



# Co-morbidity and clinically significant interactions between antiepileptic drugs and other drugs in elderly patients with newly diagnosed epilepsy

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## ABSTRACT

**Purpose:** A study was conducted to investigate the frequency of potential pharmacokinetic drug-to-drug interactions in elderly patients with newly diagnosed epilepsy. We also investigated co-morbid conditions associated with epilepsy.

**Method:** From the register of Kuopio University Hospital (KUH) we identified community-dwelling patients aged 65 or above with newly diagnosed epilepsy and in whom use of the first individual antiepileptic drug (AED) began in 2000–2013 ( $n = 529$ ). Furthermore, register data of the Social Insurance Institution of Finland were used for assessing potential interactions in a nationwide cohort of elderly subjects with newly diagnosed epilepsy. We extracted all patients aged 65 or above who had received special reimbursement for the cost of AEDs prescribed on account of epilepsy in 2012 where their first AED was recorded in 2011–2012 as monotherapy ( $n = 1081$ ). Clinically relevant drug interactions (of class C or D) at the time of starting of the first AED, as assessed via the SFINX-PHARAO database, were analysed.

**Results:** Hypertension (67%), dyslipidemia (45%), and ischaemic stroke (32%) were the most common co-morbid conditions in the hospital cohort of patients. In these patients, excessive polypharmacy (more than 10 concomitant drugs) was identified in 27% of cases. Of the patients started on carbamazepine, 52 subjects (32%) had one class-C or class-D drug interaction and 51 (31%) had two or more C- or D-class interactions. Only 2% of the subjects started on valproate exhibited a class-C interaction. None of the subjects using oxcarbazepine displayed class-C or class-D interactions. Patients with 3–5 (OR 4.22;  $p = 0.05$ ) or over six (OR 8.86;  $p = 0.003$ ) other drugs were more likely to have C- or D-class interaction. The most common drugs with potential interactions with carbamazepine were dihydropyridine calcium-blockers, statins, warfarin, and psychotropic drugs.

**Conclusions:** Elderly patients with newly diagnosed epilepsy are at high risk of clinically relevant pharmacokinetic interactions with other drugs, especially if exposed to carbamazepine, but these interactions can be controlled via rational drug choices and with prediction of the possible drug-to-drug interactions. Patients on dihydropyridine calcium-channel blockers, statins, warfarin, and risperidone face the highest risk of interactions.

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## 1. Introduction

Two of the most important challenges in the management of epilepsy in the elderly are dealing with co-morbid conditions and addressing potential pharmacokinetic drug–drug interactions between antiepileptic drugs (AEDs) and other medication [1–3].

Several studies have reported that somatic co-morbidity is commonplace among patients with epilepsy [4,5]. Hypertension, ischaemic heart disease, heart failure, cardiovascular disorders, stroke, diabetes,

gastrointestinal ulcers/bleeding, chronic pulmonary disease, and arthritis/rheumatism have been observed as being more prevalent among patients with epilepsy than in reference populations [6–9]. Elderly patients with newly diagnosed epilepsy differ greatly from younger patients with regard to co-morbidity, showing a high prevalence of hypertension and cardiovascular disorders [10]. A prior stroke and degenerative brain disorders, such as Alzheimer's disease, appear as common aetiologies of new-onset epilepsy in the elderly [10–13]. Co-morbidities in elderly patients with epilepsy are associated with increased health-care costs and also higher mortality rates [14,15].

The most common AEDs linked to interactions with other drugs are the first-generation ones: carbamazepine, phenobarbital, phenytoin,

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and primidone. These agents are potent inducers of hepatic drug-metabolising enzymes and may significantly decrease plasma concentrations of many psychotropic, immunosuppressant, antineoplastic, antimicrobial, and cardiovascular-disease drugs [16]. This may, in turn, lead to a decrease or even elimination of the therapeutic efficacy of other drugs unless their dosage is increased [17]. Valproic acid does not induce metabolising of hepatic enzymes in the elderly, but it can elevate concentrations of amitriptyline and nortriptyline, hence creating a risk of toxicity [18]. Most of the second- or third-generation AEDs are devoid of enzyme-inducing effects, and they only occasionally cause clinically significant pharmacokinetic interactions with other drugs [16]. Many drugs used in the treatment of hypertension, hyperlipidaemia, coagulation disorders, and psychiatric disorders in the elderly may exhibit interactions with AEDs that lead to adverse outcomes such as falling, fractures, and even increased mortality [3]. Nevertheless, there is great inter-individual variability in the clinical impact of interactions between AEDs and other medicines, because of genetic and environmental influences on drug metabolism [2].

There are only limited data available on the risk of interactions between AEDs and other drugs in populations with epilepsy [3,19], and, to our knowledge, only Pugh and colleagues (2010) [3] have investigated the issue among elderly patients who were newly diagnosed. Hence, we sought to investigate potential pharmacokinetic interactions of AEDs with selected drug classes in two large populations of elderly patients with new-onset epilepsy. We also studied co-morbid conditions associated with epilepsy.

## 2. Methods

### 2.1. The population and setting

Methods for the identifying patients for study have been previously described [5,20]. In summary, suitable subjects were identified from two sources: the case-record register of Kuopio University Hospital (KUH) and data from nationwide drug registers maintained by the Social Insurance Institution of Finland (SII). Included in the study were community-dwelling patients who had been diagnosed as having epilepsy, were aged 65 or above at the time of diagnosis of epilepsy; and had their first AED treatment started as monotherapy. Patients who lived in nursing homes or other long-term-care facilities at the time of the onset of epilepsy were excluded.

#### 2.1.1. The Kuopio University Hospital cohort

From the KUH register we included patients who had been diagnosed with epilepsy between 1.1.2000 and 31.12.2013. In total, 529 patients meeting the inclusion criteria were identified. The case records of the individuals identified were reviewed, and details on their demographic characteristics and medical data were gathered.

#### 2.1.2. The national cohort

The national health-insurance scheme covers all permanent residents of Finland. We collected nationwide data from the two drug registers maintained by the SII. The **Drug Reimbursement Register** was used to identify non-institutionalised patients who were entitled to reimbursement for AED medication's costs. The **Drug Purchase Register** covers all purchases of drugs prescribed by physicians with reimbursement under the National Sickness Insurance Scheme in Finland. The register data include information on drug class, quantity, and actual dispensing. Drugs are categorised in accordance with the Anatomical Therapeutic Chemical (ATC) classification system, developed by the WHO for drug-consumption statistics. According to the annual wholesale-statistics database compiled by the Finnish Medicines Agency, the SII Drug Purchase Register included data for 93.7% of all outpatient consumption of antiepileptics (N03) during the 2003 calendar year.

For purposes of the study, we extracted all patients aged 65 or above who had received special reimbursement for the cost of AEDs for epilepsy in 2012 where the first AED was recorded as monotherapy in 2011–2012 (AED treatment may have been started before reimbursement began). Only those subjects who had no record of AED purchases prior to those years were included. In this cohort, 1081 patient cases, throughout Finland, met these criteria.

#### 2.1.3. Data on co-morbid conditions

Validated ICD-10 code algorithms were used with the KUH cohort for identifying chronic somatic co-morbid conditions from which the patients were suffering on the date of the initial epilepsy diagnosis. Hence, conditions such as acute infections were not recorded. Diagnoses of somatic co-morbid conditions were confirmed by review of history and results of ancillary tests from case records. Psychiatric disorders were not recorded because diagnosis of these disorders, such as depression and anxiety, was mainly based on assessment of patients by non-psychiatry physicians.

#### 2.1.4. Evaluation of potential interactions with antiepileptic drugs

Only the three AEDs most commonly used by our patient populations (carbamazepine, oxcarbazepine, and valproic acid) were included in the analysis. The search for potential interactions between these AEDs and other drugs was restricted to agents used for chronic conditions. Specifically, possible use of calcium-channel blockers (dihydropyridine derivatives and diltiazem); statins; selected antipsychotic, antianxiety, and antidepressant drugs; warfarin; and opiates was evaluated. These drug classes were selected for their previously documented risk of clinically relevant interactions with AEDs [16]. Any other drugs for chronic conditions or used for acute conditions only, such as antibacterials for systemic use with infections, were not considered.

For the hospital cohort, electronic case records were used to identify current regular use of the medicines described above. Drugs that were used at the time of AED initiation and continued at the time of the first control visit (approximately 1–3 months after AED initiation) were recorded.

Using the national registers, we extracted data on drugs reimbursed for that were purchased on the same date as the first purchase of the first AED (or within three months of that) for all patients aged 65 or above who received special reimbursement for the cost of AEDs due to epilepsy.

The Swedish, Finnish, Interaction X-referencing (SFINX) interaction database, developed and used in Finland and Sweden, was used for assessing the possibility of clinically significant AED–other-drug interactions [21]. It covers approximately 16,000, mainly pharmacokinetic, interactions and is updated four times a year [22]. In Finland, SFINX is the main database and clinical decision tool that delivers information on potential drug interactions and their clinical relevance at the time of drug prescription. The drug-interaction details included in the SFINX database are based on extensive literature-based research with predefined inclusion and exclusion criteria. Interactions in the database are assigned to classes A–D on the basis of clinical relevance: A (green) = no data on any clinically relevant drug–drug interaction; B (grey) = an interaction of minor clinical importance; C (yellow) = a clinically relevant interaction that can be handled via, for example, dose adjustments (an interaction documented in controlled studies in appropriate patient populations); and D (red) = a clinically relevant interaction such that combination of the drugs should be avoided (an interaction documented in controlled studies in appropriate patient populations). Other medication and specific AEDs were linked to the SFINX database for checking for possible inter-drug interactions. The primary outcome was the number of potential interactions. The number of possible interaction pairs per patient (i.e., the total number of two-drug combinations that could be derived from all drugs used concomitantly during the follow-up period by an individual patient) was calculated.

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