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Concomitant therapy in people with epilepsy: Potential drug–drug interactions and patient awareness

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ABSTRACT

People with epilepsy (PWE) may use prescription and over-the-counter (OTC) drugs for the treatment of concomitant diseases. Combinations of these drugs, as well as dietary supplements, with antiepileptic drugs (AEDs) may lead to reduced control of seizures and of coexisting medical conditions and increased risk of adverse drug reactions (ADRs). The aims of this study were to obtain comprehensive lists of medications, dietary supplements, botanicals, and specific food components used by adult PWE and to evaluate the potential for interactions involving AEDs and patients' awareness of such potential interactions. We conducted a prospective, questionnaire-based study of PWE attending the Hadassah-Hebrew University Epilepsy Clinic over a period of 7 months. The questionnaire interview included the listing of medications, medicinal herbs, dietary supplements, and specific food components consumed and the knowledge of potential drug–drug interactions (DDIs), and it was conducted by a pharmacist. Drug–drug interactions were analyzed via the Micromedex online database. Out of 179 patients who attended the clinic over the study period, we interviewed 73 PWE, of which 71 were included in our final analysis. The mean number of AEDs consumed per subject was 1.7 (SD: 0.8, range: 1–4). Forty (56%) subjects were also treated with other prescription and/or OTC medications, and thirty-four (48%) took dietary supplements. Drug families most prone to DDIs involving AEDs included antipsychotic agents, selective serotonin reuptake inhibitors, and statins. Two-thirds of study participants (67%) knew that DDIs may lead to ADRs, but only half (56%) were aware of the potential for reduced seizure control. Only 44% always reported treatment with AEDs to medical professionals. This study provides for the first time a comprehensive picture of prescription and OTC drugs and food supplements used by PWE. Despite a considerable potential for DDIs involving AEDs, patient awareness is limited, highlighting the importance of patient and caregiver education.

1. Introduction

Monotherapy with antiepileptic drugs (AEDs) remains the mainstay for the initial treatment of epilepsy. However, 17–21% of people with epilepsy (PWE) and about 50% of patients with refractory epilepsy are treated with a multiple AED regimen [1–5]. Furthermore, many PWE receive polytherapy for the treatment of concomitant medical conditions. As a group, PWE use more medications on average compared to the general population [6,7]. For example, in a study based on a comprehensive patient-centered database, 23% and 39% of male and female PWE, respectively, took five or more prescription medications, whereas only 2% and 3% of males and females in the general population took these many medications [6]. Commonly used comedications included statins, calcium channel blockers (CCBs), and selective serotonin reuptake inhibitors (SSRIs). A multicenter study among patients with refractory epilepsy attending tertiary referral centers in Italy reported that 32% of adults and 17% of children are comedicated for indications other than epilepsy [8]. However, databases do not include over-the-counter (OTC) medications and supplements, and patients do not always voluntarily report to their physicians about the consumption of supplements and alternative medicines [9]. These findings were evaluated in separate studies, which did not describe the nature of AEDs or other medications used, estimating a combined prevalence of herb and dietary supplement consumption by PWE at 10% to 56% [9–12].

As a group, AEDs are highly prone to drug–drug, drug–dietary supplement, and drug–food interactions [13]. Drug interaction compendia such as 'Drug Interactions: Analysis and Management' [14] and the Micromedex online database [15] mention over 1000 drug interactions involving AEDs. Natural products are also susceptible to significant interactions with AEDs [16]. Drug–drug interactions (DDIs) involving AEDs may be pharmacokinetic, pharmacodynamic, or both.

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These interactions are often hazardous because they may lead to adverse drug reactions (ADRs), loss of seizure control, or loss of control of other diseases [17,18]. Among a list of 25 clinically important serious DDIs identified by an expert panel in 2004, two involved AEDs, carbamazepine (CBZ)–propoxyphene and barbiturates–warfarin [19]. Clinicians' awareness of these DDIs ranked 4.2 and 3.0 out of 10.0, respectively. Likewise, a cross-sectional questionnaire study in a convenience sample of 148 women with epilepsy of reproductive age (18–44) presenting for routine outpatient care demonstrated that these patients have limited knowledge of potential interactions between AEDs and oral contraceptives (OCs) [20].

Given the great variety of possible interactions involving AEDs, it is important to determine which AED interactions and AED-related patient behaviors require special attention, in terms of physician and patient education. Therefore, more data are needed on the most commonly consumed therapeutic products by PWE and on current patient knowledge on potential interactions between these and concomitant AEDs. The aim of this study was to obtain, for the first time to our knowledge, comprehensive lists of concomitant medications, dietary supplements, botanicals, and specific food components used by adult PWE, through an interview with a pharmacist and inspection of each patient's medication bag. We then evaluated the potential interactions involving AEDs, the patient's awareness of such interactions, and the patient's actions toward minimizing them.

2. Methods

2.1. Overview

This was a prospective study, entailing the gathering of data regarding AED and non-AED therapies in PWE, by questionnaire interview and inspection of the patient's medication bag conducted by a pharmacist. Patient enrollment began on February 1st, 2012 and ended on August 31st, 2012. The study was approved by the Institutional Review Board of the Hadassah-Hebrew University Medical Center, Jerusalem, Israel, and conducted in accordance with their guidelines. All subjects gave written informed consent.

2.2. Patients

The study included patients treated at the Epilepsy Outpatient Clinic of Hadassah-Hebrew University Medical Center, willing and capable of undergoing an interview with an estimated duration of 30 min, as expressed by prior written informed consent. The patients had been firmly diagnosed with epilepsy, were treated with at least one AED, were themselves capable of understanding and answering the questions of the questionnaire in English or Hebrew, or were accompanied by a relative or a caregiver capable of understanding and answering the questions of the questionnaire in Hebrew or English.

Patients were contacted by phone 2–3 days prior to the planned physician's appointment by the researcher in charge of conducting the questionnaire survey, as a reminder from the Department of Neurology at Hadassah Medical Center that the patient had an upcoming appointment to see the neurologist and that the patient's medication bag was requested for review. Potential volunteers were then approached before or following their appointment, after being identified by prior screening of medical records or during the patient–physician encounter. Upon meeting with patients, the purpose and methodology of the questionnaire interview were first explained, and informed consent was acquired.

2.3. Data acquisition

A questionnaire interview of approximately 30 min was conducted. The questions were divided into 5 sections: a) list of AEDs taken by the patient, length of therapy, dosage and regimen, ADRs, and comments; b) list of comedications taken by the patient, length of therapy, dosage and regimen, ADRs, and comments; c) self-perceived effects of epilepsy treatment; d) knowledge of specific interactions including AEDs; and e) action taken in order to minimize such interactions.

The patients' medical files were screened for acquisition of personal data, including age, gender, level of education, medical background, type of epilepsy, pharmacoresistance of epilepsy, and medication list. Level of education was defined as high or low depending on whether the study participant was or was not possessive of higher educational schooling (following high school) or of an occupation that requires a higher education. The type of epilepsy was determined as being primary generalized, focal-temporal, focal-extratemporal, or unknown, according to the ILAE criteria [21].

2.4. Database screening of drug–drug interactions (DDIs)

The Micromedex (DRUG-REAX) online database [15] was consulted for DDIs between medications. Drug–drug interactions were assigned with degrees of severity and quality in accordance with the listing in the database. Interactions were recorded according to the clinical significance, defined as interactions with a severity rating of moderate or major and a quality of evidence rating of good or excellent. Drug–drug interactions rated as minor in severity or fair in quality of evidence were excluded. Whenever necessary, we employed the PubMed online database for further information.

Drug–drug interactions were categorized as AED–AED DDIs, AED–non-AED DDIs, AED–supplement interactions, or AED–food/smoking interactions. Antiepileptic drugs were categorized as enzyme-inducing AEDs (EIAEDs; phenytoin — PHT, CBZ, phenobarbital — PB, and primidone — PRM) and non-EIAEDs (all other AEDs: valproic acid — VPA, ethosuximide — ETX, clonazepam — CLN, clobazam — CLB, lamotrigine — LTG, topiramate — TPM, oxcarbazepine — OXC, gabapentin — GBP, pregabalin — PGB, levetiracetam — LEV, zonisamide — ZSN, rufinamide — RFN) [6]. Although high-dose TPM may induce hepatic drug metabolizing enzymes [13], it was categorized as a non-EIAED, as described previously [6].

2.5. Statistical analysis

The Mann–Whitney test and Fisher's exact test were used for comparisons of sequential and categorical variables, respectively. The results are reported as mean ± standard deviation (SD), unless otherwise indicated. A P-value ≤ 0.05 was considered significant.

3. Results

A total of 179 PWE attended the outpatient clinic during the study period. Among these, 73 met the inclusion criteria, signed the informed consent form, and underwent the interview. Of the 73 study participants, two were not included in our analysis because of incomplete questionnaire interviews.

Compiled demographic data are presented in Table 1. The majority of patients were women, and most were possessive of higher education. Only 10 patients had not previously been to the epilepsy outpatient clinic. A total of 70% of the patients had focal epilepsy, and in only 11% of the patients, the type of epilepsy could not be determined. Almost half of the patients had pharmacoresistant epilepsy [22].

Thirty-eight (54%) of the study participants were treated for documented concurrent conditions. Among these, the most common were psychiatric and behavioral disorders (including depression, anxiety, psychotic disorders, and attention-deficit hyperactivity disorder; 42%), hypertension (25%), and hypercholesterolemia (18%) (data not shown). Forty-four of the patients (62%) brought their medication bag to the interview, as requested.

The mean number of AEDs used by the study participants was 1.7 (SD: 0.8, range: 1–4; Table 2). Forty (56%) were also treated with non-

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