

**EPIDEMIOLOGY OF ADULT EPILEPSY
IN TARTU, ESTONIA**

Incidence, prevalence and medical treatment

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LIST OF ORIGINAL PUBLICATIONS

- I Õun A, Haldre S, Mägi M. Incidence of adult epilepsy in Estonia. *Acta Neurologica Scandinavica* 2003; 108: 245–251.
- II Õun A, Haldre S, Mägi M. Prevalence of adult epilepsy in Estonia. *Epilepsy Research* 2003; 52: 233–242.
- III Õun A, Haldre S, Mägi M. Use of antiepileptic drugs in Estonia: an epidemiologic study of adult epilepsy. *European Journal of Neurology* (submitted).
- IV Õun A, Haldre S. Aktiivne epilepsia Tartu täiskasvanutel: epidemioloogilised näitajad ja ravi (in Estonian). *Eesti Arst* 2004; 83: 652–658.

ABBREVIATIONS

AED	antiepileptic drug
ATC	Anatomical Therapeutic Chemical classification
BB	benzobarbital
BZ	benzodiazepines
CBZ	carbamazepine
CEE	Central and Eastern Europe
CI	confidence intervals
CLB	clobazam
CNS	central nervous system
CZP	clonazepam
DDD	defined daily dose
EEG	electroencephalography
EHIF	Estonian Health Insurance Fund
ESM	ethosuximide
FAR	first attendance rate
GTCS	generalized tonic-clonic seizure
ILAE	International League Against Epilepsy
IR	incidence rate
LTG	lamotrigine
MMD	minimum maintenance dose
NWE	Northern and Western Europe
OXC	oxcarbazepine
PB	phenobarbital
PHT	phenytoin
PR	prevalence rate
PRM	primidone
SVSB	selective voltage-dependent sodium channel blocker
TPM	topiramate
TUH	Tartu University Hospital
VPA	valproate

I. INTRODUCTION

Epilepsy is a group of neurologic conditions, the common and fundamental characteristics of which are recurrent, usually unprovoked epileptic seizures (Commission 1993; Engel and Pedley 1997). It is widely acknowledged that, to the affected patient as well as to society, epilepsy is more than just seizures; no definition of epilepsy is definite or all-inclusive (Engel and Pedley 1997).

Epilepsy has profound physical, psychological, and social consequences (Scambler and Hopkins 1980; Eisenberg 1997). Lack of knowledge, misunderstanding, and negative attitudes toward epilepsy leading to low self-esteem, anxiety, depression, and feelings of stigmatization (Baker *et al.* 1996; Rätsepp *et al.* 2000). All these factors can reduce social, educational, and occupational activity, leading therefore to decreased quality of life (Cramer 1994; Baker *et al.* 1997; Herodes *et al.* 2001). The most significant predictors of poor health-related quality of life are poor seizure control, multiple seizure types, and associated handicaps (Herodes 2001). Although there is evidence that if seizures are well controlled and the condition is uncomplicated by handicap or any other disorder, the patients do not generally experience significant problems (Jacoby 1995).

Another aspect of epilepsy is its economic cost to society due to direct health care costs, as well as indirect losses in employment, and those arising from lives lived in disability, and lost years of life. It is estimated that 35% of the burden of all diseases in Europe (which is calculated as the sum of lost years due to mortality and disability) belongs to brain diseases – mainly stroke, unipolar depressive disorder, injuries, alcohol use disorders, dementias, etc. (Olesen and Leonardi 2003). The estimated burden of primary epilepsy is 0.5% for years lived in disability, and 0.4% for years of lost life; but it is important to note that epilepsy caused by other diseases and injuries was excluded from these figures (Leonardi and Bedirhan Ustun 2002; Olesen and Leonardi 2003). Furthermore, if we consider that epilepsy affects all ages, also including individuals with working capacity, epilepsy represents a significant, but largely hidden proportion of the economic burden of diseases.

It is widely acknowledged that the direct health care expenses for epilepsy have grown dramatically over the last decades (Heaney and Begley 2002) mainly due to introduction of new antiepileptic drugs, improved diagnostic techniques, and sophisticated case selection for surgical treatment, etc. Throughout the world, there is a growing interest in the cost-effectiveness of new management options (Jacoby *et al.* 1998; Begley *et al.* 2000; Heaney and Begley 2002), as well as in implementing evidence-based decisions into everyday practice (Grimshaw and Russell 1993; Murthy 2003).

In Estonia, the assessment of the social and economic burden and of the optimal use of resources are very serious considerations for health policy

(Haldre *et al.* 2003; Asser 2004). However, due to lack of correct statistics from CEE, all the abovementioned estimations of the burden and the direct cost are calculated using epidemiologic figures from Northern and Western Europe (NWE) (Leonardi and Bedirhan Ustun 2002; Olesen and Leonardi 2003). Since the estimated health and mortality indices in NWE are rather different to those in CEE populations (Bobak and Marmot 1996; Carlson 1998; Olesen and Leonardi 2003), and epilepsy-related epidemiologic measures are sensitive to socio-economic and demographic factors (Berg *et al.* 1996; Sander and Shorvon 1996; Heaney *et al.* 2002), specific characteristics of the disease in CEE countries may differ from those in NWE.

Epidemiologic figures for adults are not readily available in Estonia. A modern study on prevalence and incidence of epilepsy in Estonia has been carried out only on children (Beilmann *et al.* 1999a; Beilmann *et al.* 1999b). There are no previous studies concerning antiepileptic treatment in Estonia.

The purpose of the present study is to estimate incidence, prevalence and clinical characteristics of active epilepsy in a defined adult population in Estonia, and also to assess the antiepileptic therapy in an Estonian population.

II. REVIEW OF THE LITERATURE

1. General aspects and methodology

Epidemiology is the study of the distribution and determinants of diseases in human populations; it provides understanding about potential risk factors for a particular disease, and its incidence, prevalence, associated mortality and natural history (Commission 1997; Hauser 1997; Bell and Sander 2001; Feigin *et al.* 2004).

Usually epidemiology is divided into three domains: descriptive, analytical and experimental epidemiology. Descriptive study concerns the vital statistics of a condition and is usually observational by design. The analytical approach attempts to establish associations and determinants of a condition in cohort or case-control studies. Experimental study is conducted under conditions that allow an investigator to control relevant factors. The epidemiology of epilepsy is largely based on descriptive and analytical studies (Bell and Sander 2001; Sander 2003). The following review and study is focused on descriptive epidemiology.

1.1. Diagnostic accuracy

Specific symptoms of epilepsy, i.e. epileptic seizures, occur unpredictably, usually transiently, and, due to the complexity of the symptoms and deficient recollection are often poorly described. Thus, diagnostic accuracy presents a major difficulty in the execution of epidemiological studies.

There is no ideal diagnostic test applicable between seizures, i.e. interictally. The most specific investigation for epilepsy, electroencephalography (EEG), is not sensitive enough for use in epidemiologic studies. Incidence studies from Iceland and USA observed epileptiform patterns in EEG in only 43–44% of subjects with confirmed epilepsy (Olafsson *et al.* 1996; Zarelli *et al.* 1999). An estimated 10–45% of epileptic patients never have specific EEG abnormalities interictally, and only 33% almost always have them. Furthermore, since 0.5–2% of healthy subjects have epileptiform signs in EEG, the presence of these elements without the presence of clinical seizures, is not sufficient to diagnose epilepsy (Walczak and Jayakar 1997; Binnie and Stefan 1999). History of epileptic seizures is essential for epilepsy diagnosis, and the decision is essentially clinical (Annegers 1993; Sander and Shorvon 1996; So and Andermann 1997). Some previous studies have included EEG-confirmed patients only (deGraaf 1974), but this leads to underestimation of the statistics, and is not generally accepted (Commission 1993).

An investigator must first determine whether an epileptic seizure has actually taken place (Commission 1993; Engel and Pedley 1997). The differential diagnosis comprises all causes of transient alterations of consciousness and episodic symptoms. Due to the heterogeneity of signs, there are no clear guidelines for the diagnosis of epilepsy. The diagnosis can be said to be “confirmed” when a clear, witnessed account of the attack is supplemented by an epileptiform EEG abnormality or an abnormal imaging test that is in accord with the nature of the attack. However, most of the diagnostic decisions are made without the ideal package of evidence, and in practice, both false positive and false negative diagnoses are not uncommon (Sander and Shorvon 1987; Annegers 1993; So and Andermann 1997).

Some studies, which applied re-examination of patients, reported that 11–24% of subjects with a documented diagnosis of epilepsy did not have epilepsy (Gudmundsson 1966; Zielinski 1974; Keränen *et al.* 1989). The most common false positive disorder is psychogenic seizure disorder, which accounted for 6.6% of adult patients with a prior diagnosis of epilepsy (Keränen 1988). Another common non-epileptic disorder previously diagnosed as epilepsy is syncope, 0.2–4.5% of patients, followed by non-epileptic vertigo, transient ischaemic attack, migraine, paroxysmal movement disorders (Zielinski 1974; Keränen 1988). The problem of false negative diagnoses will be dealt with under case ascertainment questions.

If the occurrence of an epileptic seizure is established, the next step is to determine whether it is unprovoked or “non-acute” by nature. The seizures triggered by clear acute precipitants are termed “acute symptomatic seizures” (also referred as “situation-related seizures” or “provoked seizures”) and may have acute structural (head trauma, stroke, etc.) or systemic (hypoglycemia, alcohol withdrawal, fever etc.) causes. In aggregate, acute symptomatic seizures account for more than half of all newly occurring seizures (Loiseau *et al.* 1990a; Loiseau *et al.* 1990b; Sander *et al.* 1990; Hauser and Annegers 1997). Treatment of acute symptomatic seizures is directed mainly at the underlying cause, and this condition does not need to be treated with long-term antiepileptic medication. Thus, the acute symptomatic seizures do not constitute epilepsy even if repeated, and failure to treat these conditions separately will greatly modify the epidemiologic statistics of expected “epilepsy” (Annegers 1993; Commission 1993; Hauser and Annegers 1997; Sander 2003).

1.2. Criteria, clinical characteristics and classifications

In order to ensure the comparability of results, different epidemiologic studies should use standardized basic criteria and classifications. The special commission of the International League Against Epilepsy (ILAE) elaborated guidelines for epidemiologic studies on epilepsy (Commission 1993). The definitions, criteria and classifications proposed by the Guidelines are strongly

recommended for further epidemiologic research (Sander and Shorvon 1996; Commission 1997; Hauser 1997).

1.2.1. Criteria for the activeness of epilepsy

One of the basic criteria in the epidemiology of epilepsy is the activeness of the condition. It is widely acknowledged that a considerable proportion of epileptic patients (about 42–73%) enter a long-term remission of one to five years (Annegers *et al.* 1979; Goodridge and Shorvon 1983b). Most of the epidemiologic surveys are interested in active cases, since they are clinically most problematic, most expensive for health-care, and comprise the main burden of epilepsy. Nevertheless, there is no agreement on how long the freedom from seizures should last, or whether the treatment status should be taken into account, when determining that a patient is no longer an active case (Sander and Shorvon 1996).

The majority of previous studies (Granieri *et al.* 1983; Keränen *et al.* 1989; Maremmani *et al.* 1991) have applied the criteria used by Zielinski (1974) and Hauser *et al.* (1991), i.e. at least one unprovoked seizure in the preceding five years, or receiving an antiepileptic drug (AED) in the preceding five years. Some recent surveys have defined the activeness differently – at least one seizure in prior five years, or taking an AED during the previous one year (Forsgren 1992; Luengo *et al.* 2001); or last seizure or taking an AED in the previous one year (Olafsson and Hauser 1999); or a seizure withintwoyears (Goodridge and Shorvon 1983a; Cockerell *et al.* 1995). The ILAE Guidelines define active epilepsy as at least one seizure in the previous five years regardless of AED treatment (Commission 1993); this conception has been adopted only by Joensen (1986).

The influence of this group on epidemiologic data is not clear, as the proportion of seizure-free AED-receivers in prevalence studies is usually unreported. In the Faroes the overall prevalence rate (PR) is one of the highest among developed countries (Joensen 1986), but diagnoses in medical records were unconditionally accepted, and over-diagnosis was therefore not ruled out. In the study of Goodridge and Shorvon (1983a), the figures of seizure-free AED-receivers and patients with persisting seizures were essentially equal.

1.2.2. Clinical characteristics and classifications

Distribution of seizure types is often a source of disagreement between epidemiologic studies. Clinical and electroencephalographic classification of epileptic seizures, proposed by ILAE in 1981, is widely accepted (Commission 1981), but, due to heterogeneity of seizures, is rather complicated. It is

acknowledged, that specialists may disagree on seizure type, and up to one third of cases may remain unclassified (Keränen *et al.* 1988; Sander *et al.* 1990; Manford *et al.* 1992). Thus, current classification of seizures is rather complicated for epidemiological purposes (Sander and Shorvon 1987; Keränen *et al.* 1988).

Many prevalence studies have found that most patients have generalized seizures; proportions of 60% (Granieri *et al.* 1983), 88% (Li *et al.* 1985) and 63% (Olafsson and Hauser 1999) have been observed. However, in all of these studies it was not clarified how large a share of these generalized seizures were actually secondarily generalized partial ones. Studies with a reliable diagnostic workup have reported that most patients have partial seizures with or without secondarily generalization (Keränen *et al.* 1989; Hauser *et al.* 1991; Forsgren 1992; de la Court *et al.* 1996; Luengo 2001).

Another source of heterogeneous results and disagreement between epidemiologic studies is risk factors (also referred as “putative etiology”) of epilepsies. The majority of the prevalence surveys agree that the cause of epilepsy remains unknown in most cases (Granieri *et al.* 1983; Keränen *et al.* 1989; Hauser *et al.* 1991; Forsgren 1992; Olafsson and Hauser 1999), but within the group of known causes, the proportions of risk factors are rather different. Since limits between significant and insignificant prior events are sometimes not clear enough, especially for head injury, infections and perinatal factors, different approaches to putative etiology in epidemiologic studies can be suspected. In order to improve comparability of the risk factors, the Guidelines propose a classification for remote symptomatic epilepsies (Commission 1993). Analytic studies based on large cohorts (Annegers *et al.* 1980; Annegers *et al.* 1988; Annegers *et al.* 1996) suggest that moderate head injury and bacterial meningitis increase the risk of epilepsy only during the first five years after the event.

Epilepsy is not a single disease, but a broad category of different diseases and specific syndromes; the respective classification, which combines together seizure types, putative etiology and special diseases, was proposed by ILAE in 1989 (Commission 1989). There are only some large-scale studies that report hospital-based distribution of cases by this classification (Bauer 1994; Loiseau *et al.* 1991; Eadie 1996; OREp 1996; Kellinghaus *et al.* 2004); only few of them are population-based epidemiologic surveys (Loiseau *et al.* 1990a; Zarelli *et al.* 1999; Olafsson and Hauser 1999; Beilmann and Talvik 1999). However, the syndromic classification is not easily applicable even in ideal clinical settings (Sander *et al.* 1990; Manford *et al.* 1992; Kellinghaus *et al.* 2004). Thus, in essentially uncertain cases, the use of an unclassifiable class is justified in order to avoid a false impression of diagnostic precision (Sander and Shorvon 1996; Kellinghaus *et al.* 2004).

Comparisons of clinical characteristics between studies are often difficult due to the different ways that figures are expressed – most studies describe clinical characteristics as a percentage of the study sample, some as rates, i.e. the number of characteristics divided by the study population. Percentages are easily

readable figures, but since they depend largely on the completeness of the sample, they are very sensitive to under-ascertainment.

In order to improve the accuracy of diagnosis and the homogeneity of inclusion criteria in epidemiologic studies of epilepsy, a personal re-examination of cases by investigators is widely recommended (Gudmundsson 1966; Zielinski 1974; Sander and Shorvon 1987; Keränen 1988). Statistics based on the doctor's reported diagnosis (Crombie *et al.* 1960; deGraaf 1974) very probably leads to variable and irreproducible results. Reliable diagnostic skills of the investigator and his/her knowledge concerning the classification of cases are crucial elements in epidemiologic studies of epilepsy (Commission 1993; Sander and Shorvon 1996).

1.3. Case ascertainment

Even if the diagnosis of epilepsy is accurate, case ascertainment poses a variety of problems in epidemiologic studies. The majority of patients who do prognostically well, do so early, and usually are not seen in tertiary practices (Berg *et al.* 1996). It is important that all cases are included from the source population. Due to the heterogeneity of epilepsy and the complexity of its diagnosis this goal is not easily achievable, and underreporting is a common artefact (Sander and Shorvon 1987).

Early notions of epilepsy as a chronic, progressive, nonremitting condition were based on highly selected individuals, mainly institutionalised patients (Berg *et al.* 1996). It is obvious that this approach does not represent accurate data to the general population and leads to biased knowledge about epilepsy. The main approaches for case ascertainment for population-based studies are a review of medical records, usually conducted retrospectively, and a door-to-door survey, usually based on a questionnaire.

1.3.1. Reviews of medical records

The commonest method is a retrospective review of prior diagnoses. Studies using multiple sources to find potential cases in the population are capable of identifying the vast majority of persons with epilepsy, and can be considered to be population-based. Some of the reviews have included total population (Gudmundsson 1966; Granieri *et al.* 1983; Hauser *et al.* 1991; Olafsson and Hauser 1999; Luengo *et al.* 2001), some, a random sample (Zielinski 1974; Goodridge and Shorvon 1983a; Cockerell *et al.* 1995), some, adults only (Keränen *et al.* 1989; Forsgren 1992; de la Court *et al.* 1996), and some, children only (Sillanpää 1973; Sidenvall *et al.* 1996; Endziniene *et al.* 1997; Eriksson and Koivikko 1997; Beilmann *et al.* 1999a; Beilmann *et al.* 1999b).

Series that have used selected sources for case identification, such as antiepileptic drug (AED) users (Beghi *et al.* 1991; Hart and Shorvon 1995a), hospital attenders (Danesi 1985; Loiseau *et al.* 1991; Bauer 1994; Eadie 1996), prisoners (Fazel *et al.* 2002), or insurance holders (Wajsbort *et al.* 1967) are not representative of the general population. Some community-based epidemiologic studies distributed by the methods of case ascertainment are presented in Table 1 and Table 2.

Table 1. Incidence rates of epilepsy (per 100 000 person-years) in community-based studies

Author (year) country	Age	Incidence rate	Number of cases	Comments
<i>Retrospective incidence studies</i>				
Sillanpää (1973) Finland	≤15 years	25	397	
Granieri <i>et al.</i> (1983) Italy	all ages	33.1	230	
Li <i>et al.</i> (1985) China	all ages	25	16	
Joensen (1986) Faroes, Denmark	all ages	42.8	194	
Lühdorf <i>et al.</i> (1986) Denmark	≥60 years	77	112	criteria unclear
Keränen <i>et al.</i> (1989) Finland	≥16 years	24	230	
Placencia <i>et al.</i> (1992a) Ecuador	all ages	190	137	door-to-door study
Hauser <i>et al.</i> (1993) USA	all ages	44	880	time trends observed
Olafsson <i>et al.</i> (1996) Iceland	all ages	46.5	42	
Zarelli <i>et al.</i> (1999) USA	all ages	52.3	157	
<i>First attendance rate studies</i>				
Zielinski <i>et al.</i> (1974) Poland	all ages	20	–	
Cockerell <i>et al.</i> (1995) UK	all ages	48.3	29	time trends observed
<i>Prospective incidence studies</i>				
Loiseau <i>et al.</i> (1990a) France	all ages	23.7	268	SS*, AS excluded
Loiseau <i>et al.</i> (1990b) France	≥60 years	34	76	SS*, AS excluded
Lavados <i>et al.</i> (1992) Chile	all ages	113	102	
MacDonald <i>et al.</i> (2000) UK	all ages	46	31	criteria unclear
Beilmann <i>et al.</i> (1999a) Estonia	≤19 years	45	216	
<i>Studies of all epileptic seizures</i>				
Jallon <i>et al.</i> (1997) Switzerland	all ages	46	176	SS* included
Forsgren <i>et al.</i> (1996) Sweden	≥17 years	56	160	SS* included
Sidenvall <i>et al.</i> (1993) Sweden	≤15 years	73	61	SS* included

*SS = single seizures; AS = acute symptomatic seizures

Table 2. Prevalence rates of epilepsy (per 1000 population) in community-based studies

Author (year) country	Age	Prevalence rate	95% CI	Number of cases	Criteria of activeness ¹⁾	Comments
<i>Retrospective studies</i>						
Zielinski (1974) Poland	all ages	7.8	ns ²⁾	33	S 5 or AED 5	random sample
Goodridge <i>et al.</i> (1983a) UK	all ages	5.3 ³⁾	3.5–7.5	32	S 2	random sample
Granieri <i>et al.</i> (1983) Italy	all ages	6.2	5.4–6.9	278	S 5 or AED 5	
Juul-Jensen <i>et al.</i> (1983) Denmark	all ages	12.7	ns	1068	ns	activeness not studied
Joensen (1986) Faroes, Denmark	all ages	7.6	6.8–8.6	333	S 5	
Keränen <i>et al.</i> (1989) Finland	≥16 years	6.3	6.1–6.5	1233	S 5 or AED 5	extensive screening
Hauser <i>et al.</i> (1991) USA	all ages	6.8	ns	383	S 5 or AED 5	special register
Maremmani <i>et al.</i> (1991) Italy	all ages	5.1	3.7–6.5	51	S 5 or AED 5	
Forsgren (1992) Sweden	≥17 years	5.5	5.1–5.9	713	S 5 or AED 1	
Lavados <i>et al.</i> (1992) Chile	all ages	17.7	ns	314	S 5 or AED 5	prospective study
Cockerell <i>et al.</i> (1995) UK	all ages	4.3	2.8–6.3	26	S 2	random sample
Gekht <i>et al.</i> (1999) Russia	≥14 years	2.2	ns	76	ns	outpatient clinics
Olafsson <i>et al.</i> (1999) Iceland	all ages	4.8	ns	428	S 5 or AED 1	
Luengo <i>et al.</i> (2001) Spain	≥10 years	4.1	3.8–4.4	405	S 5 or AED 1	period prevalence
<i>Door-to-door studies</i>						
Beran <i>et al.</i> (1982) Australia	all ages	7.5	ns	35	ns	activeness not studied
Li <i>et al.</i> (1985) China	all ages	4.6	4.1–5.1	289	ns	lifetime prevalence
Haerer <i>et al.</i> (1986) USA	all ages	6.8	ns	160	S 3 or S 1 ⁴⁾	blacks > whites
Placencia <i>et al.</i> (1992a) Ecuador	all ages	8.0	ns	575	S 1 or AED	rural > urban
de la Court <i>et al.</i> (1996) Netherlands	55–94 years	7.7	ns	43	S 5	
Aziz <i>et al.</i> (1997) Pakistan	all ages	10.0	ns	241	S 5 or AED 5	rural > urban
“ Turkey	all ages	7.0	ns	81	S 5 or AED 5	rural > urban
Radhakrishnan <i>et al.</i> (2000) India	all ages	4.9	4.6–5.2	1175	S 5	
Rocca <i>et al.</i> (2001) Italy	all ages	3.3	ns	81	S 5 or S 1 ⁴⁾	
<i>Studies of AED users</i>						
Beghi <i>et al.</i> (1991) Italy	all ages	3.9	ns	199	ns	
Giuliani <i>et al.</i> (1992) Italy	all ages	5.2	ns	235	S 5 or AED	
Hart <i>et al.</i> (1995a) UK	all ages	4.5	ns	1628	cases on AED	

¹⁾ S # = at least one seizure in the previous # years; AED # = usage of antiepileptic drugs in the previous # years;

²⁾ ns = not specified; ³⁾ rate is 10.5/1000 for those with S 2 or receiving AED;

⁴⁾ S# or S1 = to those with AED at least one seizure in the previous # years or to those without AED at least one seizure in the previous 1 year

A somewhat different method is a review that uses a special record-keeping system as a source of case ascertainment. This method was applied in Aarhus, Denmark (Juul-Jensen and Foldspang 1983), and in Rochester, USA (Hauser *et al.* 1991; Hauser *et al.* 1993; Annegers *et al.* 1996; Melton 1996). It has the advantage that the methodology may be planned in advance, and it provides data for analytical epidemiology for a prolonged period. However, this approach requires a complicated structure and does not exclude dependence from prior medical judgements, i.e. does not guarantee complete enrolment, and may present the same diagnostic problems as an ordinary retrospective review (Melton 1996; Sander and Shorvon 1996).

It is obvious that reviews that rely on prior diagnosis can not present the cases that are missing in medical registers. Only a few studies have attempted to estimate figures for false negative epilepsy diagnosis in a community. The most impressive results are reported by a study in Warsaw – a prevalence rate of active epilepsy based on medical records data alone is 5.1/1000, but it rises to 10.4/1000 in a sample of 0.5% of the community (Zielinski 1974). However, the study sample is quite small (98 cases with epilepsy), and may not be representative of the whole population. In Finland, a study with an extensive screening-phase identified only six new epileptic patients out of 226 prior non-epileptics examined due to paroxysmal symptoms, which constituted 0.4% of all confirmed epileptic cases (Keränen 1988). Furthermore, other surveys using extensive screening methods have failed to report large epidemiologic figures (Hauser *et al.* 1991; Maremmani *et al.* 1991; Luengo *et al.* 2001).

The assumption that all subjects with disorders seek medical advice is incorrect; this seems to be especially true for epilepsy. Some patients with seizures never seek medical attention, either due to concealment, denial, or ignorance. Actual proportion of these subjects is not known, but they inevitably contribute to the underestimation in epidemiologic studies (Beran *et al.* 1985; Sander and Shorvon 1996). A door-to-door prevalence survey in Sicily, Italy (Rocca *et al.* 2001) found that 7% of epileptic patients did not have previously diagnosed epilepsy. A questionnaire-based study from the UK found that patients reported seizures to a doctor almost 25% less than to an anonymous questionnaire. The main motivations for concealment were associated with employment, driving licence, and psychological distress (Dalrymple and Appleby 2000). In Australia, a survey that compared answers of a questionnaire and medical records, found that 23% of epileptic respondents denied having epilepsy in the questionnaire (Beran *et al.* 1985).

1.3.2. Door-to-door studies

The case identification method, which does not rely on prior diagnosis, like a door-to-door study (also referred to as a “field study”), is supposed to be more effective in finding hidden cases. This study is carried out in several (two or

more) phases: screening of households by questionnaire, evaluation of screen-positive cases and confirmation of diagnosis-positive cases (Zielinski 1974; Li *et al.* 1985; Haerer *et al.* 1986; Maremmani *et al.* 1991; Placencia *et al.* 1992b; Radhakrishnan *et al.* 2000; Rocca *et al.* 2001). Such surveys depend crucially on the balance between sensitivity and specificity of the screening method. However, a pragmatic screening instrument for seizures without florid clinical symptomatology, especially for absence and myoclonic seizures, has not been designed. Despite thorough validation of a questionnaire by some authors (Placencia *et al.* 1992b), there is still no ideal screening instrument for a door-to-door study of epilepsy (Placencia *et al.* 1992b, Sander and Shorvon 1996). In addition, the field study is particularly sensitive to the concealment of the condition (Rocca *et al.* 2001).

There are only two field studies, in Poland (Zielinski 1974) and in Australia (Beran *et al.* 1982), that have reported notably higher epidemiologic figures for epilepsy than other surveys. Although Beran *et al.* (1982) did not adopt the concept of activeness, and thus, cases in remission were probably included. Other door-to-door surveys have failed to present higher figures than record-based retrospective studies (Li *et al.* 1985, Maremmani *et al.* 1991; Placencia *et al.* 1992a; Radhakrishnan *et al.* 2000; Rocca *et al.* 2001). These screening aspects, expensiveness, and poor reproducibility of a door-to-door study (Maremmani *et al.* 1991; Placencia *et al.* 1992b; Sander and Shorvon 1996) are very probably the reason why most of the epidemiologic surveys in industrialized countries are conducted as record-based studies.

Thus, the complexity of the diagnostic workup in epilepsy, lack of an ideal case ascertainment method, and concealment of epilepsy by the patients themselves are the most important confounding factors in epidemiologic studies for epilepsy.

2. Incidence of epilepsy

2.1. General aspects of incidence

Incidence is an epidemiologic measure that expresses the number of new cases of epilepsy occurring during a given time interval, usually one year, in a specified population. Incidence rate (IR) is the ratio of new cases to the population at risk, usually expressed as cases per 100 000 person-years (/100 000). Criteria for defining an incident case must be clearly stated, including specification of whether it is based on date of diagnosis or date of onset (Commission 1993). The incidence cohort provides the most adequate data to determine those who are at risk of epilepsy and to understand its causes and prognosis. Prevalence may be misleading for these purposes, since it is influenced by mortality, AED therapy, prognosis, and migration (Hauser *et al.* 1993).

Some recent community-based incidence studies of epilepsy are outlined in Table 1. Incidence studies should ideally be prospective to minimize deficient case ascertainment and maximize information on clinical characteristics (Sander and Shorvon 1996; Commission 1997). Nevertheless prospective studies face other problems, which are mainly associated with complexity and cost of implementation. Furthermore, prospective surveys have not reported significantly higher figures (Beilmann *et al.* 1999a; Forsgren *et al.* 1996), or have even shown lower rates (Loseau *et al.* 1990a, Loseau *et al.* 1990b), probably due to the same dependence on active attendance of patients and essentially similar diagnostic problems as seen in retrospective surveys. Most incidence studies are conducted retrospectively (Hauser *et al.* 1993; Zarelli *et al.* 1999), often in conjunction with retrospective prevalence studies (Gudmundsson 1966; Granieri *et al.* 1983; Juul-Jensen and Foldspang 1983; Joensen 1986; Keränen *et al.* 1989; Olafsson *et al.* 1996).

Some authors have reported first attendance rate (FAR) per 100 000 person-years (/100 000) (Zielinski 1974; Cockerell *et al.* 1995), which is defined as rate of patients attending a specialist. The FAR is basically the same as incidence, but tends to be lower than IR. It may be affected by behavioural factors, like concealment, migration, and availability of medical services (Cockerell *et al.* 1995).

Reported IR of epilepsy varies considerably in different studies, ranging from 11 to 230/100 000; the majority of the results cluster between 24 and 53/100 000 in developed countries, and between 77 and 114/100 000 in developing countries (Sander and Shorvon 1996; Hauser 1997). Very high incidence in developing countries is usually attributed to medico-social conditions: poor sanitation (i.e. resultant infection diseases) may be the single most important causal factor, as well as pre- and perinatal factors, undernutrition, violence etc. (Berg *et al.* 1996; Commission 1996; Sander and Shorvon 1996; Jallon 1997).

Incidence studies of epilepsy find the disorder to be more common in males than females (Granieri *et al.* 1983; Joensen 1986; Keränen *et al.* 1989; Hauser *et al.* 1993; Olafsson *et al.* 1996), or with minor or no difference between sexes (Sander *et al.* 1990, Forsgren *et al.* 1996). There is no clear explanation for that difference. In a childhood population, incidence was higher in girls than boys (Sidenvall *et al.* 1993), but no difference was found in Estonia (Beilmann *et al.* 1999a).

There is very little published information on the incidence from CEE. A retrospective study for all age groups, carried out in Poland (Zielinski 1974), found that the FAR for epilepsy was rather low, 20/100 000, but essentially within the range of that in developed countries. Another incidence study has recently been published from Estonia (Beilmann *et al.* 1999a), but for children only.

2.2. Age-specific incidence

Only surveys limited to adult populations have been published from Denmark (Lühdorf *et al.* 1986), from Finland (Keränen *et al.* 1989), Sweden (Forsgren *et al.* 1996) and France (Loiseau *et al.* 1990b). Included were persons aged ≥ 16 years in Finland, ≥ 17 years in Sweden, and ≥ 60 years in Denmark and France. In Finland, the IR is 24/100 000, and in Sweden, 56/100 000. It is important to note, that the studies from Denmark, Sweden and France do not include epilepsy only. In Denmark and Sweden, there are single unprovoked seizures involved as well; furthermore, the data from Denmark is based on poorly defined criteria and comparisons with other studies are limited. The survey from France includes all possible seizures in the elderly – the IR is 34/100 000 for epilepsies, 16/100 000 for isolated seizures, and the highest, 77/100 000 for acute symptomatic seizures.

The IRs in Europe that are limited to a childhood population cluster between 50 and 82/100 000 (Blom *et al.* 1978; Brorson and Wranne 1987; Sidenvall *et al.* 1993). An early study from Finland reported the IR to be 25/100 000 (Sillanpää 1973). A recent prospective study from Estonia has found the IR for children, i.e. persons aged less than 20 years, to be 45/100 000 (Beilmann *et al.* 1999a), which is basically comparable to that in other European countries.

Recent incidence surveys in industrialized countries report consistent evidence suggesting that the general age-specific incidence curve for epilepsy has a characteristic U-shaped form, with the highest rates in the youngest children and in the elderly (Sander and Shorvon 1996; Hauser 1997). During adulthood, incidence has a growing pattern – being relatively low in ages 20–49 years, it starts to grow progressively thereafter, with a dramatic increase from the age of 70 years (Zielinski 1974; Lühdorf *et al.* 1986; Hauser *et al.* 1993; Annegers *et al.* 1995; Cockerell *et al.* 1995; Forsgren *et al.* 1996; Olafsson *et al.* 1996; Zarelli *et al.* 1999). In Finland, this pattern was observed for males (Keränen *et al.* 1989). In a prospective population-based study from England, about 25% of newly diagnosed seizures occurred in those aged 60 years or more (Sander *et al.* 1990).

However, the age-specific figures in some incidence studies do not show an increasing pattern (Gudmundsson 1966; Granieri *et al.* 1983; Juul-Jensen and Foldspang 1983; Joensen 1986). It has now been acknowledged that the most probable cause for low rates in the elderly may be underascertainment, which may also affect the overall figures as well. Case collection tends to be particularly complicated among aged people, as is strongly suggested by two studies using similar methodology in largely the same area in Sweden. In the first prospective study on adults with a first unprovoked seizure, the annual IR was 34/100 000 (Forsgren 1990). The following prospective study with intensified search among the elderly found a higher overall IR, 56/100 000, compared to the

first study, and particularly much higher rates in the elderly (Forsgren *et al.* 1996).

However, little is known about natural time trends of the epidemiological figures. It has been noted that the incidence of childhood epilepsy has declined in recent series while the age-specific incidence for the elderly increases over the same period (Sander *et al.* 1990; Hauser *et al.* 1993; Annegers *et al.* 1995; Cockerell *et al.* 1995). No clear explanation for these changes has yet been found. In children, improved perinatal care and improved maternal health during pregnancy may play an important role (Sander and Shorvon 1996). In the elderly, the popular belief that an increase in survival of cerebrovascular diseases is a crucial factor is not convincing, since incidence of cerebrovascular diseases has decreased, and the proportion of syndromes with unknown etiology is still the largest in the elderly (Hauser 1997).

The pattern of age-specific incidence is quite different in developing countries. In studies from Chile (Lavados *et al.* 1992) and Tanzania (Rwiza *et al.* 1992), the peak incidence of epilepsy occurs in adolescence and young adults. In Chile, there were no epilepsy patients older than 60 years (Lavados *et al.* 1992).

2.3. Seizure types

The incidence studies that include all age groups (Joensen 1986, Loiseau *et al.* 1990a, Hauser *et al.* 1993, Zarelli *et al.* 1999) have found that more than 50% of incidence cases have partial seizures, most of them complex partial and secondarily generalized seizures. The study in Iceland (Olafsson *et al.* 1996) reported 31% of cases with partial seizures; unusually only one subject with secondarily generalized seizures was found. Most probably, this very common seizure type is hidden within the group of subjects classified as having generalized seizures. A study of epileptic syndromes in the USA (Zarelli *et al.* 1999) found a total share for localization-related epilepsies as high as 70%, or estimated IR of 35/100 000, having increasing tendency with advancing age. The same tendency is observed in Iceland (Olafsson *et al.* 1996). A prospective study in France reported an IR for localization-related epilepsies of 15.3/100 000 (Loiseau *et al.* 1990a). In children, incidence studies report 41–51% to have partial seizures/localization-related epilepsies (Blom *et al.* 1978, Sidenvall *et al.* 1993, Beilmann *et al.* 1999a). Seizures were classified for almost all cases in these studies.

Most incidence studies that include adult populations have reported unclassifiable seizures – 10% in Denmark (Joensen 1986), 8% (IR 1.9/100 000) in France (Loiseau *et al.* 1990a), 9% in the UK (Sander *et al.* 1990), and 17% in Sweden (Forsgren *et al.* 1996). There is a contradiction between studies based on the record-linkage cohort in Rochester, USA – Hauser *et al.* (1993) found unclassified seizures for 3% of cases, but Zarelli *et al.* (1999) reported 18% (IR

9.7/100 000) for undetermined syndromes. The former includes diagnoses for a 50-year period (1935–1984), but the latter is based on a recent time period (1980–1984), and probably reflects the modern notion of the classification.

Several incidence studies of epileptic seizures in all ages have reported a distribution of seizure types, but some of them have included isolated seizures and acute symptomatic seizures (Sander *et al.* 1990; Forsgren *et al.* 1996), or have defined them poorly (Olafsson *et al.* 1996). In addition, comparisons between reports are difficult due to the different expression of figures – most of the studies express results as a percentage of the study sample, but some express them as IRs, i.e. related to study population.

Summarizing the distribution of seizure types in incidence studies, partial seizures and primarily generalized seizures are equally common in children, while partial seizures are much more common in adults, having an increasing tendency with advancing age; and unclassifiable seizures are quite common, especially among adults.

2.4. Risk factors

Only four population-based incidence studies in developed countries, which include all ages, report on presumed etiology of epilepsy (Loiseau *et al.* 1990a; Hauser *et al.* 1993; Olafsson *et al.* 1996; Zarelli *et al.* 1999); there are no studies involving adults only. Reported occurrence of presumed etiology cluster between 24–35% of all cases, or estimated IRs vary from 7 to 17.2/100 000. The studies of Olafsson *et al.* (1996) and Zarelli *et al.* (1999) report that the age-specific incidence for symptomatic cases has increasing tendency with advancing age.

It is likely that that various risk factors of epilepsy differ between various industrial countries, as a reflection of different habits and living conditions. However, these differences are expected to have a mild to moderate impact on incidence and prevalence. The most common remote symptomatic etiology for epilepsy in industrial countries is cerebrovascular diseases, with 10–19%. Neoplasms, trauma and congenital disorders are other common causes.

3. Prevalence of active epilepsy

3.1. General aspects of prevalence

Prevalence is an epidemiologic index that expresses the proportion of patients with epilepsy in a given population at a specified time (i.e. point prevalence) or during a defined time interval (i.e. period prevalence). Inclusion criteria should be specified (i.e. active epilepsy, epilepsy in remission with treatment, and epilepsy in remission without treatment) (Commission 1993). Most of the studies survey point prevalence. Lifetime prevalence expresses the proportion of patients with a history of epilepsy, regardless of treatment or recent seizure activity. Prevalences, which represent the ratios of identified cases to the total population, are usually expressed as cases per 1000 persons (/1000) (Commission 1993).

Prevalence is a measure of the interaction of different factors such as incidence, mortality, and remission of illness, and is also affected by migration and access to sources of medical care. Prevalence data are of primary value in health-care and research planning; they are of little benefit in determining the etiology or prognosis of epilepsy (Hauser 1997). Since the majority of the epidemiologic surveys in epilepsy are related to prevalence, most of the methodological details mentioned above, in the part about general aspects, concern prevalence studies.

Some recent community-based prevalence studies of epilepsy are outlined in Table 2. The reported point prevalence rate (PR) of active epilepsy varies considerably in different populations, ranging from 1.5 to 57/1000. The PR tends to be lower in developed and some developing countries, 4.3–10.0/1000, and remarkably higher in tropical countries, 17–57/1000; higher than average rates are reported also in rural areas. Though a considerable part of the variation may be explained by variations in case-finding and inclusion criteria, a high prevalence in developing countries is usually attributed to geographical and medico-social conditions (Berg *et al.* 1996; Commission 1996; Sander and Shorvon 1996; Hauser 1997; Jallon 1997).

Contrary to popular belief, there is no evidence that antiepileptic treatment has a favourable effect on the natural history of epilepsy and, thus, decreases prevalence of epilepsy. Numerous prognostic surveys from Africa and Europe report that, despite lack of treatment, approximately 50% of individuals with epilepsy enter a remission spontaneously, i.e. seizures cease without any intervention (Sander 1993; Chadwick 1995; Berg *et al.* 1996; Temkin 2001). Further, it is widely acknowledged that AED treatment prevents acute febrile and posttraumatic seizures, but has no effect on subsequent unprovoked seizures. There is no evidence that AED treatment prevents epilepsy from becoming chronic (Berg *et al.* 1996; Temkin 2001; McCorry *et al.* 2004). However, as mortality of epilepsy is related to seizure frequency, there are some indications of the favourable effect of AEDs on survival (Sander and Sillanpää 1997).

3.2. Age-specific prevalence

Only four studies have been reported in which only adults with epilepsy have been included. Persons aged ≥ 16 years in Finland (Keränen *et al.* 1989), ≥ 17 years in Sweden (Forsgren 1992), and ≥ 14 years in the Russian Federation (Gekht *et al.* 1999) were included. The rates from the two northern European studies range from 5.5 to 6.3/1000 inhabitants. A low rate in Russia, 2.2/1000, is very probably an underestimate. A study from the Netherlands, which observed the age group 55–94 years, found PR to be 7.7/1000 with active epilepsy (de la Court *et al.* 1996).

Several prevalence rates for children with active epilepsy are available: from Finland (Sillanpää 1973; Eriksson *et al.* 1997), Spain (Sangrador and Luaces 1991), Sweden (Sidenvall *et al.* 1996), Lithuania (Endziniene *et al.* 1997), Estonia (Beilmann *et al.* 1999b), and England (Tidman *et al.* 2003). The ages of children included in these studies vary. Rates in these studies range from 3.2 to 4.3/1000.

Although epilepsy is a condition acquired throughout life, the reported patterns, the reported age-specific prevalence seldom reflect this. Most of the studies, especially earlier ones, have found a relatively constant age-specific prevalence throughout adulthood (Joensen 1986; Keränen *et al.* 1989; Forsgren 1992; Lavados *et al.* 1992; Cockerell *et al.* 1995; Luengo *et al.* 2001), some with a tendency to decrease in the elderly (Granieri *et al.* 1983; Li *et al.* 1985; Haerer *et al.* 1986; Maremmani *et al.* 1991; Placencia *et al.* 1992a; Aziz *et al.* 1997; Radhakrishnan *et al.* 2000). However, some series, especially the recent ones, have observed steadily increasing rates with advancing age (Hauser *et al.* 1991; de la Court *et al.* 1996; Olafsson and Hauser 1999). In many cases, these differences can be partially explained by statistical fluctuation, since age-specific estimates are unstable due to the small numbers within age groups (Hauser 1997). On the other hand, the increasing pattern of age-specific prevalence can be explained by improved case-ascertainment (Maremmani *et al.* 1991).

In industrialized countries, it is likely that the “true” prevalence of active epilepsy in the elderly is higher than in other age groups. This assumption is supported by a Dutch study in the elderly, where the prevalence increased with age from 6.1/1000 at age 55–64 years to 9.7/1000 at age 85–94 years (de la Court *et al.* 1996).

The influence of age-specific mortality on age-specific prevalence is largely unknown. Some studies have found that the younger patients have considerably higher relative mortality rates than older individuals with epilepsy (Hauser *et al.* 1980; Cockerell *et al.* 1994). However, the general increase in mortality is largely due to the causes of acquired epilepsy – cerebrovascular diseases, brain tumours – rather than epilepsy itself (Annegers 1997).

3.3. Clinical characteristics

Since the current classification of seizures has been available for the last two decades, recent data concerning seizures in prevalence studies are easily-comparable (Commission 1981). However, interpretation of some details (i.e. clarification of how many generalized seizures are actually secondarily generalized partial ones) may vary. Prevalence studies of all ages found 33–65% to have partial seizures or localization-related epilepsies, 17–60% to have generalized seizures, and 2–8% to have unclassifiable seizures (Granieri *et al.* 1983; Joensen 1986; Maremmanni *et al.* 1991; Olafsson and Hauser 1999). Studies in adults and the elderly have found that 55–69% of patients have partial seizures or localization-related epilepsies, 6–32% have primarily generalized seizures, and 8–18% have seizures that are unclassifiable (Keränen *et al.* 1989; Forsgren 1992; de la Court *et al.* 1996). In children, partial seizures and primarily generalized seizures are almost equally common (Sidenvall *et al.* 1996; Endziniene *et al.* 1997; Eriksson *et al.* 1997; Beilmann and Talvik 1999; Sillanpää *et al.* 1999).

Some studies have reported seizure frequency (Keränen and Riekkinen 1988; Forsgren 1992; Olafsson and Hauser 1999). Based on the results in Sweden, the proportion of patients that has been seizure free during the preceding year is 44%, the percentage with 1–11 seizures per year is 25.5%, 14.4% have 12–51 seizures per year, and 17% have more than one seizure per week (Forsgren 1992). Keränen and Riekkinen (1988) reported the prevalence of severe complex partial epilepsy, defined as one seizure or more per month, to be 0.78 per 1000 (12%) in adults. However, it is a well-known impression from clinical practice that seizure frequency in one person may be highly variable, and errors due to poor recollection and concealment are rather common.

3.4. Prevalence in Central and Eastern Europe

It is likely that the various components of prevalence differ between various European regions as a reflection of different habits and living conditions. In recent years, several studies have revealed differences in public health and mortality estimates between populations in NWE and those in CEE (Bobak and Marmot 1996; Carlson 1998). Although differences are expected to have a mild or moderate impact on prevalence, there are not sufficient studies from CEE to allow comparisons (Jallon 1997; Halatchev 2000; Malmgren *et al.* 2003).

A classical study in Warsaw has shown the PR of active epilepsy to be 7.8/1000 (Zielinski 1974), which is essentially similar to that in developed countries. However, the study is based on a small sample of cases, and the randomised study population may not be representative of the whole population. Some assumptive prevalence figures from Hungary (Halasz 1995) and Bulgaria

(Halatchev 2000) have been published. In Hungary, the prevalence of epilepsy is reportedly 5/1000. Based on official data, the numbers of registered epilepsy patients in Bulgaria are only half of those in developed countries. But both figures are only assumptions and no special studies have been reported.

In the former Soviet Union the prevalence of epilepsy has been studied extensively. According to an early epidemiological study in Moscow (Borinovich 1967), the PR of epilepsy was reportedly 6/1000, but in the absence of diagnostic criteria, it is not clear whether acute and provoked syndromes were excluded, and the term “activeness” is poorly defined. Later surveys have found the PR of epilepsy to be remarkably lower: 1.9/1000 in Saint Petersburg (Morozov and Kerimov 1988), 2.4/1000 in the province of Moscow (Gekht *et al.* 1999), and 0.96/1000 in Yerevan, Armenia (Gekht *et al.* 1999). The most recent study conducted in Moscow reports the PR of epilepsy to be 2.23/1000 (Gekht *et al.* 1999). These lower rates are based on only a few medical registers and are very probably underestimates.

A modern study on the prevalence of epilepsy in Estonia has been carried out only for children (Beilmann *et al.* 1999b). Reported PR of active epilepsy was 3.6/1000, being essentially similar to those in developed countries. Reliable figures for adults are not readily available in Estonia.

4. Treatment of epilepsy

4.1. General aspects of antiepileptic treatment

The mainstay of antiepileptic treatment is drug therapy. In Estonia, the conventional AEDs, i.e. carbamazepine (CBZ), valproate (VPA), phenytoin (PHT), phenobarbital (PB), primidone (PRM), ethosuximide (ESM), and clonazepam (CZP), were available and their cost compensated in full for insured persons with a diagnosis of epilepsy in 1997. A barbiturate called benzobarbital (BB, or Benzonal[®]) was extensively prescribed in the former Soviet Union. In 1997, BB was no longer registered in Estonia, but people brought it in from abroad and factually used it. Some AEDs of a new generation, lamotrigine (LTG), topiramate (TPM), oxcarbazepine (OXC), were included in the catalogue of fully compensated drugs later and thus, due to their very high cost, were not available for wide use in 1997.

Blockade of voltage-gated sodium channels is the most common mechanism of action amongst available AEDs; it is the primary mechanism for CBZ, PHT, and OXC. These agents are effective for partial and generalized tonic-clonic seizures with or without secondary generalization, but they are ineffective against, and may even exacerbate, myoclonic and absence seizures (Brodie and Dichter 1996; Rho and Sankar 1999; Leppik 2000).

Some AEDs, like VPA, LTG, TPM, have multiple mechanisms, or less-well-defined mechanisms of action. These agents have broad-spectrum anti-seizure activity, i.e. they are effective for the wide range of generalized-onset and partial-onset seizures, and are particularly advantageous drug when several generalized-onset seizure types coexist or seizures remain unclassified (Ben-Menachem *et al.* 2003; McCorry *et al.* 2004). Other conventional broad-spectrum drugs, like PB, PRM, CZP, exert their pharmacological effects through γ -aminobutyric acid-related chloride channels, but these drugs often cause sedation at therapeutic levels, and are second- or even third-line drugs for epilepsy (Brodie and Dichter 1996; Rho and Sankar 1999; Leppik 2000; Deckers *et al.* 2003; McCorry *et al.* 2004).

It is important to acknowledge that AEDs have no antiepileptogenic properties, i.e. they just suppress seizures on a temporary basis, and have no effect on prevention of seizures or on entering long-term remission (Berg *et al.* 1996; McCorry *et al.* 2004). The issue of compliance is very critical, one of the main causes of treatment failure is noncompliance (Leppik 2000).

Currently, monotherapy is considered to be a gold standard for treatment of epilepsy, being initially effective for 44–79% of patients (Brodie and Dichter 1996; Kwan and Brodie 2001; Lhatoo *et al.* 2001; Deckers 2002). Two decades ago, polytherapy was the standard of antiepileptic medication until different authors demonstrated the complexity of drug interactions and underlined the importance of AED adverse effects (Shorvon and Reynolds 1977; Schmidt 1983). However, some authors in NWE still highlight problems of unnecessary overtreatment due to underestimation of side-effects (Deckers 2002).

4.2. Population-based reviews of antiepileptic treatment

There are varied reports on medication in epileptic populations from NWE. Some epidemiologic studies of active epilepsy have reported data of anti-epileptic treatment (Keränen 1988; Rutgers 1986; Forsgren 1992; Olafsson and Hauser 1999); others either use data based on AED prescriptions (McCluggage *et al.* 1984; Giuliani *et al.* 1992; Hart and Shorvon 1995a; Muir *et al.* 1996), or use special databases or drug sales data (Lammers *et al.* 1996; RoCHAT *et al.* 2001).

A population-based epidemiologic study enables direct comparisons with clinical characteristics, includes drug-free cases, and reliably reflects the situation of general treatment patterns in the studied sample. The drawback of epidemiologic studies is that they are time-consuming and relatively expensive, and, as epidemiologic samples are not usually very large, there is a possibility that the studied sample is not representative of the general population.

Data of drug sales provides a rather quick general overview for the whole population, but use of AEDs for the treatment of other diseases and the heterogeneity of seizure disorders complicate the interpretation of data – clinical

characteristics, age distribution, and even general treatment strategies remain obscure. Prescription-based studies and audits are somewhat more clinically relevant, since the diagnoses of doctors are usually applied, but drug-free subjects are automatically excluded, and clinical criteria are not usually very strict and uniform – non-active, false-positive and acute symptomatic cases may be included in the studies.

Most of the reviews in NWE report common and almost equal use of carbamazepine (CBZ) and phenytoin (PHT); polytherapy is used by 23–51% of the patients (Table 3, Figure 1). There is almost no published data from CEE to allow respective comparisons. Short prescription-based reports concerning antiepileptic treatment are available from Bulgaria (Peytchev and Marazova 1992; Peytchev *et al.* 1996), and some general figures based on AED sales data have been published in Hungary (Halasz 1995); see Table 4. Both indicate some differences compared to NWE – comparatively extensive use of carbamazepine and barbiturates, scanty use of valproate, and small overall quantities of drug sales.

In Estonia, only national drug sales data, collected by the Estonian State Agency of Medicines, are readily available (Estonian SAM 2004a; Estonian SAM 2004b). These figures reveal clear domination of CBZ among other AEDs, and increasing but still rather small aggregate AED consumption in Estonia, especially if compared with that in Finland (Finnish NAM 1998; Finnish NAM 2004), and Sweden (Svensk läkemedelsstatistik 1999), see Table 4. For children, only a brief overview of antiepileptic treatment, based on the prevalence study in Tartu, has been prepared (Beilmann *et al.* 2000). In it, CBZ was found to be the most frequently prescribed drug (44%), followed by VPA (29%) and CZP (2.5%). Polytherapy was used for 9% of patients, and 11% of children with active epilepsy did not take any AED.

Table 3. Population-based reviews on antiepileptic medication according to study design

Studies	Country	Year of study	Inclusion criteria*	Age groups years	Not treated %	Polytherapy %	Most frequent AEDs drug ** (%)
<i>Prevalence studies</i>							
Keränen 1988	Finland	1979	active epil.	≥16	20	33	PHT (56) CBZ (50)
Rutgers 1986	Holland	1982	active epil.	15–66	7	41	PHT (56) PB (34)
Forsgren 1992	Sweden	1985	active epil.	≥17	9	30	PHT (56) CBZ (30)
Olafsson <i>et al.</i> 1999	Iceland	1993	active epil.	all ages	9	23	CBZ (50) PHT (24)
Goodridge <i>et al.</i> 1983	UK	1983	all seizures	all ages	61	32	PHT (51) PB (32)
<i>Studies of AED users and diagnoses</i>							
McCluggae <i>et al.</i> 1984	UK	1979–1981	AED + Dgn	all ages	–	50	PB (30) PHT (20)
Giuliani <i>et al.</i> 1991	Italy	1985–1986	AED + Dgn	all ages	–	51	PB (77) PHT (31)
Muir <i>et al.</i> 1996	UK	1993–1994	AED + Dgn	all ages	–	24	CBZ (43) PHT (34)
Hart <i>et al.</i> 1995	UK	1994	AED + Dgn	all ages	–	34	PHT (43) CBZ (33)
Peitchev <i>et al.</i> 1992	Bulgaria	1987–1991	AED + Dgn	≥adolescence	–	80	PB (32) CBZ (27)
Peitchev <i>et al.</i> 1996	Bulgaria	1990–1994	AED + Dgn	all ages	–	40	CBZ (39) VPA (23)
<i>Prescription databases</i>							
Lammers <i>et al.</i> 1996	Holland	1989–1992	AED	all ages	–	20	CBZ VPA
Rochat <i>et al.</i> 2001	Denmark	1998	AED	all ages	–	26	CBZ (37) OXC (26)

* AED = use of antiepileptic drug, Dgn = diagnosis of epilepsy in medical records;

** CBZ = carbamazepine; OXC = oxcarbazepine; PB = phenobarbital; PHT = phenytoin; VPA = valproate

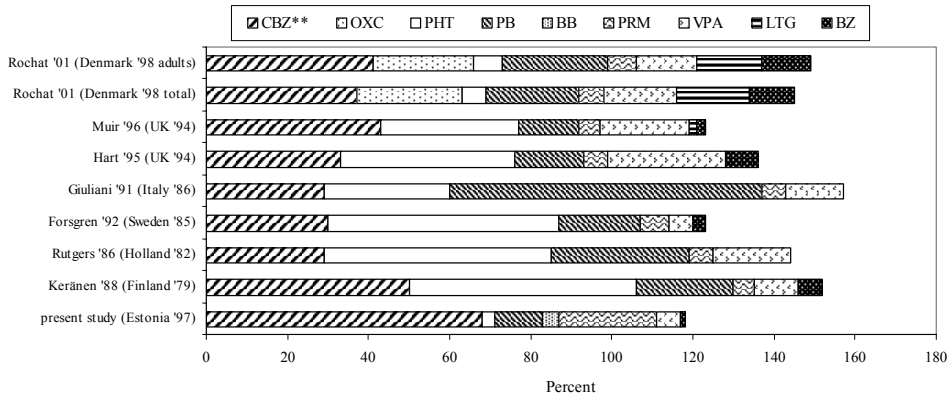


Figure 1. Utilization of antiepileptic drugs in different series*

* The sum of percentages is greater than 100 due to polytherapy

** CBZ = carbamazepine; OXC = oxcarbazepine; PHT = phenytoin; PB = phenobarbital; BB = benzobarbital; PRM = primidone; VPA = valproate; LTG = lamotrigine; BZ = benzodiazepines

Table 4. Consumption of antiepileptic drugs (given in DDD/1000 inhabitants/ day) in different populations

Drugs	Hungary 1993 ¹⁾	Bulgaria 1994 ²⁾	Sweden 1997 ³⁾	Finland 1997 ⁴⁾	Finland 2003 ⁵⁾	Estonia 1997 ⁶⁾	Estonia 2003 ⁷⁾
Barbiturates	–	–	0.7	0.62	0	0.62	0.51
Hydantoins	–	–	1.3	1.27	0.95	0.08	0.09
phenytoin	1.5	0.04	–	–	0.93	0.08	0.09
Carboxamides	–	–	2.1	4.07	4.31	1.32	2.22
carbamazepine	1.8	0.65	–	2.89	2.55	1.32	2.21
oxcarbazepine	–	–	–	1.19	1.76	0	0.01
Fatty acids	–	–	0.9	1.51	2.92	0.28	0.70
valproate	0.5	0.28	–	1.31	2.84	0.28	0.69
Others	–	–	0.4	0.20	1.95	0	0.24
lamotrigine	–	–	–	0.16	0.69	0	0.13
Total	4.7	–	5.7	8.29	10.95	2.4	4.09

¹⁾ Halasz 1995; ²⁾ Peytchev *et al.* 1996; ³⁾ Svensk 1999; ⁴⁾ Finnish NAM 1998; ⁵⁾ Finnish NAM 2004; ⁶⁾ Estonian SAM 2004a; ⁷⁾ Estonian SAM 2004b

III. AIMS OF THE STUDY

The general objective of the present study was to describe the epidemiologic characteristics of epilepsy in a defined adult population in Estonia.

The specific objectives were:

- a) to evaluate retrospectively the incidence of epilepsy and its clinical characteristics in an adult population of Tartu;
- b) to evaluate retrospectively the point prevalence of active epilepsy and its clinical characteristics in an adult population of Tartu;
- c) to assess the general antiepileptic treatment patterns and use of particular antiepileptic drugs based on the prevalence study of adult active epilepsy in Tartu.

IV. PATIENTS AND METHODS

1. Study area and population

Estonia regained independence after the collapse of the Soviet Union in 1991. Estonia is situated in the northeastern part of Europe on the eastern coast of the Baltic Sea. The statistical data of the population was provided by the Statistical Office of Estonia, based on the 1989 census (Statistical Office of Estonia 1994–1997). The study area was chosen based on the availability of sufficiently high quality health-care services and the representativeness of the sample population to the population of the whole country.

The study was conducted in the university town of Tartu. It is the second largest town in Estonia, situated in the southeastern part of the country. Since every person in Estonia has a registered place of residence, the office in Tartu adjusts the population data every year according to the registration list.

The age-limit of 20 years for adults was used as a result of the age criteria of ≤ 19 years used in the earlier study of childhood epilepsy (Beilmann *et al.* 1999a; Beilmann *et al.* 1999b).

In the present study, the data on registered residents was used as a denominator for calculating crude epidemiologic indices. Adult population (aged 20 years and older) varied from 77,066 on January 1, 1994 to 75,245 on January 1, 1997. On the prevalence day, January 1, 1997, the total population of Tartu was 101 901, of whom 75,245 were aged 20 years and over (Statistical Office of Estonia 1994–1997). Most of the population were ethnic Estonians.

Tartu is the location of Tartu University Hospital (TUH) which is a tertiary referral centre for the southeastern part of Estonia. It provides tertiary, secondary, and partially primary care to local residents in all medical specialities, including neurology. In Tartu, EEG is available since 1961, computerised tomography scanning since 1983, and magnetic resonance imaging since 1992. In 1996, the measurement of AED concentration just became available for routine use.

Medical care, i.e. consultations, medical investigations, and most drugs, is paid for by the Estonian Health Insurance Fund (EHIF). Approximately 90% of the population has EHIF insurance cover. Compensation of medication in Estonia depends on the diagnosis and on the catalogue of drugs accorded full or partial compensation. In 1997, with a diagnosis of epilepsy, the conventional AEDs were compensated in full for insured persons.

The patients are registered at a family doctor. Those with a suspected diagnosis of epilepsy are referred to a neurologist who makes a diagnostic work-up and begins therapy if needed. Usually patients with epilepsy are routinely supervised by a family doctor. Previously, in the former Soviet Union, long-term and complicated cases of epilepsy were officially supervised by psychiatrists. In

the late 80's, the system was changed and general management of epilepsy was officially given to neurologists. However, a mixed pattern of supervision still existed in 1997.

2. Definitions

2.1. Epileptic seizure and epilepsy

Special attention was paid to the adoption of definitions and criteria proposed by the ILAE Guidelines for epidemiologic studies (Commission 1993).

A seizure was considered epileptic if clinical features were presumed to result from an abnormal and excessive discharge of neurons in the brain.

We considered epilepsy as a condition characterized by recurrent (two or more) epileptic seizures occurring at least 24-h apart, unprovoked by any immediate identifiable cause. Individuals who had had provoked or acute symptomatic seizures were excluded from the study. Diagnosis of epilepsy was made mainly on a clinical basis, relying on a description of seizures, results of EEG, and other investigations, where available. Investigations were not applied as independent inclusion or exclusion tools.

An active case of epilepsy in the present study was defined as a person with at least one epileptic seizure in the previous five years, regardless of anti-epileptic drug treatment. As the majority of the recent studies have included cases without seizures but with antiepileptic drug administration, we recorded cases in remission, but with treatment in the previous five years, separately.

2.2. Classification of seizure types

Seizures were classified according to the ILAE classification, which separates seizures into partial, generalized, and unclassifiable (Commission 1981). The classification of seizures was based on descriptions obtained from patients or eye-witnesses, and EEG recordings where available. The distribution of seizure types was presented according to the most frequent seizure type.

A seizure was classified as partial when there was evidence of a clinical or an EEG focal onset. These seizures were further classified as simple partial seizures (when alertness is maintained during a seizure), complex partial seizures (when impairment of consciousness, amnesia or confusion is reported), and secondarily generalized seizures, which are always included in the group of partial seizures in the current study.

The term "generalized seizure" was reserved only for primary generalized seizures, i.e. when clinical symptomatology provided no evidence of focal onset and preferably, but not obligatorily, EEG signs suggested primary generali-

zation. The three main generalized types were: generalized convulsive seizures, absence seizures, and myoclonic seizures.

The category of unclassified seizures were used when it was impossible to classify seizures due to lack of adequate information.

2.3. Risk factors

For the risk factors of epilepsy, the present study applied the classification proposed by the ILAE Guidelines (Commission 1993). Seizures occurring within seven days after a short-lasting event (head injury, intracranial operation, cerebrovascular accident), in the course of active condition (infection, CNS tumor, systematic disturbance, exposure to drugs, fever) or associated with elimination of some agents (alcohol, benzodiazepines, barbiturates) were classified as acute symptomatic or provoked seizures.

The following conditions were considered to be the remote risk factors for epilepsy: (a) head injury (only severe and moderate traumas were included); (b) cerebrovascular disease (cerebral infarction, intracerebral hemorrhage, subarachnoid hemorrhage); (c) CNS infection (abscesses, encephalitides with all etiologies, and bacterial meningitides); (d) pre- and perinatal risk factors (developmental malformations of brain, severe neonatal encephalopathy with residual motor disorder, mental retardation and/or motor disorder in persons without other defined etiology); (e) progressive neurologic conditions (CNS neoplasm, Alzheimer disease, slow virus infections etc.); (f) other predisposing causes (i.e. post encephalopathic states, chronic alcohol abuse with no evidence of acute withdrawal or intoxication, structural brain lesions probably related to genesis of seizures not defined above).

Head injuries were divided into severe, moderate, and mild groups. Those with severe head injuries were characterised by one or more of the following features: open head injury including brain surgery, intracranial hematoma, documented brain contusion, focal neurologic deficit, depressed skull fracture, 24 hours or more of either unconsciousness or documented posttraumatic amnesia. The moderate group contained patients who were excluded from the severe group, but had non-depressed skull fractures, or >30 minutes of either unconsciousness or documented posttraumatic amnesia. Those without fracture but with either unconsciousness or documented posttraumatic amnesia for less than 30 minutes were included in the mild group, and were not considered as injury-related cases.

Analytic studies based on massive cohorts (Annegers *et al.* 1980; Annegers *et al.* 1988; Annegers *et al.* 1996) suggest that moderate head injury and bacterial meningitis increase the risk of epilepsy only during the first five years after the event. Thus, in order to consider these particular factors as possible causes for epilepsy, the first unprovoked seizure had to occur within five years of the event.

Recurrent seizures associated with progressive neurologic condition are characterized by a pathophysiology which is in slow evolution (incompletely or unsuccessfully treated CNS tumors, Alzheimer disease, slow virus infections, multiple sclerosis, phenylketonuria etc.); it is unclear whether these seizures conform to remote or acute symptomatic criteria. However, these conditions usually need long-term treatment with AEDs, being akin to the concept of chronic epilepsy.

2.4. Classification of epilepsies and epileptic syndromes

Classification of epilepsies and epileptic syndromes was based on the criteria proposed by the ILAE, which connects together seizure types, presumed etiology, and special diseases (Commission 1989).

First, it divides diagnoses into the four major classes: (a) localization-related and (b) generalized syndromes, (c) epilepsies for which it is undetermined whether they are related to focal or generalized conditions (commonly due to insufficient data) and (d) special syndromes (commonly situation-related seizures). Subjects with special syndromes were excluded because of the definition of epilepsy in the present study.

Thereafter, these classes are grouped by presumed causes, mainly to symptomatic, idiopathic or cryptogenic syndromes. Symptomatic syndromes are considered to be the consequence of known or suspected disorders that are risk factors for epilepsy. The term “idiopathic” is reserved only for certain age-related epileptic syndromes with particular clinical and EEG characteristics and presumed genetic etiology. Cryptogenic epilepsies are the entities whose etiology is presumed to be symptomatic, but is actually unknown, i.e. the criteria of symptomatic or idiopathic diagnoses are not met. These diagnoses are commonly associated with partial and less often, almost always in childhood, with generalized seizures.

3. Case ascertainment and data collection

3.1. Case ascertainment

The provisional study group was compiled by carrying out a retrospective search of all putatively epilepsy-related databases in the area, to identify all persons aged 20 years and older diagnosed with epilepsy, seizure, convulsions, amnesic attack, brain tumours, stroke, and dementia from 1 January 1992 to 31 December 1996.

The sources included in the search were: (a) files of family doctors practicing in Tartu; (b) case records of patients treated as out- or inpatients at the TUH; (c)

files of neurologists at the municipal outpatient clinic; (d) files of the Emergency Department of TUH; (e) medical prescriptions of antiepileptic drugs provided by the Regional Health Insurance Fund of Tartu; (f) the register of the EEG unit; (g) files of social welfare institutions; (h) a list of the members of the Estonian Epilepsy Association.

All the names on the provisional list were checked against the data in the Regional Statistical Office of Tartu, and non-permanent residents of the area and those under 20 years of age at the date of onset were excluded from the final study group.

3.2. Collection of general data

All suitable persons were contacted by mail and were invited for re-examination. Two additional letters were sent to non-respondents, and they were contacted by telephone if possible. All respondents were interviewed and re-examined following an identical protocol by A. Õun and by S. Haldre.

Further classification and exclusion of cases was carried out following personal re-examinations and/or analyses of medical records. Only definite cases meeting the inclusion criteria were included in the study.

In the incidence study, the date of the second unprovoked seizure was considered to mark the onset of epilepsy, and if the date of second seizure reported by a patient was significantly different from that in the medical record, the date in the record was used.

The prevalence day was set to 1 January 1997. In the present study the inclusion criteria for a prevalent case on the prevalence day were the following: (a) a resident of the town of Tartu; (b) at least 20 years of age; (c) at least two verified unprovoked epileptic seizures, at least 24-h apart; (d) at least one seizure within the previous five years counted from the prevalence day.

3.3. Collection of treatment data

All used drugs and doses of AEDs on the prevalence day were recorded. For those who did not take any AED, either the doctor or the subject was asked for the reason. In the current paper, the term “polytherapy” is reserved for the treatment strategy in which two or more AEDs are prescribed simultaneously.

Used drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification (WHO 1996). The used doses of AEDs were compared to defined daily doses (DDD) (WHO 1996), and to the clinically more relevant minimum maintenance doses (MMD) usually recommended for adults by reviews (Brodie and Dichter 1996), manufacturers (Pharmaca Estica 2004), and handbooks (Duncan *et al.* 1995; Leppik 2000), see Table 14.

Measurement of AED concentration was not systematically used in 1996, only a few patients were tested, and these random results were not included in the study. Special concentration measurements for the study were neither feasible nor justified.

An attempt was made to record seizure frequency as a treatment effectiveness measure, but very few subjects had well-documented records of seizures, the data on the remainder being poorly recorded and controversial. Therefore seizure frequency was not included in the analysis.

4. Statistical analysis

The numerator for incidence calculations was defined above; the denominator was the sum of the mean population figures for the years 1994, 1995, and 1996 in Tartu (Statistical Office of Estonia 1994–1997).

Prevalence rates were calculated using the population of Tartu on 1 January 1997 as the denominator (Statistical Office of Estonia 1994–1997).

Incidence and prevalence rates were age-adjusted by the direct method using the 1989 standard population in Estonia (Baburin *et al.* 1997), the total 1970 U.S. population (U.S. Bureau 1970) and the European standard population (Waterhouse *et al.* 1976).

Confidence intervals (CI) for the rates were calculated according to a method described by Frank and Althonen (1994). Statistical calculations were performed with the Statistica program, version 6.1.

5. Ethics

The study was approved by the Ethical Committee of Medical Research at Tartu University.

V. RESULTS

1. Incidence of adult epilepsy

1.1. Provisional study group

A total of 153 adult subjects were included in the provisional group, 71 of them (46%) were personally re-examined, and 20 (13%) were interviewed by telephone. For the non-reviewed 62 subjects (41%), inclusion in the final analysis was based on reliable and sufficient data from medical records.

Seventy-two provisional subjects were excluded from the final analysis: 33 of them (45.8%) had acute symptomatic seizures (24 of them, 33.3%, alcohol withdrawal seizures); 15 cases (20.8%) were excluded due to insufficient data; nine persons (12.5%) had only a single seizure; and eight subjects (11.1%) were not permanent residents of the area.

Seven subjects (9.7%) were rejected due to nonepileptic episodes: four cases of them were psychogenic seizures, two cases were syncopal attacks, and one subject had transient ischaemic attacks.

Eighty-one persons (55 men, 26 women) fulfilled the criteria for inclusion in the final analysis; 39 of them (48%) had been personally re-examined, and nine (11%) had been interviewed by telephone. The differences between the main characteristics of the personally re-examined and non re-examined groups were not statistically significant ($p > 0.05$), see Table 5.

Table 5. Main characteristics of responder and non-responder groups in the incidence study in Tartu

Characteristics	Responders	Non-responders	P-value of difference
	Cases (%)	Cases (%)	
Partial seizures	38 (79)	23 (70)	0.33
Generalized seizures	2 (4)	1 (3)	0.3
Unclassifiable seizures	8 (17)	9 (27)	0.25
Symptomatic etiology	27 (56)	16 (48)	0.49
Aged ≥ 60 years	20 (42)	10 (30)	0.3
Men	33 (69)	22 (67)	0.84
Women	15 (31)	11 (33)	0.85

1.2. Incidence rates

The crude IR of epilepsy for the 3-year period was 35.4/100 000 person-years (95% CI 27.7–43.1). The rate was higher for men than for women, 54.4 and 20.4/100 000 respectively; but the overall difference was not statistically significant ($p>0.05$). The age-adjusted IR was 35.5/100 000 using the 1989 Estonian standard population aged ≥ 20 years, 34.7/100 000 using the 1970 U.S. population aged ≥ 20 years, and 35.3/100 000 using the European standard population aged ≥ 20 years.

The age-specific rates tended to increase with advancing age; the incidence in elderly people (aged >60 years) was 51/100 000, being higher than that in any other age group. The age-specific figures for men showed lower rates for those aged 20–49, and notably higher rates for those aged over 60 years; in women, the rates remained rather constant above the age of 30, but the highest IR was obtained for women aged over 80 years. The sex- and age-specific incidence rates are outlined in Table 6 and in Figure 2.

1.3. Seizure types

Seizures with partial onset occurred in 61 of the cases (75.3%), making the incidence for this group 27/100 000. The largest subgroup was that of secondarily generalized seizures, which included 40 of the patients (49.4%). Only three subjects (3.7%) had generalized seizures; two of them had tonic-clonic, and one had myoclonic seizures. Available data was inappropriate to classify seizures for 17 of the subjects (21%), corresponding to an incidence of 7/100 000. A more specific distribution of seizures is presented in Table 7.

1.4. Risk factors

Risk factors specific to epilepsy were identified in 45 of the patients (55.5 %), corresponding to an incidence of 19.7/100 000. Epilepsy was considered remote symptomatic in 36 (44.4%) and progressive symptomatic in nine (11.1%) of the patients. Cerebrovascular diseases, especially infarcts, and head injuries were the most frequent risk factors, 16 (19.7%) and 13 (16%) cases respectively. Among those with tumours, nine subjects (11.1%), meningiomas were present in five patients, and the other neoplasms were oligodendroglioma (WHO grade 2), astrocytoma (WHO grade 2) and metastasis of lung cancer. Two of these patients had diagnosed tumour disease prior to the first seizure (both were meningiomas); one patient (oligodendroglioma) had recurrent seizures before a tumour was diagnosed. Prenatal risk factors included those with hypoplasia of *corpus callosum* and arteriovenous malformations, one and two patients respectively. Distribution of risk factors by pathology and age is presented in Table 8.

Table 6. Age- and sex-specific incidence rates (per 100 000 person-years) in Tartu

Age (years)	Men			Women			Total					
	Population ¹⁾	Cases	Rate	95% CI	Population ¹⁾	Cases	Rate	95% CI	Population ¹⁾	Cases	Rate	95% CI
20–29	27622.5	9	32.6	11.3–53.9	25858.5	2	7.7	0.0–18.4	53481	11	20.6 ²⁾	8.4–32.8
30–39	20318	10	49.2	18.7–79.7	22309.5	4	17.9	0.3–35.5	42627.5	14	32.8	15.6–50.0
40–49	17065	6	35.2	7.1–63.3	20444	5	24.5	3.1–45.9	37509	11	29.3	12.0–46.6
50–59	15685.5	9	57.4	19.9–94.9	20758	6	28.9	5.8–52.0	36443.5	15	41.2	20.4–62.0
60–69	12829.5	14	109.1	52.0–166.2	19324.5	4	20.7	0.4–41.0	32154	18	56.0 ²⁾	30.1–81.9
70–79	5444	5	91.8	11.3–172.3	12098.5	2	16.5	0.0–39.4	17542.5	7	39.9 ²⁾	10.3–69.5
≥80	2173	2	92.0	0.0–219.5	6903	3	43.5	0.0–92.7	9076	5	55.1	6.8–103.4
Total	101137.5	55	54.4	40.0–68.8	127696	26	20.4	12.6–28.2	228833.5	81	35.4	27.7–43.1

¹⁾ The mean populations of the years 1994–1996 (population at risk) in Tartu.

²⁾ Difference between men and woman was statistically different ($p < 0.05$).

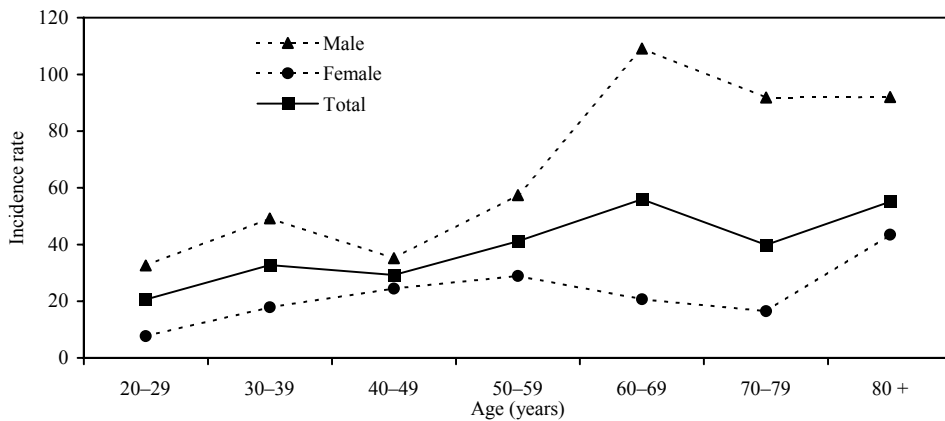


Figure 2. Age- and sex-specific incidence rates (per 100 000 person-years) in Tartu

Table 7. Incidence (per 100 000) and prevalence (per 1000) of seizure types in Tartu

Seizure types	Incidence		Prevalence	
	Cases (%)	Rate	Cases (%)	Rate
Partial seizures	61 (75.3)	26.7	294 (74.2)	3.91
Simple partial	11 (13.6)	4.8	55 (13.9)	0.73
Complex partial	10 (12.3)	4.4	80 (20.2)	1.06
Partial secondarily generalized	40 (49.4)	17.5	159 (40.2)	2.11
Primary generalized seizures	3 (3.7)	1.3	23 (5.8)	0.31
Absence			6 (1.5)	0.08
Myoclonic	1 (1.2)	0.4	6 (1.5)	0.08
Tonic-clonic	2 (2.5)	0.9	11 (2.8)	0.15
Unclassifiable	17 (21.0)	7.4	79 (19.9)	1.05

Table 8. Incidence (rate per 100 000) and prevalence (rate per 1000) of risk factors in Tartu

Risk factors	Incidence		Prevalence	
	Cases (%)	Rate	Cases (%)	Rate
1. Remote symptomatic	36 (44.4)	15.7	137 (34.6)	1.82
1.1. Head injuries	13 (16.0)	5.7	53 (13.4)	0.70
a) Severe head injury	10 (12.3)	4.4	33 (8.3)	0.44
b) Moderate head injury	3 (3.7)	1.3	20 (5.1)	0.26
1.2. Cerebrovascular diseases	16 (19.7)	7.0	26 (6.6)	0.35
a) Infarction	13 (16.0)	5.7	18 (4.5)	0.24
b) Hemorrhage	3 (3.7)	1.3	8 (2.0)	0.11
1.3. Pre- and perinatal risk factors	3 (3.7)	1.3	27 (6.8)	5.70
a) Developmental malformations of brain	3 (3.7)	1.3	7 (1.8)	0.09
b) Severe neonatal encephalopathies with residual deficit	0	0	13 (3.3)	0.17
c) Mental retardation or motor disorder without other causes	0	0	7 (1.8)	0.09
1.4. CNS infections	1 (1.2)	0.4	17 (4.3)	0.23
1.5. Others	3* (3.7)	1.3	14** (3.5)	0.19
2. Progressive symptomatic	9 (11.1)	3.9	20 (5.1)	0.26
2.1. Neoplasms	8 (9.9)	3.5	19 (4.8)	0.25
2.2. Alzheimer disease	1 (1.2)	0.4	1 (0.3)	0.01
3. Unknown	36 (44.4)	15.7	239 (60.4)	3.18

* Structural brain lesion (1), alcohol-related encephalopathies (2).

** Structural brain lesions (9 cases), alcohol-related encephalopathies (3 cases), post-anoxic (1 case) and post-eclamptic (1 case) encephalopathy.

Sex-specific rates for men were higher in both symptomatic epilepsies and in syndromes without apparent causes, 29 and 26/100 000 respectively; the estimates for women were 13 and 8/100 000.

1.5. Syndromic diagnoses

Localization-related epilepsies accounted for 61 patients (74.3%), making an incidence for this class of 27/100 000. Among them, symptomatic epilepsy accounted for 41 (50.6%), and cryptogenic syndrome for 20 (24.7%) of the cases. In the class of generalized epilepsies, only three cases were recorded; all were idiopathic syndromes – juvenile myoclonic epilepsy, epilepsy with *grand mal* on awakening, and unspecified *grand mal* epilepsy. For 17 patients (21%), the epilepsy was classified as undetermined, making the IR of this category 7/100 000. Most of them were syndromes manifested with major motor seizures without clinical or electroencephalographic evidence of focal or generalized onset; four of them were symptomatic and 13 cryptogenic epilepsies. The detailed age-specific incidences of syndromic diagnoses are presented in Table 9.

Table 9. Age- specific incidence rates of epileptic syndromes (per 100 000) in Tartu

Age (years)	Localization-related epilepsies				Generalized epilepsies		Undetermined	
	Symptomatic		Cryptogenic		Idiopathic		Undetermined	
	Cases	Rate	Cases	Rate	Cases	Rate	Case	Rate
20–29	2	3.7	5	9.3	3	5.6	1	1.9
30–39	7	16.4	5	11.7	0	0	2	4.7
40–49	5	13.3	3	8.0	0	0	3	8.0
50–59	10	27.4	1	2.7	0	0	4	11.0
60–69	11	34.2	4	12.4	0	0	3	9.3
70–79	4	22.8	0	0	0	0	3	17.1
≥80	2	22.0	2	22.0	0	0	1	11.0
Total	41	17.9	20	8.7	3	1.3	17	7.4

2. Prevalence of adult epilepsy

2.1. Provisional study group

Altogether 609 adult cases with screening diagnoses during the 5-year period were identified, 213 of them were excluded. The causes for the rejection were acute symptomatic or single seizures for 59 subjects (27.7% of the excluded group), 58 subjects (27.2%) were not permanent residents of the area, 24 (11.3%) died before the prevalence day, and 23 cases (10.8%) were excluded due to insufficient data.

Twenty-two subjects (10.3%) were rejected due to nonepileptic episodes; 12 of these cases were very probably psychogenic seizures, six cases were syncopal attacks, two were very probably vertiginous episodes, and two subjects had transient ischaemic attacks.

Twenty-seven patients (12.7%) were in clinical remission, 14 of them had received antiepileptic drugs in the previous five years. These latter patients were recorded separately, but were not included in further analysis.

A total of 396 fulfilled the inclusion criteria, 236 of them (59.6%) were personally re-examined; an additional 33 subjects (8.3%) were interviewed by telephone. The inclusion of the remaining cases was based on sufficient data from the medical records.

2.2. Prevalence rates

The crude PR of active epilepsy in adults was 5.3/1000 (95% CI 4.8–5.8). The study group included 227 (57.3%) men and 165 (42.7%) women, making the prevalence 6.9/1000 and 4.0/1000 respectively. The PR was higher for men than for women in every age-group, but the overall difference between sexes was not statistically significant ($p>0.05$). The age-adjusted PR was 5.3/1000 using the 1989 Estonian standard population aged ≥ 20 years, 5.3/1000 using the 1970 U.S. population aged ≥ 20 years, and 5.4/1000 using the European standard population aged ≥ 20 years.

If the 14 cases in remission but receiving antiepileptic drugs in the previous five years were included the crude prevalence rate would be 5.5/1000.

The overall age-specific prevalence rates remained rather constant in age-groups 30–69 years, and diminished above the age of 70 years. Highest age-specific rates in men were observed in the oldest age-group and in the 40–59 year-old age group; highest rates in women were noticed in the 60–69, and 30–39 year-old age groups. The age- and sex-specific prevalence rates are outlined in Table 10 and in Figure 3.

Table 10. Age- and sex-specific prevalence rates (per 1000 persons) in Tartu

Age (years)	Men			Women			Total					
	Population	Cases	Rate	95% CI	Population	Cases	Rate	95% CI	Population	Cases	Rate	95% CI
20–29	8970	41	4.6	3.2–6.0	8536	35	4.1	2.7–5.5	17506	76	4.3	3.3–5.3
30–39	6768	44	6.5	4.6–8.4	7301	36	4.9	3.3–6.5	14069	80	5.7	4.5–6.9
40–49	5601	51	9.1	6.6–11.6	6853	24	3.5	2.1–4.9	12454	75	6.0	4.6–7.4
50–59	4896	46	9.4	6.7–12.1	6660	25	3.8	2.3–5.3	11556	71	6.1	4.7–7.5
60–69	4206	32	7.6	5.0–10.2	6284	34	5.4	3.6–7.2	10490	66	6.3	4.8–7.8
70–79	1960	6	3.1	0.7–5.5	4306	8	1.9	0.6–3.2	6266	14	2.2	1.0–3.4
≥80	698	7	10.0	2.6–17.4	2206	7	3.2	0.9–5.5	2904	14	4.8	2.3–7.3
Total	33099	227	6.9	6.0–7.8	42146	169	4.0	3.4–4.6	75245	396	5.3	4.8–5.8

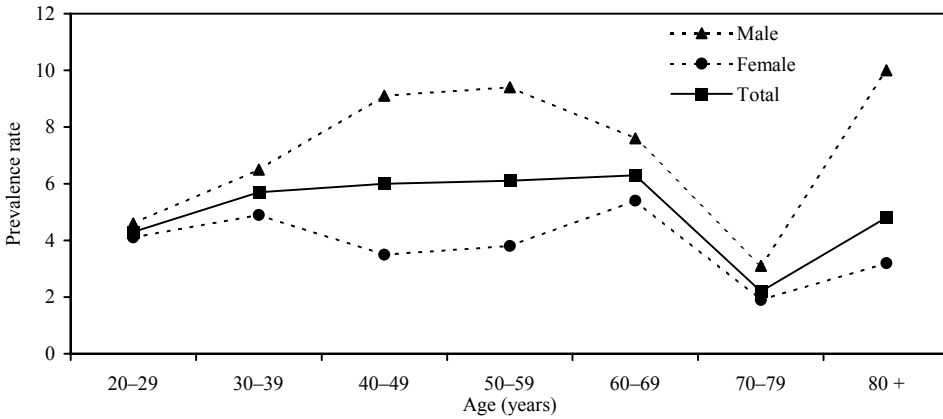


Figure 3. Age- and sex-specific prevalence rates (per 1000 persons) in Tartu

2.3. Seizure types

The seizure types were verified for 317 of the patients (80.1%). Some 294 patients (74.3%) had seizures with partial onset, and 23 (5.8%) had generalized seizures. Available data did not allow the unequivocal classification of seizures for 79 (19.9%) of the cases. A total of 171 of the patients (43.2%) had more than one seizure type. A more specific categorization according to seizure types is presented in Table 7.

2.4. Risk factors

Specific causes for epilepsy were identified in 157 (39.6%) cases. Epilepsy was considered remote symptomatic in 137 (34.6%) cases. The category of head injuries was by far the largest subgroup, 53 (13.4%) subjects, followed by pre- and perinatal risk factors and vascular diseases, 27 (6.8%) and 26 (6.6%) cases respectively.

Progressive symptomatic diseases accounted for 20 (5.1%) cases. The vast majority of them were different types of neoplasms: meningiomas, six cases; astrocytomas, five cases; oligodendrogliomas, three; glioblastomas, two; metastasis of lung cancer, one; and unspecified tumours, two subjects. Specific causes of symptomatic epilepsies are presented in Table 8.

2.5. Syndromic diagnoses

Available data enabled specific syndromes to be diagnosed for 317 (80.1%) of the cases. The largest subgroups were localization-related symptomatic and localization-related cryptogenic syndromes, 149 (37.6%) and 145 (36.6%) subjects respectively. Generalized syndromes were diagnosed in 23 (5.8%) cases, childhood absence epilepsies, in three; juvenile absence epilepsies, five; juvenile myoclonic epilepsies, six; epilepsies with GTCS on awakening, six; other not defined generalized idiopathic epilepsies, one; and seizures precipitated by specific modes of activation, two subjects. Syndromes remained undetermined for 79 (19.9%) patients, mainly due to unclassifiable seizures. Age-adjusted prevalence of syndromes is presented in Table 11.

Table 11. Age- specific prevalence rates of epileptic syndromes (per 1000 persons) in Tartu

Age (years)	Localization-related epilepsies				Generalized epilepsies		Undetermined	
	Symptomatic		Cryptogenic		Idiopathic		Undetermined features	
	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate
20–29	23	1.31	29	1.66	16	0.91	8	0.46
30–39	32	2.27	26	1.85	6	0.43	16	1.14
40–49	36	2.89	20	1.61	1	0.08	18	1.45
50–59	22	1.90	34	2.94	0	0	15	1.30
60–69	29	2.76	23	2.19	0	0	14	1.33
70–79	4	0.64	8	1.28	0	0	2	0.32
≥80	3	1.03	5	1.72	0	0	6	2.07
Total	149	1.98	145	1.93	23	0.31	79	1.05

3. Medical treatment

3.1. General characteristics

Of all 396 subjects with active epilepsy, 309 patients (78%) were known to be taking AEDs (ATC code N03) on the prevalence day, 75 subjects (18.9% of all cases) did not take any AED on the prevalence day, and the antiepileptic medication status of 12 subjects (3.0% of all cases) remained unknown.

The reasons for not taking AED medication on the prevalence day were: the discontinuation of treatment on the patient's own decision (non-compliance) in

33 cases (8% of all cases, 44% of the 75 AED-free active cases); delayed diagnosis on the prevalence day in 15 cases (20% of the AED-free group); no insurance on the prevalence day in 14 cases (3.5% of all cases, 19% of the AED-free group); no need for AED treatment on the doctor's decision in 10 cases (2.5% of all cases, 13% of the AED-free group); and unknown in three cases (4% of the AED-free group).

Regularly coprescribed drugs other than AEDs were reported for 95 subjects (24%). The most frequent agents were psycholeptics and psychoanaleptics (ATC code N05 and N06), reported for 28 subjects (30% of those with comedication); 16 of them were anxiolytics, eight antipsychotics (two of them phenothiazines as proconvulsants), and four antidepressants (two of them were tricyclic as proconvulsants). Other common agents were cardiovascular medicines (ATC code C01–C08), which were taken by 27 subjects (28% of those with comedication).

3.2. Medication strategies

Altogether 257 subjects (83% of those on medication) were taking a single agent; two and three AEDs simultaneously were prescribed in 46 (15% of those on medication) and six (2% of those on medication) cases respectively.

General treatment profile and treatment patterns in the particular subgroups of epileptic syndromes are summarized in Table 12. The diagnosis of localization-related symptomatic epilepsy corresponded to the largest percentage of treated and polytherapy cases, 87.9% and 19.9% respectively. The figures for localization-related cryptogenic epilepsy and for undetermined syndromes were rather similar – 73.8% of cases were treated in both groups; the latter one included no patients on three AEDs. The treatment pattern of generalized idiopathic syndromes was different, since there were no patients on polytherapy, and the proportion of cases without any AED was the highest.

3.3. Utilization of particular drugs

The prescription frequencies of each AED, and their distribution in relation to syndromic diagnoses are presented in Table 13 and Figure 4; the sum of the given percentages is greater than 100 due to polytherapy.

In general, drug prescription followed the frequency pattern of localization-related syndromes – the most frequently prescribed agent was CBZ (67.6% of the treated patients), followed by barbiturates – PRM and PB with 24% and 12% respectively, and a considerable number of subjects (4.5%) were taking BB. Some 178 (85%) CBZ users, and 66 (53%) barbiturate users were taking drugs

Table 12. Distribution of treatment patterns by epileptic syndromes in Tartu

Syndromes	Syndromes	Treated*	1 AED**	2 AED**	3 AED**	Not treated*	Unknown*
	Total (%)	Cases (%)	Cases (%)	Cases (%)	Cases (%)	Cases (%)	Cases (%)
Localization-related	149 (37.6)	131 (87.9)	105 (80.1)	22 (16.8)	4 (3.1)	17 (11.4)	1 (0.7)
Symptomatic	145 (36.6)	107 (73.8)	89 (83.2)	16 (15.0)	2 (1.9)	33 (22.8)	5 (3.5)
Cryptogenic	23 (5.8)	13 (56.5)	13 (100)	0	0	9 (39.1)	1 (4.4)
Generalized idiopathic	79 (20.0)	58 (73.8)	50 (86.2)	8 (13.8)	0	16 (20.3)	5 (6.3)
Undetermined							
Total	396 (100)	309 (78.0)	257 (83.2)	46 (14.9)	6 (1.9)	75 (18.9)	12 (3.0)

* % is calculated from the total number of cases in particular syndrome

** % is calculated from the treated cases of particular syndrome

Table 13. Distribution of used drugs and epileptic syndromes in Tartu

Syndromes	CBZ*	PRM	PB	VPA	BB	PHT	CZP	ESM	CLB
	Cases (%)	Cases (%)	Cases (%)	Cases (%)	Cases (%)	Cases (%)	Cases (%)	Cases (%)	Cases (%)
Localization-related	101 (77.1)	23 (17.6)	15 (11.5)	8 (6.1)	7 (5.3)	3 (2.3)	2 (1.5)	1 (0.8)	1 (0.8)
Symptomatic**	75 (70.1)	26 (24.3)	13 (12.0)	4 (3.7)	3 (2.8)	5 (4.7)	1 (0.9)	0	0
Cryptogenic**	5 (38.5)	3 (23.1)	0	5 (38.5)	0	0	0	0	0
Generalized idiopathic**	28 (48.3)	22 (37.9)	9 (15.5)	2 (3.4)	4 (6.9)	0	0	1 (1.7)	0
Undetermined**	209 (67.6)	74 (23.9)	37 (12.0)	19 (6.2)	14 (4.5)	8 (2.6)	3 (1.0)	2 (0.6)	1 (0.3)

* CBZ = carbamazepine; PHT = phenytoin; PRM = primidone; PB = phenobarbital; BB = benzobarbital; VPA = valproate; ESM = ethosuximide; CZP = clobazepam; CLB = clobazam

** % is calculated from the treated cases of particular syndrome

*** % is calculated from the total number of treated cases

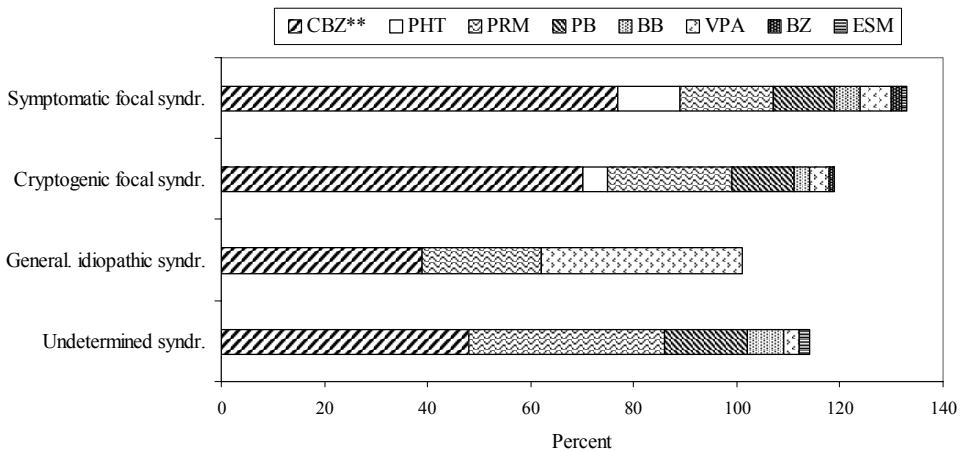


Figure 4. Utilization of AEDs according to syndromic diagnoses in Tartu*

* The sum of percentages is greater than 100 due to polytherapy

** CBZ = carbamazepine; PHT = phenytoin; PRM = primidone; PB = phenobarbital; BB = benzobarbital; VPA = valproate; BZ = benzodiazepines; ESM = ethosuximide

as monotherapy. In general, VPA (6.2%) and PHT (2.6%) were not common drugs. Patients with generalized idiopathic epilepsy were treated equally with CBZ and VPA as monotherapy. ESM and BZs were used in two and four cases respectively, for persons with localization-related and undetermined syndromes, as a part of polytherapy (one case with CZP monotherapy).

Among the 50 patients taking two or more AEDs, the most common combinations were PB/PRM (11 cases, 22% of the polytherapy group), CBZ/PB (nine cases, 18%), and CBZ/PRM (eight cases, 16%); followed by VPA/CBZ (four cases, 8%), and PRM/BB (three cases, 6%). The six combinations of three simultaneous agents were CBZ/VPA/BB, CBZ/PRM/PB, PHT/PRM/PB, CBZ/PHT/PRM, CBZ/ESM/PB, and CBZ/PRM/CLB.

3.4. Doses of drugs

Of a total of 367 AED prescriptions, data on doses was available on 351 occasions (95.6%). Some most common drugs were compared with DDD and MMD; the results are presented in Table 14. For CBZ, PRM, and VPA the doses were much smaller than the recommended DDD; in comparisons with MMD, most doses were equal or higher than MMD for all these drugs. PB had the lowest proportion of less than MMD prescriptions, 8.3%; but for other given drugs, the percentage of less than MMD prescriptions ranged from 33% to 50%.

Table 14. Relationship of used doses to defined daily doses (DDD) and minimal maintenance doses (MMD) in Tartu

Drugs*	Users		DDD	<DDD	≥DDD	Unknown	MMD	<MMD	≥MMD
	Cases	Cases (%)	mg/day	Cases (%)	Cases (%)	Cases (%)	mg/day	Cases (%)	Cases (%)
CBZ**	209	176 (84.2)	1000	28 (13.4)	5 (2.4)	600	69 (33.0)	135 (64.6)	
PRM**	74	65 (87.8)	1250	6 (8.1)	3 (4.1)	750	27 (36.5)	44 (59.5)	
PB**	37	3 (8.1)	100	29 (78.4)	5 (13.5)	100	3 (8.1)	29 (78.4)	
VPA**	19	15 (78.9)	1500	3 (15.8)	1 (5.3)	900	7 (36.8)	11 (57.9)	
PHT**	8	4 (50.0)	300	4 (50.0)	0	300	4 (50.0)	4 (50.0)	
Total	347	263 (75.8)	-	70 (20.2)	14 (4.0)	-	110 (31.7)	223 (64.3)	

* CBZ = carbamazepine, PRM = primidone, PB = phenobarbital, VPA = valproate, PHT = phenytoin;

** % is calculated from the total number of particular drug users

Table 15. Distribution of treatment patterns and duration of epilepsy according to speciality of doctors in Tartu

Characteristics	Psychiatrist	Neurologist	General practitioner	No permanent doctor	Doctor unknown	Total
	Cases (%)	Cases (%)	Cases (%)	Cases (%)	Cases (%)	Cases (%)
Epilepsy 5 yrs*	24 (17.1)	53 (50.5)	43 (52.4)	14 (42.4)	18 (50.0)	152 (38.4)
Epilepsy >5 yrs*	116 (82.9)	52 (49.5)	39 (47.6)	19 (57.6)	18 (50.0)	244 (61.6)
0 AED*	16 (11.4)	19 (18.1)	14 (17.1)	24 (72.7)	2 (5.6)	75 (18.9)
2 and 3 AED*	34 (24.3)	9 (8.6)	5 (6.1)	0	2 (5.6)	50 (12.6)
Comedication*	27 (19.3)	24 (22.9)	40 (48.8)	3 (9.1)	1 (2.8)	95 (24.0)
Total	140 (35.4)	105 (26.5)	82 (20.7)	33 (8.3)	36 (9.1)	396 (100)

* % is calculated from the total number of cases at particular specialist

3.5. Speciality of permanent doctors

Management of epilepsy was permanently supervised by psychiatrists in 140 cases (35.4%), followed by neurologists, and general practitioners. Specialist varied for 33 subjects (8.3%), and there was no data about doctors for 36 subjects (9.1%). The proportion of long-term cases was largest for psychiatrists, as they had 116 patients with epilepsy lasting more than five years (82.9% of the 244), and psychiatrists had also the highest percentage of the polytherapy group. General practitioners frequently used concomitant medication – for 40 subjects (48.8%). The treatment profile in the group without a permanent specialist was very different from the others – 24 of them (72.7%) did not take any AED, and nobody was on polytherapy. Treatment patterns and duration of epilepsy by speciality of doctors are shown in Table 15.

VI. DISCUSSION

1. General aspects and methodology

The case identification in the present study was based on all existing registers and official lists in the area, and the biased results of a single data source or a selected group were avoided.

In the period 1992–1997, the majority of the medical registers in Tartu were paper-based, and were not well organised for finding individuals by diagnosis. No matter how meticulous the case collection is, this shortage inevitably contributes to the under-identification of provisional cases. The TUH and EHIF registers were computer-based, but no single register was found to be substantially more complete than any other. The author of the present study agrees with the widely reported impression that patients with epilepsy are poorly represented in medical lists (Beran *et al.* 1985; Forsgren *et al.* 1996; Sander and Shorvon 1996). Experience has shown that data acquisition is particularly complicated in the elderly, mainly due to ignorance, ambiguous descriptions of episodes, and other problems associated with diagnostic management in the elderly. The difficulty of case-ascertainment in the present study bears out the claim that this is one of the most important confounding factors in epidemiologic studies of epilepsy.

A substantial number of patients were personally re-examined: 59% in the incidence series and 68% in the prevalence series. Special home visits and sending of more than three invitations to the non-responders were considered neither ethical nor justified. The difference in the incidence characteristics between responders and non-responders was not statistically significant. The percentage of responders in studies varied from 39% to 88% (Beran *et al.* 1982; Granieri *et al.* 1983; Keränen *et al.* 1989; Forsgren 1992; Hart and Shorvon 1995a; Olafsson *et al.* 1996). Most of the epidemiological studies, especially earlier ones, have not used personal interview and re-examination of the initial selection group (Juul-Jensen and Foldspang 1983; Joensen 1986; Hauser 1991; Gekht *et al.* 1999; Olafsson and Hauser 1999). An incomplete response rate is inevitable, and it is generally considered acceptable, particularly due to the perceived stigma attached to epilepsy, and due to ethical limits in data-collection (Hart and Shorvon 1995a). It is possible that some non-responders may not have qualified as cases of epilepsy, however, the inclusion criteria were used conservatively for both groups in the present study, and all indeterminate cases, especially among non-responders, were excluded.

As the present study was carried out among adults only, comparisons between this data and data involving all age groups must be made with caution. General epidemiological indices can easily be compared if age-specific figures are presented. However, the distribution of clinical characteristics, like seizure

types, syndromic diagnoses, and etiology, are influenced by age, but are not usually presented as age-specific rates. Thus, comparisons of these figures are particularly limited.

To the best of my knowledge, this is the first published epidemiologic study of epilepsy carried out in an adult population in CEE that extensively adopts the recommendations of the Guidelines of ILAE for epidemiologic studies. Thus, there is no published data from CEE to allow direct comparisons.

2. Incidence of adult epilepsy

2.1. Incidence rates

The incidence of epilepsy in the adult population of Tartu is within the same range as reported in developed countries. Essentially similar rates were reported in Italy, 33/100 000 (Granieri *et al.* 1983); and in the 1965–1974 series from Rochester, USA, 35/100 000 (Hauser *et al.* 1993). The incidence was higher in the Faroes – 42/100 000 (Joensen 1986), in the 1975–1984 Rochester series USA – 48/100 000 (Hauser *et al.* 1993), in the UK – 46/100 000 (Cockerell *et al.* 1995) and in Iceland – 47/100 000 (Olafsson *et al.* 1996). Lower figures were found in Poland, the FAR was 20/100 000, (Zielinski 1974); the IR in Finland was 24/100 000 (Keränen *et al.* 1989), in China – 25/100 000 (Li *et al.* 1985) and in France – 24/100 000 (if special syndromes are excluded) (Loiseau *et al.* 1990a). See Table 1.

The male preponderance found in the present study is reported in the majority of incidence studies (Keränen *et al.* 1989; Loiseau *et al.* 1990b; Hauser *et al.* 1993; Olafsson *et al.* 1996). In the present series, this phenomenon can not be explained only by the higher incidence of symptomatic epilepsies in males, since the IR for syndromes without risk factors is also remarkably higher in males than in females. The present findings support the impression (Hauser 1997) that males *per se* seems to be at higher risk of epilepsy than females.

2.2. Age-specific incidence

In agreement with the data of recent studies (Keränen *et al.* 1989; Hauser *et al.* 1993; Cockerell *et al.* 1995; Olafsson *et al.* 1996; Zarelli *et al.* 1999), the age-specific rates in the present study are remarkably higher in the elderly than in young adults, this being especially noticeable in males. However, the age-specific rates in the elderly found in the present study are somewhat lower than those in other recent series (Hauser *et al.* 1993; Olafsson *et al.* 1996; Zarelli *et al.* 1999).

According to the incidence study of childhood epilepsy in Estonia (Beilmann *et al.* 1999a), the IR for those aged less than 15 years is 56/100 000. This figure is rather similar to that for subjects aged over 60 in the present study, 51/100 000. It suggests that the characteristic curve of age-specific incidence, with the highest rates in the youngest children and in the elderly, is presented in our population as well. It can, however, be presumed that some cases with epilepsy, especially in the elderly, are missed, mainly due to diagnostic problems on the one hand, and the conservativeness of the inclusion criteria in the present study, on the other. Elderly patients with epilepsy seem to be under-represented, and probably under-diagnosed in the medical documents.

2.3. Seizure types

Most of the incidence surveys that have presented seizure types (Joensen 1986; Hauser *et al.* 1993) have found that slightly more than 50% of incidence cases have partial seizures, and most of them have complex partial and secondarily generalized seizures. An essentially similar pattern is found in our population; however, the proportion of partial seizures, 75%, is notably larger. This is probably due to the age distribution in the present study. The same reason is probably responsible for the small estimates for generalized seizures.

The incidence of unclassified seizures in the present study, 7.4/100 000, is higher than that in other incidence studies involving adults, in which incidence usually ranges from 1.9 to 4.2/100 000 (Granieri *et al.* 1983; Joensen 1986; Loiseau *et al.* 1990a; Hauser *et al.* 1993), but is essentially comparable to the 9.7/100 000 found in Rochester, USA (Zarelli *et al.* 1999). This is partially related to the applied conservative criteria in the present study – the majority of the late-onset apparently *grand mal* seizures without clear evidence of partial or generalized onset were recorded as unclassifiable ones. However, even in everyday practice with a complete set of data, a remarkable number of seizures remain unclassified (Sander and Shorvon 1996).

2.4. Risk factors

In the present study, the relative number of subjects with defined risk factors, 55.6%, is higher than that reported in Italy – 39% (Granieri *et al.* 1983), in an early series from the USA – 34.5% (Hauser *et al.* 1993), and in Iceland – 31% (Olafsson *et al.* 1996), but it is essentially comparable to that reported recently from the USA – 46.5% (Zarelli *et al.* 1999) and from France – 46% (if special syndromes are excluded) (Loiseau *et al.* 1990a). The rather high figure for those with risk factors is probably related to the age distribution in the present study. In agreement with other epidemiologic studies (Hauser *et al.* 1993; Forsgren

et al. 1996; Zarelli *et al.* 1999), the proportion of symptomatic cases increases with the advancing age of the particular population.

The majority of incidence studies (Loiseau *et al.* 1990a; Hauser *et al.* 1993; Olafsson *et al.* 1996; Zarelli *et al.* 1999) have reported that cerebrovascular diseases are the most frequent organic cause for epilepsy; the presented results are consistent with this. The remarkably high figure for post-traumatic epilepsies point to the possibility of preventing a notable proportion of epilepsies in Estonia.

2.5. Syndromic diagnoses

There is little knowledge regarding the incidence of syndromic diagnoses among the population. The majority of surveys addressing syndrome distribution among patients are based on data from referral centres (Loiseau *et al.* 1991; Bauer 1994; Eadie 1996; OREp 1996; Kellinghaus *et al.* 2004) and are not therefore representative of the general population. Of the incidence studies involving all ages, only Loiseau *et al.* (1990a; 1990b) and Zarelli *et al.* (1999) have reported figures for epileptic syndromes. Both studies agree that the most frequent syndromes are localization-related epilepsies, and this predominance increases with advancing age.

The group of undetermined epileptic syndromes is the second largest category of epilepsies in our population. The rather high proportion for this category, 7.4/100 000 (21% of cases), is comparable to that reported by Manford *et al.* (1992) – 37% (if special syndromes are excluded), and Zarelli *et al.* (1999) – 8/100 000, but is remarkably higher than that reported by Loiseau *et al.* (1990a) – 8% or 1.9/100 000. The difference between these two latter studies is probably related to a difference in diagnostic criteria, since both were implemented using a prospective design and a complete set of data.

Since the first manifestation of idiopathic syndromes is strongly age-related, and the present study involves only those older than 20 years, the small fraction of idiopathic syndromes is an expected result. The data supports the view that the majority of special syndromes are rare in a general population (Manford *et al.* 1992; Kellinghaus *et al.* 2004), which seems to be particularly valid among adults.

3. Prevalence of adult epilepsy

3.1. Prevalence rates

The point PR of active epilepsy in the adult population of Tartu is generally comparable to those reported from developed countries. Essentially similar figures are reported in the UK – 5.3/1000 (Goodridge and Shorvon 1983a), in Tuscany, Italy – 5.1/1000 (Maremmanni *et al.* 1991), in Sweden – 5.5/1000 (Forsgren 1992), and in Iceland – 4.8/1000 (Olafsson and Hauser 1999). Somewhat higher rates are reported in Poland – 7.8/1000 (Zielinski 1974), in the Faroes – 7.6/1000 (Joensen 1986), in Copparo, Italy – 6.2/1000 (Granieri *et al.* 1983), in Finland – 6.3/1000 (Keränen *et al.* 1989), and in Rochester, USA – 6.8/1000 (Hauser *et al.* 1991). See Table 2.

The proportion of seizure-free AED-receivers in prevalence studies is not assessed. Goodridge *et al.* (Goodridge and Shorvon 1983a) have reported a number of seizure-free AED-receivers almost equal to that of the group with seizures, but the criteria for activeness were essentially different to ours. In the present study, the number of cases without seizures but receiving AED, i.e. 14 cases, is very small. Moreover, since the proportion of subjects with seizures but not taking AED, 19%, is rather large, this strongly suggests that there is a rather conspicuous lack of continual medication in our adult population. The author of the present study prefers a definition of activeness that does not include behaviour-dependent factors such as “taking of medication”.

3.2. Age-specific prevalence

Age-specific prevalence rates in Tartu tend to remain rather constant during adulthood, and diminish above the age of 70 years. Similar declining figures in the elderly are reported in a number of prevalence studies (Beran *et al.* 1982; Granieri *et al.* 1983; Keränen *et al.* 1989; Maremmanni *et al.* 1991; Forsgren 1992), but some recent series have observed steadily increasing rates with advancing age (Zielinski 1974; Hauser *et al.* 1991; de la Court *et al.* 1996; Olafsson and Hauser 1999). This latter trend is usually explained with improved case-ascertainment (Maremmanni *et al.* 1991), and it may be partially true.

All population-based studies on AED users have reported declining prevalence in the elderly (Giuliani *et al.* 1992; Hart and Shorvon 1995a), suggesting probable under-treatment in this age-group. Case finding tends to be more complicated in the older aged – differential diagnosis of episodic symptoms is more complicated in the elderly, and ignorance as well as poor compliance tend to be more common at this age (Zielinski 1974; Rowan 1998).

However, there are reasons to believe that incomplete case finding may not be the only cause for this difference. Prevalence is a complex measure and

reflects changes in incidence, remission, mortality, demographic situation, migration, etc. Despite observed higher incidence of seizures among elderly people in Sweden (Forsgren 1990), the simultaneous prevalence study does not demonstrate higher rates in that age group (Forsgren 1992). Even in surveys that are based on extensive case-ascertainment methods, the age-adjusted prevalence figures in the elderly show a declining pattern (Joensen 1986; Haerer *et al.* 1986). The time trends concerning incidence, mortality, and frequency of epilepsy-related risk factors observed in different surveys (Massey and Schoenberg 1985; Hauser *et al.* 1993; Annegers *et al.* 1995; Cockerell *et al.* 1995; Berg *et al.* 1996; Annegers 1997) very probably have a resultant effect on the prevalence figures.

3.3. Seizure types

In agreement with surveys among adults (Keränen *et al.* 1989; Forsgren 1992), the highest rates in the present study are recorded for partial seizures and the lowest for generalized seizures. For over half of patients with partial seizures, the dominant seizure type is secondarily generalized seizure.

As generalized epilepsies are most common in the pediatric population (Beilmann *et al.* 1999b), the small fraction of generalized seizures is mainly related to the age distribution of the present study. However, the author of the present study agrees with the suggestion that different results of sophisticated classifications between large scale surveys should be viewed with caution (Keränen *et al.* 1988; Sander and Shorvon 1996). The percentage of classifiable seizures in the present study is essentially similar to that found in some previous series from the UK (Goodridge and Shorvon 1983a) and from Finland (Keränen *et al.* 1989).

3.4. Risk factors

In the present study, the proportion of subjects with defined risk factors is slightly larger than that in the USA (Hauser *et al.* 1991), but essentially comparable to those reported in other recent studies from western Europe (Granieri *et al.* 1983; Keränen *et al.* 1989; Forsgren 1992; Olafsson and Hauser 1999). The largest proportion of defined organic causes has recently been published in Moscow – 69.7% (Gekht *et al.* 1999); this figure is probably related to the underreporting of mild cases with unknown causes, which is a well-known bias for hospital-based surveys.

The most eminent risk factor for epilepsy in our population is head injury. In the studies involving only adults, injury-related epilepsies form the largest proportion in Finland (Keränen *et al.* 1989) and in Moscow (Gekht *et al.* 1999),

and the second largest subgroup in Sweden (Forsgren 1992). In the studies involving all ages (Granieri *et al.* 1983; Hauser *et al.* 1991; Olafsson and Hauser 1999), the frequency of post-traumatic epilepsies is lower probably due to the very low prevalence in childhood (Beilmann *et al.* 1999b).

3.5. Syndromic diagnoses

In the present sample, localization-related syndromes clearly predominate, and idiopathic epilepsies form the smallest subgroup. This pattern is also witnessed in other prevalence studies that have analysed epileptic syndromes among adults (de la Court *et al.* 1996; Olafsson and Hauser 1999), being a rather expected result due to the age-related nature of idiopathic syndromes.

The reason for a remarkable proportion of undetermined syndromes lies partially in the retrospective nature of the data collection, since difficulties in the identification of seizures and specific causes tend to accumulate in the syndromic classification. However, the results agree with recent reviews of prospective case-collections (Manford *et al.* 1992) and referral centres (Eadie 1996; OREp 1996), which have shown even larger fractions of undetermined cases.

4. Medical treatment

4.1. General characteristics

The proportion of subjects without medical treatment on the prevalence day in the present study, 19%, is comparable to that found earlier in Finland (Keränen 1988), but is generally larger than the 7% to 9% reported later in NWE (Rutgers 1986; Forsgren 1992; Olafsson and Hauser 1999). See Table 3. A prospective cohort study from the UK (Lhatoo *et al.* 2001) has observed that 23% of subjects with newly diagnosed epilepsy remain without medication, but this is mainly due to symptomatic seizures and death, and only a further 2% of treated cases stopped medication because of non-compliance. Another population-based study from the UK (Goodridge and Shorvon 1983b) revealed a large proportion of AED-free epileptics, 61%. However, neither of the latter reports is directly comparable with the present data, due to different study design.

In the present prevalence sample, the most important cause for being drug-free is non-compliance. Moreover, it could be argued that the number of these patients may be even larger, due to the difficulties in finding them in epidemiologic case-ascertainment (Zielinski 1974; Sander and Shorvon 1996). It seems that our doctors should focus more on strategies to improve compliance.

4.2. Medication strategies

A comparatively small percentage of patients, 17%, were treated with polytherapy, being notably smaller than the 23% to 51% indicated in other studies. See Table 3. It is obvious that there is no universal percentage for polytherapy, but a proportion around 30% can be expected. Therefore, overtreatment of epilepsy does not seem to be a problem in Estonia; on the contrary, the notably small percentage of polytherapy points to undertreatment.

According to the comparatively large percentage of combination therapy cases and the small fraction of AED-free cases, it would appear that the treatment of localization-related syndromes is more problematic than the treatment of other epilepsies in the present study; this result agrees with other series (Sander and Shorvon 1996).

4.3. Utilization of particular drugs

The figures for CBZ usage are notably higher than those in other population-based reviews, see Table 3 and Figure 1. On the other hand, most of the reports found that the selective voltage-dependent sodium channel blockers (SVSB), like CBZ, PHT, OXC are, on the whole, the most frequently prescribed agents among epileptic patients. Their total share ranges from 55% in Iceland (Olafsson and Hauser 1999) to 87% in Sweden (Forsgren 1992), which is generally comparable to the 70% in the present sample. As SVSBs are effective against focal and generalized tonic-clonic seizures (Brodie and Dichter 1996; Ben-Menachem *et al.* 2003), which prevail in adults (Keränen 1988), the predominance of SVSB use in adulthood is an expected result. A predominance of CBZ use has been observed in Bulgaria (Peytchev *et al.* 1996) and to a somewhat lesser extent in Hungary (Halasz 1995) as well, and may be a common pattern in CEE countries.

The prescription pattern of barbiturates has some special features in the present sample – rather large total percentage, 40%, and the predominance of PRM. The total figure is much higher than that the 20% to 27% reported in studies from the UK and Northern Europe (Forsgren 1992; Hart and Shorvon 1995b; Muir *et al.* 1996). An essentially similar share of barbiturates was reported in the 1980s from the Netherlands (Rutgers 1986) – 40%, and a significantly larger figure was reported from Italy (Giuliani *et al.* 1992) – 83%. Barbiturates can not be considered to be “obsolete AEDs” – recent data from Denmark (Rochat *et al.* 2001) indicates rather a large proportion of barbiturate use – 33% in adulthood, being used frequently in polytherapy.

In the present study, barbiturates are the most frequently utilized AEDs for polytherapy, being even combined with each other, mainly in long-term cases. This pattern makes the actual proportion of barbiturate users smaller, but not

significantly. However, this combination is not rational, and should not be encouraged.

The proportion of VPA is rather small, being comparable with results from Northern Sweden (6%) in 1985 (Forsgren 1992). Other reports from Western Europe (Rutgers 1986; Hart and Shorvon 1995b; Muir *et al.* 1996; Lammers *et al.* 1996; Olafsson and Hauser 1999; Rochat *et al.* 2001) have found the share of VPA to be significantly larger, ranging from 14 to 29%. The data of Estonian AED sales in recent years show a significant increase in the prescriptions of VPA, see Table 4. However, these trends are difficult to interpret due to an increasing number of psychiatric and other diagnoses requiring VPA prescription in recent years.

In the present sample, some potential VPA users may have been treated with CBZ and barbiturates. On the other hand, according to AED treatment data from a prevalence study in children (Beilmann *et al.* 2000), VPA was the second most commonly prescribed drug (29%) after CBZ (45%) in Tartu in the same year. Very probably the age distribution in the present study (no subjects <20 years old) has resulted in an underestimation in VPA usage. The large figure of VPA, 23%, at a later date in Bulgaria (Peytchev *et al.* 1996) may be affected by the age-distribution of the sample as well – 63% of subjects were aged less than 18 years.

BZs and ESM were prescribed for only a few patients in the study, but the justifications were not quite rational – none of them were used for idiopathic syndromes, and ESM was used for symptomatic focal syndrome, see Figure 4.

As the general proportions of AED sales in DDD/1000 inhabitants/day in 1997 are very similar to the present results – distinct predominance of CBZ, large amount of barbiturates, and a small share of VPA and PHT – the data of the present study were considered to be generally representative of the whole population of Estonia.

4.4. Doses of drugs

In agreement with other reviews (Lammers *et al.* 1996; Rochat *et al.* 2001; Deckers 2002), most of the doses in the present study were less than DDDs. Very probably this reflects a statistical artefact, since DDDs for some drugs are set rather high, and that DDD, and therefore also PDD/DDD ratio (prescribed daily dose divided by DDD) used by some authors (Lammers *et al.* 1996; Deckers 2002), has a mainly statistical rather than clinical relevance. In a series from the UK (Kwan and Brodie 2001), the majority of patients required only a moderate AED dose, some of them even less than the usually proposed MMD. In the present sample, the percentage (32) of patients taking doses less than MMD was more than expected, but can not be considered inappropriate given proper surveillance.

4.5. Speciality of permanent doctors

The differentiation of patients according to the speciality of their doctor is not a very strict measure, since, based on personal communication, almost all general practitioners and most psychiatrists consult with a neurologist, especially in questions concerning medication. In the Soviet Union it was common that epileptic patients, after being diagnosed, were referred to a psychiatrist, and this seems to have been the case in Bulgaria too (Peytchev and Marazova 1992). Despite a change in the referral pattern in Estonia, psychiatrists still manage a rather large fraction of epileptic patients, especially long-term and polytherapy cases. There is a distinct group of subjects without a regular doctor – 72% of them are without AEDs. The lack of a regular doctor seems to be a strong risk-factor for being AED-free.

VII. CONCLUSIONS

1. The crude incidence of epilepsy for the period 1 January 1994 to 31 December 1996 was 35.4/100 000. The incidence of epilepsy in the adult population of Tartu is within the same range as reported in other industrialized countries.
2. The age-specific incidence tended to increase with advancing age. The characteristic curve of age-specific incidence, with the highest rates in the youngest children and in the elderly, is presented in our population as well.
3. The crude prevalence rate of active epilepsy in adults on 1 January 1997 was 5.3/1000. The point prevalence of active epilepsy in the adult population of Tartu is generally comparable to those reported from other industrialized countries.
4. Age-specific prevalence rates in Tartu tend to remain rather constant during adulthood, and diminish above the age of 70 years, suggesting probable under-reporting and under-treatment of epilepsy in the elderly.
5. The distribution of clinical characteristics in the incidence as well as in the prevalence series in Tartu is influenced by the age distribution in the present study: the predomination of partial seizures and localization-related syndromes, and the large proportion of symptomatic epilepsies. The remarkably high incidence of post-traumatic epilepsies points to the possibility of preventing a notable proportion of epilepsies in Estonia.
6. The majority of the patients with active epilepsy used monotherapy. The prescription of particular antiepileptic agents followed the frequency pattern of localization-related syndromes – the most frequently prescribed agent was carbamazepine, followed by barbiturates. Valproate and phenytoin were not common drugs.
7. The large percentage of medication-free epileptics, notably small figures for polytherapy, and the associating low aggregate antiepileptic drug sales in Estonia, indicate a tendency for undermedication in the population, and the need to focus on strategies to improve compliance in everyday practice.

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SUMMARY IN ESTONIAN

EPILEPSIA EPIDEMIOLOOGIA TARTU TÄISKASVANUTEL

Haigestumus, levimus ja epilepsiavastane ravi

Käesoleva uuringu eesmärk oli selgitada aktiivse epilepsia haigestumus- ja levimusnäitajad Tartu täiskasvanud rahvastikus ning saada ülevaade epilepsia kliiniliste tunnuste jaotumisest ja epilepsiavastasest ravist.

1. MEETODID

Definitsioonide, klassifikatsioonide ja etioloogiliste rühmade määratlemisel võeti aluseks Rahvusvaheline Epilepsiavastane Liiga (REL) epidemioloogiliste uuringute juhend. Epilepsiaks loeti seisundit, mida iseloomustasid korduvad (kaks või enam) mitteprovotseeritud epileptilist hoogu. Mitut hoogu, mis toimusid 24 tunni jooksul, loeti üheks diagnostiliseks hooeks. Aktiivseks epilepsiaks loeti epilepsiajuhtu, mille korral inimesel oli esinenud vähemalt üks epileptiline hoog eelnenud viie aasta jooksul. Kui epileptilisi hoogusid polnud esinenud vähemalt viie aasta jooksul epilepsiavastase raviga või ilma, oli tegemist remisioonis epilepsiaga. Ravimite jaotamisel kasutati ravimite ATC klassifikatsiooni WHO järgi.

Uuring teostati retrospektiivselt Tartu linnas. Kõikide juhtude avastamiseks vaadati läbi linna jaoskonna- ja perearstide ning neuroloogide ja psühhiaatrite ambulatoorsed ja statsionaarsed nimekirjad, külastati hooldekodusid ja pikaarvahaiglaid, samuti töötati läbi Tartu Haigekassa andmebaas antikonvulsantide kasutajate selgitamiseks. Seejärel kutsuti posti teel välja võimalikud uuringusse sobivad isikud.

Haigestumusuuringusse arvati Tartu linna elanikud, kellel esines perioodil 01.01.1994–31.12.1996 teine epileptiline hoog ja kes olid teise hoo ajaks ≥ 20 aastat vanad. Üldhaigestumuse arvutamiseks kasutati aastate 1994., 1995. ja 1996. inimaastate arvu Tartus.

Levimusuuringusse arvati Tartu linna elanikud, kes olid levimuspäevaks (01.01.1997) ≥ 20 aastat vanad ja kellel oli enne levimuspäeva olnud vähemalt kaks mitteprovotseeritud epileptilist hoogu, millest vähemalt üks hoog oli olnud eelneva viie aasta jooksul. Üldlevimuse arvutamiseks kasutati Tartu 01.01.1997. a rahvastikuarvu.

2. TULEMUSED

2.1. Haigestumus

Kokku 81 isikut, nendest 55 meest ja 26 naist, vastasid haigestumusuuringu valikukriteeriumitele, mis tegi üldiseks haigestumuskordajaks (HK) $35,4 / 10^5$ (100 000 inimaasta kohta). Eesti standardi järgi kohandatud HK oli $35,5 / 10^5$. HK Euroopa standardi järgi oli $35,3 / 10^5$ ja 1970. a USA standardi järgi $34,7 / 10^5$. HK meestel oli $54,4 / 10^5$ ja naistel $20,4 / 10^5$, erinevus polnud statistiliselt oluline ($p > 0,05$). Haigestumuse vanusekordajad omasid selget kalduvust suurenemisele vanemates vanuserühmades, vanuses ≥ 60 a oli HK $51 / 10^5$.

Epilepsia riskitegurid olid identifitseeritavad 45 juhul (55,5%), neist sagedaimad olid ajuveresoonkonna haigused ja peatraumad, vastavalt 20% ja 16%. Peaajuhaigusi epilepsia põhjusena esines vanemates vanuserühmades (≥ 60 a) mõnevõrra rohkem kui noorematel (< 60 a), vastavalt 63% ja 51%. Naiste hulgas oli sümptomaatilisi juhte 61,5% ja meeste hulgas 52,7%.

Fokaalne sümptomaatiline epilepsia moodustas 41 juhuga (50,6%) suurima diagnostilise alarühma, millele järgnes krüptogeenne (ehk ebaselge etioloogiaga) fokaalne alarühm 20 juhuga (24,7%). Generaliseerunud idiopaatilist epilepsiat diagnoositi vaid 3 patsiendil (1,3%). Epilepsia vormi polnud võimalik täpsustada 17 patsiendil (21%) hoogude klassifitseerimata tõttu.

2.2. Levimus

Levimusuuringu kriteeriumitele vastas 396 patsienti, nendest mehi 227 (57,3%) ja naisi 165 (42,7%). Uurijad intervjuerisid ja vaatasid läbi 236 patsienti (59,6%), peale selle intervjuerisid nad telefoni teel veel 33 (8,3%). Ülejäänud patsiendid ülevaatusel ei ilmunud, aga nende andmed pärinesid usaldusväärse kvaliteediga ambulatoorsest dokumentatsioonist.

Aktiivse epilepsia üldine levimusmäär (LM) Tartu täiskasvanutel oli $5,3 / 10^3$ (1000 elaniku kohta). Eesti standardi järgi kohandatud LM oli samuti $5,3 / 10^3$. LM Euroopa standardi järgi oli $5,4 / 10^3$ ja 1970 a. USA standardi järgi $5,3 / 10^3$.

Üldine LM oli meestel $6,9 / 10^3$ ja naistel $4,0 / 10^3$. Meeste LM oli suurem kõigis vanuserühmades, erinevus polnud statistiliselt oluline ($p > 0,05$).

Andmed võimaldasid epilepsia vormi diagnoosida 317 patsiendil (80,0%). Kõige rohkem esines fokaalset sümptomaatilist ja krüptogeenset epilepsiat, vastavalt 149 (37,6%) ja 145 juhtu (36,6%). Generaliseerunud epilepsiat diagnoositi 23 patsiendil (5,8%). Epilepsia riskitegureid leiti 157 juhul (39,6%).

2.3. Epilepsiavastane ravi

Levimuspäeval tarvitas epilepsiavastaseid ravimeid (ATC kood N03) 309 patsienti levimusrühmast (78%), 75 isikut (19%) ei tarvitanud antikonvulsante ja epilepsia ravi kohta polnud andmeid 12 juhul (3%). Ravi puudumise põhjused olid ravi omavoliline katkestamine (ravikuulekuse puudumine) 33 juhul (44% ravita juhtudest), ebaselge diagnoos levimuspäeval 15 juhul (20%), ravikindlustuse puudumine 14-1 (19%). Vaid 10 patsienti (13%) ei kasutanud antikonvulsanti arsti otsuse põhjal, 3 juhul jäi põhjus ebaselgeks.

257 patsienti (83% ravitustest) võtsid ühte antikonvulsanti, kahte ja kolme ravimit korraga tarvitas 52 patsienti (17% ravitustest). Karbamasepiin (CBZ) oli 67,6%ga (ravitud patsientidest) ülekaalukalt sagedaim antikonvulsant. Kasutusageduselt järgnesid barbituraadid: primidoon (PRM) 24%, fenobarbitaal (PB) 12% ja bensobarbitaal (BB) 4,5% ravitud juhtudest. Valproaati (VPA) ja fenütoiini (PHT) tarvitati raviks suhteliselt harva, vastavalt 6,2% ja 2,6%. Etosuksimiidi (ESM) ja bensodiasepiini (BZ) kasutati vaid üksikutel juhtudel, peamiselt kombinatsioonravi osana. Kõige sagedamad ravikombinatsioonid olid PB/PRM (22% polüteraapiaga rühmast), CBZ/PB (18%) ja CBZ/PRM (16%).

3. ARUTELU

3.1. Haigestumus

Epilepsia haigestumuskordaja Tartu täiskasvanutel on võrreldav USA, Põhja- ja Lääne-Euroopa rahvastike vastavate näitajatega.

Haigestumuse vanusekordajad Tartus on selge suurenemistendentsiga vanemates vanuserühmades. Sellist tendentsi on kirjeldatud ka enamikus viimasel ajal avaldatud haigestumusuuringutes.

Haigestumuse kasvu vanemaaliste seas seletatakse tihti epilepsia riskitegurite suurema sagedusega ja peaajuhaiguste paranenud elulemusega. Käesolev uuring näitab siiski, et vanemas eas on sümptomaatiliste juhtude osakaal vaid ebaoluliselt suurem kui noorematel. Seega ei saa riskitegurite kuhjumine olla kirjeldatud tendentsi peamiseks põhjuseks. Ka meeste suurema haigestumuse põhjused pole selged. Kuna riskitegurite osakaal sugude vahel oluliselt ei erine, siis sümptomaatiliste põhjuste mõju ei saa olla erinevuse seletuseks.

3.2. Levimus

Aktiivse epilepsia levimusmäär Tartu täiskasvanutel on võrreldav USA, Põhja- ja Lääne-Euroopa rahvastike vastavate näitajatega.

Levimuse vanusemäärad antud uuringus ei olnud selge suurenemistendentsiga vanemates eärühmades, kuigi sellist trendi on kirjeldatud teistes

viimase aja levimusuuringutes. Levimus on kompleksne näitaja, mis on väga tundlik aktiivse epilepsia kriteeriumite ja andmekogumise meetodite suhtes. Paljud uuringud on erinevalt REL juhendist võtnud üheks aktiivse kriteeriumiks antikonvulsantide kasutamise levimuspäeval, isegi kui hood puuduvad. Selline metoodika võib eriti kõrge ravimikasutusega rahvastikes nihutada levimusmäära oluliselt suuremaks.

Käesolevas uuringus on epilepsia diagnoosi kasutatud konservatiivselt, uuringurühma on arvatud vaid uurijate arvates kindlad epilepsiakriteeriumitele vastavad juhud. Kuna epilepsiajuhtude leidmisel on probleemiks harvade ja kergete hoogudega patsientide halb kättesaadavus ja korrektne diagnoos, siis viitavad paljud autorid juhtude võimalikule alaregistreerimisele. Kirjanduses aktsepteeritakse sellist konservatiivsust enam kui põhjendamatu üleregistreerimist.

1997. a oli Tartus suurim hulk haigeid psühhiaatrite jälgimisel. Tõenäoliselt oli see seotud varasema dispanseerimissüsteemiga: paljudel psühhiaatrite patsientidel oli haigus kestnud kaua ja neist veerandil oli ravitaktikaks polüteraapia.

3.3. Epilepsiaavastane ravi

Ravita patsientide hulk käesolevas uuringus (19%) on võrreldav Soome näitajaga 1979. a (20%), kuid see on märgatavalt suurem kui viimase aja Põhja- ja Lääne-Euroopa näitajad (7–9%). Tartu levimusrühmas oli ravi puudumise peamiseks põhjuseks puudulik ravikuulekus. Kui veel lisada uuringu autorite kogemus, et mõned ravitud haigetest olid tõenäoliselt osaliselt ebakuulekad, s.t. ei tarvitanud ravimeid pidevalt või eelistasid neid tarvitada määratust madalamas annuses, siis on ravikuulekuse parandamine meie patsientide seas väga aktuaalne ülesanne. Kindla arstita patsientidel oli suurim risk olla ilma ravita.

Antud uuringurühma polüteraapiaga patsientide osa oli suhteliselt väike, 16%. Industriaalmaades on see näitaja tavaliselt 23–51%, üldiselt peetakse põhjendatuks umbes 30%. Kuigi industriaalmaade kirjanduses on praegu aktuaalne epilepsia üleravimise probleem, siis meie uuringurühma suur ravita ja väike polüteraapiaga patsientide hulk viitab pigem alaravimise tendentsile. Seda kinnitavad ka Eesti Raviameti andmed antikonvulsantide tarbimisest. Eestis müüdud üldkogus oli 1997. a üle kahe korra väiksem kui Soomes.

Kui võrrelda üksikute ravimite kasutamist rahvastikurühmiti, siis CBZ osakaal Tartus oli märgatavalt suurem kui teistes maades. Kuivõrd täiskasvanute hulgas domineerivad fokaalne epilepsia ja nende esmavaliku ravimiks on CBZ ja PHT, siis selle ravimirühma esindaja domineerimine on põhjendatud.

Barbituraadid oli kasutussageduselt teine antikonvulsantide rühm, mille sagedaimaks esindajaks oli PRM. Määratud oli ka barbituraatide omavahelisi kombinatsioone, mida ei saa ratsionaalseks valikuks pidada nende ravimite ühesuguse toimemehhanismi tõttu.

VPA on laia hoogudevastase toimega antikonvulsant, mida oli Tartus võrreldes teiste industriaalmaadega määratud suhteliselt harva. VPA on esmavaliku ravim eelkõige idiopaatiliste generaliseerunud epilepsiate korral, aga vaid 40% selle rühma haigetest tarvitab VPAi. Kuigi CBZi ei peeta idiopaatiliste epilepsiate puhul soovitud ravimiks võimaliku hoogusid provotseeriva toime tõttu, on 40%-l mainitud juhtudest tarvitatud CBZi. Märkimisväärne on, et ainult absansside korral näidustatud ESMi oli kasutatud sümptomaatilise fokaalse epilepsia raviks.

4. JÄRELDUSED

1. Epilepsia haigestumuskordaja ja levimusmäär Tartu täiskasvanud rahvastikus on võrreldav USA, Põhja- ja Lääne-Euroopa rahvastike vastavate näitajatega.
2. Epilepsia haigestumus vanemates vanuserühmades suureneb.
3. Epilepsia levimus on täiskasvanueas suhteliselt püsiv, aga omab vähenemistendentsi vanemates vanuserühmades; viimane viitab võimalikule alaregistreerimisele ja alaravimisele nendes vanuserühmades.
4. Nii haigestumus- kui levimusrühmas domineerib Tartu täiskasvanutel fokaalne epilepsia.
5. Ülekaalukalt sagedamini kasutatud antikonvulsant Tartu täiskasvanute seas on karbamasepiin ja põhjendamatumult harva on kasutatud valproaati. Ravikvaliteedi parandamiseks tuleb arstkonnale süstemaatiliselt tutvustada epilepsia käsitlemise tänapäevaseid seisukohti.
6. Suur ravita ja väike polüteraapiaga patsientide hulk viitab alaravimisele Tartu täiskasvanute seas. Senisest enam tuleb tähelepanu pöörata haigete ravikuulekuse parandamisele.

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PUBLICATIONS

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Use of antiepileptic drugs in Estonia: an epidemiologic study of adult epilepsy

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ABSTRACT

An evaluation of general antiepileptic treatment patterns and utilization of particular drugs was carried out based on the prevalence study of adult active epilepsy in a sample of the Estonian population. Used antiepileptic drugs (AEDs), and their doses were recorded and compared to clinical characteristics. 19% of subjects did not take any AED on the prevalence day. 83% of those on medication were taking a single drug, 15% two, and 2% three AEDs. Localization-related symptomatic epilepsies were most frequently treated with AEDs and were also the largest group receiving polytherapy. The most common agent was carbamazepine (68%), followed by barbiturates. Valproate and phenytoin were used much less. The study design and its impact on the interpretation of results is discussed. The percentage of sodium channel blockers is generally comparable to that reported from other European countries. The small share of valproate is probably a result of the extensive utilization of barbiturates, and is partially related to the age distribution in the study. The high figure of AED-free cases, and small percentage of polytherapy refers to a tendency for undertreatment. Some points for improvement in AED therapy are discussed.

INTRODUCTION

Epilepsy is the second most common neurological disorder after cerebrovascular diseases (MacDonald *et al.*, 2000). Being largely a treatable condition, primary epilepsy causes no less than 0.5% of the total burden of diseases on society (Olesen and Leonardi, 2003).

There are varied reports on medication in epileptic populations from Northern and Western Europe (NWE). Some epidemiologic studies of active epilepsy have reported data of antiepileptic treatment (Goodridge and Shorvon, 1983; Keränen, 1988; Rutgers, 1986; Forsgren, 1992; Olafsson and Hauser, 1999), others either use data based on antiepileptic drug (AED) prescriptions (McCluggae *et al.*, 1984; Giuliani *et al.*, 1992; Hart and Shorvon, 1995; Muir *et al.*, 1996), or use special databases or drug sales data (Lammers *et al.*, 1996; Rochat *et al.*, 2001). Most of them report almost equal use of carbamazepine (CBZ) and phenytoin (PHT), 23–51% of patients use polytherapy (Table 1, Fig.

1), and problems of overtreatment are often highlighted (Deckers, 2002). There is almost no published data from Central and Eastern Europe (CEE) to allow respective comparisons. Short prescription-based reports concerning anti-epileptic drug (AED) treatment are available from Bulgaria (Peytchev and Marazova, 1992; Peytchev *et al.*, 1996), and some general figures based on AED sales data have been published in Hungary (Halasz, 1995), see Table 2. Both indicate some differences compared to those in NWE – comparatively extensive use of carbamazepine and barbiturates, scanty utilization of valproate, and small overall quantities of drug sales.

In Estonia, only national drug sales data, collected by the Estonian State Agency of Medicines, are readily available. These figures reveal clear domination of CBZ among other AEDs, and increasing but still rather small aggregate AED consumption in Estonia, especially if compared with this in Finland (Finnish NAM, 1998; 2004), see Table 2.

The present review is a part of an epidemiologic project on adult epilepsy in Tartu, Estonia (Õun, *et al.*, 2003a; b). The aim of the present review is to evaluate general antiepileptic treatment patterns and utilization of particular AEDs based on the prevalence study of adult active epilepsy in Tartu, Estonia.

MATERIAL AND METHODS

Study area and population

The study was conducted in the university town of Tartu. On the prevalence day, January 1, 1997, the total population of Tartu was 101 901, of whom 75,245 were aged 20 years and over. Medical care, i.e. consultations, medical investigations, and partially drugs, is paid by the Estonian Health Insurance Fund (EHIF). Approximately 85% of the population has EHIF insurance cover. In 1997, with a diagnosis of epilepsy, the conventional AEDs, like CBZ, PHT, valproate (VPA), phenobarbital (PB), primidone (PRM), ethosuximide (ESM), and benzodiazepines (BZ) as clonazepam (CZP) and clobazam (CLB), were compensated in full for insured persons.

A barbiturate called benzobarbital (BB) or Benzonal[®] was extensively prescribed in the former Soviet Union. In 1997, BB was no longer licensed for sale in Estonia, but people brought it in from abroad, and factually used it. Some new generation AEDs, i.e. lamotrigine (LTG), topiramate (TPM), and oxcarbazepine (OXC), were included in the catalogue of fully compensated drugs later, and, due to their high cost, were not available for wide use in 1997.

Definitions

The strict criteria and definitions proposed by the ILAE Guidelines for epidemiologic studies were adopted (Commission, 1993). Epilepsy was defined as a condition characterized by recurrent (two or more) epileptic seizures occurring

at least 24-h apart, unprovoked by any immediate identified cause. An active case of epilepsy was a person with at least one unprovoked epileptic seizure in the previous 5 years with or without antiepileptic drug treatment. Epilepsies and epileptic syndromes were classified according to the ILAE classification (Commission, 1989).

Case ascertainment and data collection

In order to collect population-based data, all medical lists and databases in Tartu were searched to enrol subjects with possible diagnosis of epilepsy. Medical records of all provisional cases were re-examined following an identical protocol. Being basically a prevalence study of adult active epilepsy, only adults (at least 20 years of age) and residents of the town of Tartu with active epilepsy were included. Individuals who had had provoked or acute symptomatic seizures were excluded from the study, since, according to the definition, these were considered to have a condition other than epilepsy (Commission, 1993).

A total of 396 persons met the inclusion criteria making the crude prevalence rate of active epilepsy 5.3 per 1,000 inhabitants. The largest subgroups of syndromic diagnoses were localization-related symptomatic syndromes, 149 subjects (37.6%), and localization-related cryptogenic syndromes, 145 subjects (36.6%). Generalized syndromes were diagnosed in 23 (5.8%) cases, and a small fraction of these syndromes is mainly related to the adult population in our study. Available data did not allow the diagnosis of a specific syndrome for 79 (19.9%) cases, mainly due to unclassifiable seizure types (Õun *et al.*, 2003b).

Data on medical treatment

All used drugs and doses on the prevalence day were recorded and classified according to the Anatomical Therapeutic Chemical (ATC) classification, the used daily doses were compared to defined daily doses (DDD) (WHO, 1996), and to the clinically more relevant minimum maintenance doses (MMD) usually recommended for adults by reviews (Brodie and Dichter, 1996), and handbooks (Duncan *et al.* 1995; Leppik, 2000).

An attempt was made to record seizure frequency as a treatment effectiveness measure, but very few subjects had well-documented records of seizures, the data on the remainder being poorly recorded and controversial. Therefore seizure frequency was not included in the analysis. In Tartu, measurement of AED concentration was not available for systematic use in 1997, only few patients were tested, and these random results were not included in the study.

RESULTS

General characteristics

Of all 396 subjects with active epilepsy, 309 (78%) patients were known to be taking AEDs (ATC code N03) on the prevalence day, 75 (18.9% of all cases) subjects did not take any AED on the prevalence day, and the antiepileptic medication status of 12 subjects (3.0% of all cases) remained unknown.

The reason for not taking AED medication on the prevalence day were: the discontinuation of treatment on the patient's own decision (probable non-compliance) in 33 cases (8% of all cases, 44% of the 75 AED-free active cases); delayed diagnosis on the prevalence day in 15 cases (20% of the AED-free group); no insurance on the prevalence day in 14 cases (3.5% of all cases, 19% of the AED-free group); no need for AED treatment on the doctor's decision in 10 cases (2.5% of all cases, 13% of the AED-free group); and unknown in 3 cases (4% of the AED-free group).

General treatment profile is summarized in Table 3. The diagnosis of localization-related symptomatic epilepsy corresponded to the largest percentage of treated and polytherapy cases, 87.9% and 19.9% respectively. In generalized idiopathic syndromes, there were no patients on polytherapy, and the proportion of cases without any AED was the highest.

Regularly coprescribed drugs other than AEDs were reported for 95 (24%) subjects.

Utilization of particular drugs

The prescription frequencies of each AED, and their distribution in relation to syndromic diagnoses are presented in Fig. 1 and Fig. 2; the sum of the given percentages is greater than 100 due to polytherapy.

In the aggregate, drug prescription followed the patterns of localization-related syndromes – the most frequently prescribed agent was CBZ (67.6% of the total number of treated patients), followed by barbiturates – PRM and PB with 24% and 12% respectively, and a considerable number of subjects (4.5%) were taking BB. Some 178 (85%) CBZ users, and 66 (53%) barbiturate users were taking drugs as monotherapy. VPA (6.2%) and PHT (2.6%) were not common drugs, ESM and BZs were used in 2 and 4 subjects respectively.

In the 50 patients taking two or more AEDs, the most common combinations were PB/PRM (11 cases, 22% of the polytherapy group), CBZ/PB (9 cases, 18%), and CBZ/PRM (8 cases, 16%); followed by VPA/CBZ (4 cases, 8%), and PRM/BB (3 cases, 6%). The 6 combinations of three simultaneous agents were CBZ/VPA/BB, CBZ/PRM/PB, PHT/PRM/PB, CBZ/PHT/PRM, CBZ/ESM/PB, and CBZ/PRM/CLB.

Doses of drugs

Of a total of 367 AED prescriptions, data on doses was available on 351 (95.6%) occasions. Some most common drugs were compared with DDD and MMD, see Table 4. For CBZ, PRM, and VPA the doses were much smaller than the recommended DDD, but most of the doses were equal or higher than MMD for all these drugs.

DISCUSSION

The results of the present study can be directly compared with some prevalence studies of active epilepsy, that have reported data on antiepileptic treatment, see Table 1. Population-based epidemiologic studies gather data through multi-source collection in a well defined population, and enables direct and reliable comparisons of drug utilization and clinical characteristics. To our knowledge, the present review is the first widely published evaluation of antiepileptic treatment based on an epidemiologic study carried out in a population in a CEE country.

Data of drug sales provides a rather quick general overview for the whole population, but utilization of AEDs for other diseases and the heterogeneity of seizure disorders complicate the interpretation of data. Prescription-based studies and -audits are somewhat more clinically relevant since the diagnoses of doctors are usually applied, but drug-free subjects are automatically excluded, and clinical criteria are not strict and uniform.

General characteristics

The proportion of subjects without medical treatment on the prevalence day in our study is comparable to that found in Finland in the late 70s (Keränen, 1988), but is generally larger than the 7% to 9% reported later in NWE (Rutgers, 1986; Forsgren, 1992; Olafsson and Hauser, 1999), see Table 1. The prospective cohort study from the UK (Lhatoo *et al.*, 2001) has observed that 2% of treated epileptic cases stopped medication because of non-compliance. In our prevalence sample, the most important cause for being drug-free is non-compliance, for 8% of all cases. Moreover, it could be argued that the number of these patients may be even larger due to difficulties in finding them in epidemiologic case-ascertainment (Öun *et al.*, 2003b). Our doctors should focus more on strategies to improve compliance.

A comparatively small percentage of patients, 17%, were treated with polytherapy, being notably smaller than the 23% to 51% indicated in other studies, see Table 1. Generally, monotherapy is considered to be a gold standard for treatment of epilepsy being initially effective for 44% to 79% of patients (Kwan and Brodie, 2001; Lhatoo *et al.*, 2001; Deckers, 2002). Thus, a proportion around 30% for polytherapy can be expected. Overtreatment of epilepsy

does not seem to be a problem in Estonia; on the contrary, the notably small percentage of polytherapy refers to undertreatment.

According to the comparatively small fraction of AED-free cases, and the large percentage of polytherapy cases, the treatment of localization-related syndromes seems to be more problematic than the treatment of other epilepsies, this result agrees with other series (Kwan and Brodie, 2001).

Utilization of particular drugs

The percentage of CBZ usage is notably higher than those in other population-based reviews, see Fig. 1. On the other hand, most of the reports have found that the selective voltage-dependent sodium channel blockers (SVSBs), like CBZ, PHT, OXC, are in the aggregate the most frequently prescribed agents among epileptic patients. Their total share clusters between 50% and 86% in NWE, and is comparable to the 70% in our sample. As SVSBs are effective against focal and generalized tonic-clonic seizures (Duncan *et al.*, 1995; Brodie and Dichter, 1996; Leppik, 2000), which prevail in adults (Õun *et al.*, 2003b), the predominance of SVSBs in adulthood is an expected result. The preference of one or another drug mainly seems to depend on the time of the survey – the predominance of PHT earlier has decreased, and, according to a recent report, OXC has the potential to increase (Rochat *et al.*, 2001).

The prescription pattern of barbiturates has some special features in our sample – rather large total percentage, 40%, and the predominance of PRM. The total figure is much higher than that the 20% to 27% reported in studies from the UK and Northern Europe (Forsgren, 1992; Hart and Shorvon, 1995; Muir *et al.*, 1996). An essentially similar share of barbiturates was reported in the 1980s from the Netherlands (Rutgers, 1986), 40%, and a significantly larger figure was reported from Italy (Giuliani *et al.*, 1992), 83%. Barbiturates can not be considered to be “old obsolete AEDs” – recent data from Denmark (Rochat *et al.*, 2001) report a rather large proportion of barbiturates, 33% in adulthood, being used frequently in polytherapy.

In the present study, barbiturates are the most frequently utilized AEDs for polytherapy, being even combined with each other, mainly in long-term cases. This pattern probably exists as an inheritance from the unstable situation of AED market in the late 80s, and early 90s. However, this combination has proven to be neither effective nor rational, and is generally discouraged in Estonia.

The proportion of VPA is rather small, being comparable with results from Northern Sweden (6%) in 1985 (Forsgren, 1992). Other reports from Western Europe (Rutgers, 1986; Olafsson and Hauser, 1999; Hart and Shorvon, 1995; Muir *et al.*, 1996; Lammers *et al.*, 1996; Rochat *et al.*, 2001) have found the share of VPA to be significantly larger, ranging from 14 to 29%. The classical indications of VPA are idiopathic generalized epilepsies, but patients with these syndromes were treated equally with CBZ and VPA in our sample (Fig. 2). In a

case of generalized tonic-clonic seizure, the use of CBZ can not be considered inappropriate given proper surveillance. On the other hand, since generalized syndromes occur mainly in children and adolescence, probably the age distribution in our study (no subjects < 20 years old) has resulted in a small figure of VPA usage. The large figure of VPA in Bulgaria, 23%, may be affected by the age-distribution of the sample as well – 63% of subjects were aged less than 18 years (Peytchev *et al.*, 1996).

Based on the data of Estonian AED sales, the usage of VPA has significantly increased in recent years. These and other trends, like the addition of new AEDs (Table 2), suggest that antiepileptic treatment has somewhat changed by today. However, these tendencies are difficult to interpret due to an increasing number of psychiatric and other diagnoses requiring AED, especially VPA, prescriptions in recent years.

Doses of AEDs

In agreement with other reviews (Lammers *et al.*, 1996; RoCHAT *et al.*, 2001; Deckers, 2002), most of the doses were less than DDDs in our study. DDDs for some drugs are set rather high, and has a mainly statistical rather than clinical relevance. In a series from the UK, the majority of patients required only a moderate AED dose, some of them even less than the usually proposed MMD (Kwan and Brodie, 2001). However, the percentage of patients taking doses less than MMD in our sample, 32%, was more than expected. It seems, that our doctors tend to use too small doses.

CONCLUSIONS

The large percentage of AED-free epileptics, notably small figures for polytherapy, rather small doses, and the associating low AED sales in Estonia, indicate the tendency of undertreatment in our population, and the need to improve compliance in everyday practice. These worrisome features of antiepileptic treatment in Estonia prompted us to compile national guidelines for epilepsy management. The data of AED sales in Estonia suggests that antiepileptic treatment has somewhat changed by today.

ACKNOWLEDGEMENTS

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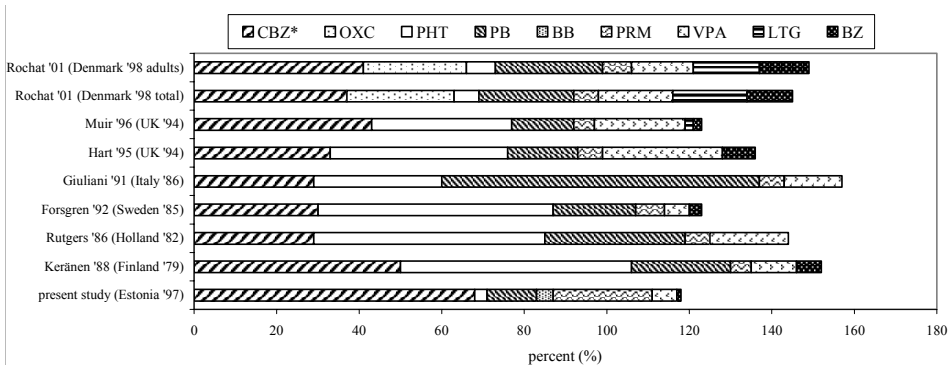
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FIGURES AND TABLES



* CBZ = carbamazepine; OXC = oxcarbazepine; PHT = phenytoin; PB = phenobarbital; BB = benzobarbital; PRM = primidone; VPA = valproate; LTG = lamotrigine; BZ = benzodiazepines

Figure 1. Utilization of AEDs in different series

Table 1. AED utilization in different population-based reviews

studies	country	year of study	target ^{a)}	age groups years	not treated %	polytherapy %	the most frequent AEDs drug ^{b)} (%)
<i>Prevalence studies</i>							
present study	Estonia	1997	active epil.	≥ 20	19	16	CBZ (68) PRM (24)
Keränen, 1988	Finland	1979	active epil.	≥ 16	20	33	PHT (56) CBZ (50)
Rutgers, 1986	Holland	1982	active epil.	15–66	7	41	PHT (56) PB (34)
Forsgren, 1992	Sweden	1985	active epil.	≥ 17	9	30	PHT (56) CBZ (30)
Olafsson <i>et al.</i> , 1999	Iceland	1993	active epil.	all ages	9	23	CBZ (50) PHT (24)
Goodridge <i>et al.</i> , 1983	UK	1983	all seizures	all ages	61	32	PHT (51) PB (32)
<i>Studies on treated epilepsies</i>							
McCluggae <i>et al.</i> , 1984	UK	1979–1981	AED + Dgn	all ages	–	50	PB (30) PHT (20)
Giuliani <i>et al.</i> , 1991	Italy	1985–1986	AED + Dgn	all ages	–	51	PB (77) PHT (31)
Muir <i>et al.</i> , 1996	UK	1993–1994	AED + Dgn	all ages	–	24	CBZ (43) PHT (34)
Hart <i>et al.</i> , 1995	UK	1994	AED + Dgn	all ages	–	34	PHT (43) CBZ (33)
Peitchev <i>et al.</i> , 1992	Bulgaria	1987–1991	AED + Dgn	≥ adolescence	–	80	PB (32) CBZ (27)
Peitchev <i>et al.</i> , 1996	Bulgaria	1990–1994	AED + Dgn	all ages	–	40	CBZ (39) VPA (23)
<i>Prescription databases</i>							
Lammers <i>et al.</i> , 1996	Holland	1989–1992	AED only	all ages	–	20	CBZ VPA
Rochat <i>et al.</i> , 2001	Denmark	1998	AED only	all ages	–	26	CBZ (37) OXC (26)

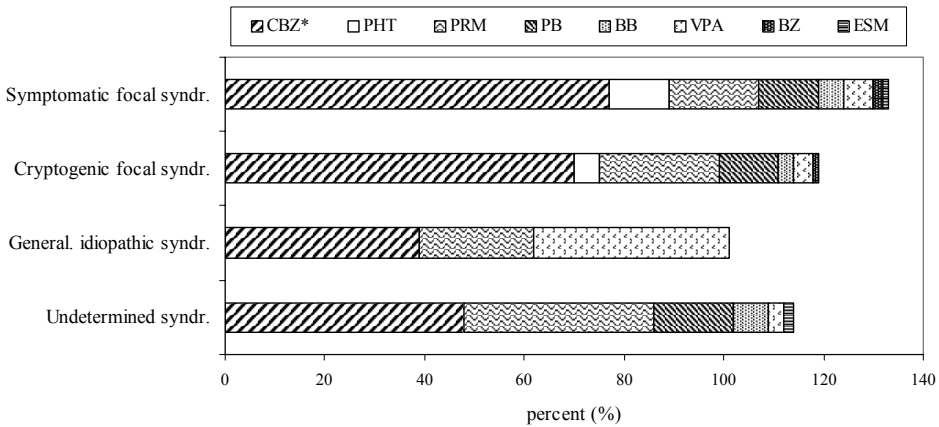
^{a)} AED = use of antiepileptic drug, Dgn = recorded diagnosis;

^{b)} CBZ = carbamazepine; OXC = oxcarbazepine; PB = phenobarbital; PHT = phenytoin; PRM = primidone; VPA = valproate

Table 2. AED consumption in different populations (given in DDD/1000 inhabitants/day)

Drugs	Estonia 1997	Estonia 2003	Finland ^{a)} 1997	Finland ^{b)} 2003	Hungary ^{c)} 1993	Bulgaria ^{d)} 1994
Barbiturates	0.62	0.51	0.62	0	–	–
Hydantoin	0.08	0.09	1.27	0.95	–	–
phenytoin	0.08	0.09	–	0.93	1.5	0.04
Carboxamides	1.32	2.22	4.07	4.31	–	–
carbamazepine	1.32	2.21	2.89	2.55	1.8	0.65
oxcarbazepine	0	0.01	1.19	1.76		
Fatty acids	0.28	0.70	1.51	2.92	–	–
valproate	0.28	0.69	1.31	2.84	0.5	0.28
Others	0	0.24	0.20	1.95	–	–
lamotrigine	0	0.13	0.16	0.69	–	–
Total	2.4	4.09	8.29	10.95	4.7	–

^{a)}Finnish NAM, 1998; ^{b)}Finnish NAM, 2004; ^{c)}Halasz, 1995; ^{d)}Peytchev *et al.*, 1996



CBZ = carbamazepine; PHT = phenytoin; PRM = primidone; PB = phenobarbital; BB = benzobarbital; VPA = valproate; BZ = benzodiazepines; ESM = ethosuximide

Figure 2 Utilization of AEDs in syndromic subgroups

Table 3. Distribution of treatment patterns by epileptic syndromes in Tartu

Syndromes	Syndromes	Treated ^{a)}	1 AED ^{b)}	2 AED ^{b)}	3 AED ^{b)}	Not treated ^{a)}	Unknown ^{a)}
	Total (%)	Cases (%)	Cases (%)	Cases (%)	Cases (%)	Cases (%)	Cases (%)
Localization-related							
Symptomatic	149 (37.6)	131 (87.9)	105 (80.1)	22 (16.8)	4 (3.1)	17 (11.4)	1 (0.7)
Cryptogenic	145 (36.6)	107 (73.8)	89 (83.2)	16 (15.0)	2 (1.9)	33 (22.8)	5 (3.5)
Generalized idiopathic	23 (5.8)	13 (56.5)	13 (100)	0	0	9 (39.1)	1 (4.4)
Undetermined	79 (20.0)	58 (73.8)	50 (86.2)	8 (13.8)	0	16 (20.3)	5 (6.3)
Total	396 (100)	309 (78.0)	257 (83.2)	46 (14.9)	6 (1.9)	75 (18.9)	12 (3.0)

a) % is calculated from the total number of cases in particular syndrome

b) % is calculated from the treated cases of particular syndrome

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Eesti Epilepsiavastane Liiga (sekretär)

L. Puusepa nim. Eesti Neuroloogide ja Neurokirurgide Selts

Tartu Arstide Liit

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