independent variables included demographic, disease-related, family support, medication related, and health care system variables.

Demographic variables included: age (in years, on the interview day); gender, marital status, categorized as married (in a stable relation) or unmarried (single, widowed or separated); race, self-referred as White (including Asians) or non-White; religion was based on self-classification as religious or nonreligious; education was categorized as 4 or less years of schooling and more than 4 years of schooling; work status was categorized as employed (included self-employed) or not employed (retired, unemployed, on health-benefit, never employed, student and homemaker); per capita income was calculated according to patient's information regarding total family income divided by the number of people living on this income.

Disease related variables included: medical diagnosis (obtained through chart review, considering ILAE classification),[8] disease and treatment duration in years (including periods without AED treatment), previous 30-day seizure frequency (according to patient's information, categorized as at least one seizure in the previous 30 days or no seizures during this period), patient perception of seizure control (categorized as controlled or uncontrolled/not always controlled), seizure control (classified as controlled: no seizures in the previous 6 months or uncontrolled: at least one seizure in the previous 6 months).

Family support was categorized as continuous/almost continuous friends and family support or rare/absent support.

Medication related included number of AEDs (categorized as mono- or polytherapy), therapeutic complexity (measured by the EMTCI scores, according to the original instrument's scoring guide).[11]

The EMTCI is a specifically designed tool to assess medication regimen complexity in adult patients with epilepsy. EMTCI is a four-item questionnaire, which collects information on medication use, medication administration frequency, and special directions and actions to ensure that medications are taken as prescribed. The Brazilian-Portuguese version of the EMTCI, adapted for use in Brazil, has shown good reliability and validity.[12]

Healthcare related variables included access to medication (public system or private), action taken when medication is not accessible (categorized as does not take medication or buys medication/obtains from alternative source), frequency of medical visits (expressed in days), difficulty to obtain physician's appointment (categorized by the patient as easy or difficult), unscheduled clinic visit (categorized as always available/never needed or rarely/never available), quality of medical care (categorized as very good/good or bad/no opinion) and perception of health status since initiating treatment in the clinic (much better/better or slightly better/no improvement/does not know).

2.2. Statistical analysis

Statistical analysis was carried out with the Statistical Package for the Social Sciences (SPSS) 18.0 (SPSS Inc., Chicago, IL, USA). Association between treatment adherence and nominal independent variables was tested with Pearson's chi-square test or likelihood ratio statistics. Data were tested for normal distribution with the Kolmogorov–Smirnov test and for homogeneity of variances. Comparisons of means between high and moderate-to-low adherence groups were performed with Student's t-test when variables were normally distributed; otherwise, non-parametric Mann–Whitney test was applied.

Backward stepwise multiple logistic regression analysis was used to identify factors associated with treatment non-adherence. Variables associated with non-adherence ($p < 0.20$) were included in the model. Model adequacy was measured with receiver-operating characteristics (ROC) under the curve area. Statistical tests were performed with a 5% significance level ($p < 0.05$).