Use of antiepileptic drugs in a community-dwelling Dutch population

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Article abstract—We compared the treatment policy for patients with epilepsy in six Dutch cities, comprising 302,149 inhabitants, with the treatment policies of a secondary referral center (a university hospital) and tertiary referral centers (outpatient departments of epilepsy centers). By comparing the prevalence of individuals receiving antiepileptic drugs in the six cities with the epidemiologic data for epilepsy in Rochester, Minnesota, we concluded that prescription data offer a suitable means by which to estimate the prevalence of epilepsy in a community. To compare prescriptions in cases of polytherapy, we normalized data by using defined daily doses published by the WHO Collaborating Center for Drugs Statistics Methodology and the Nordic Council on Medicines and concluded that the defined daily doses of antiepileptic drugs should be further elaborated. There is a need to obtain complete dose-response curves of equivalent antiepileptic drugs in humans. The trend of drug use found in the six cities, the university hospital, and the epilepsy centers is, however, in accord with the expectations regarding primary, secondary, and tertiary referral centers.

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Wijsman et al[1,2] compared the treatment offered by secondary- and tertiary-referral epilepsy centers and found substantial differences in drug utilization that disappeared when they matched patients for duration of epilepsy and seizure type, despite the fact that scores on a composite index of impairment incorporating information about seizure frequency, seizure severity, and drug toxicity were higher at the tertiary level. To determine how the general population of epileptics differs from those seen at secondary and tertiary referral centers, we examined the pattern of antiepileptic drug (AED) utilization in the community. A drug database (PHARMO) from all pharmacies in a group of cities in The Netherlands provided the necessary information. Although AEDs can also be used for other indications, when they are, it is usually only for brief periods. Therefore, we included only the data of those who used AEDs consecutively for at least 6 months. As AEDs are available only on prescription, and as the collaborating pharmacies covered a population of known size, our data also yield an estimate of epilepsy prevalence. There are several studies on the prevalence of epilepsy in The Netherlands,[3-6] but those focusing on the use of AEDs included only a small population of patients, most of them hospitalized.[7,8] We compared the data from the PHARMO drug database with previously published data and with recently collected data from a secondary and a tertiary referral center.[1,2]

We also analyzed the data with respect to new AEDs and to the role of monotherapy versus polytherapy.

Methods. For the study on the use of AEDs, we obtained data from the PHARMO drug database. The structure of the PHARMO drug database has been described by Herings.[9] The data extracted were compared with data previously reported and also with more recently collected data using the same methodology.[1] The cases studied were from the neurologic department of the University of Nijmegen (university hospital [UH]; N = 120) and from both the Instituut voor Epilepsiebestrijding "Meer en Bosch-De Cruquiushoeve" and the Dr Hans Berger Kliniek (epilepsy centers [EC]; N = 559). The studies were approved by the ethics committees of the participating institutions, and all patients involved gave informed consent.

The PHARMO drug database contains histories obtained from 27 pharmacies covering all prescription drugs dispensed in six middle-sized Dutch cities with a total of approximately 300,000 inhabitants. Information on drug prescription by means of the PHARMO drug database has been collected for some cities since 1986, and for all six cities since 1989. The PHARMO drug database is restricted to the community-dwelling part of the population in these six cities, i.e., data from nursing homes or institutions for the mentally retarded are excluded.

For our study, we used data collected from 1989 onwards. These included the patient's age and gender, drug prescribed, number of units dispensed, units per day used, and anticipated duration of use. From this data we defined patients as being exposed to one (monotherapy) or more (polytherapy) AEDs.

Next, normalized doses were obtained by dividing the

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Table 1 *Use of AEDs in the PHARMO population in 1992 by age and gender, compared with epilepsy prevalence in Rochester, Minnesota*

Age	PH men n = 1,257 (%)	PH women n = 1,439 (%)	PH total n = 2,696		RO total n = 383	
			n	(%)	n	(%)
0–4	0.21	0.38	55	0.27	6	0.14
5–9	0.41	0.34	71	0.34	16	0.39
10–14	0.58	0.41	102	0.49	26	0.63
15–24	0.65	0.64	301	0.64	71	0.62
25–34	0.81	0.90	416	0.83	68	0.63
35–44	0.82	1.02	446	0.92	61	0.92
45–54	1.00	1.14	370	1.07	38	0.76
55–64	1.29	1.20	320	1.25	33	0.77
65–74	1.42	1.79	337	1.62	22	0.68
74+	2.45	1.98	278	2.05	43	1.48
Total	0.83	0.94	2,696	0.89	383	0.68

n = number of patients using AEDs; % = percentage of patients using AEDs of the total population of the six Dutch cities or of all people with epilepsy in Rochester; PH = the PHARMO population from the six Dutch cities (=302,149); RO = the Rochester population (=56,447; Hauser et al, 1991). Based on diagnosis of epilepsy.

prescribed daily dose (PDD) by the defined daily dose (DDD). For example, 50 mg twice a day (PDD = 100 mg) phenobarbital, which has a DDD of 100 mg, yields a PDD/DDD ratio of 100 mg/100 mg, or 1.00. The normalized doses express the strength of the medication and, in cases of polytherapy, these units can be added to obtain the total strength of the combination (eg, if a patient is prescribed daily 600 mg carbamazepine [DDD = 1,000 mg] and 900 mg valproate [DDD = 1,500 mg], the total PDD/DDD is 1.2).

If the total daily dose was 0 or if the PDD/DDD ratio was >6, these entries were considered incorrect and deleted. This was the case for 1.8% of all records in 1989, 1.5% in 1990, 0.6% in 1991, and 1.5% in 1992. The DDD was taken from the publications of the WHO Drug Utilization Research Group, the WHO Collaborating Center for Drugs Statistics Methodology, and the Nordic Council on Medicines.[10] The DDD is based on the assumed average dose per day expressed as the amount of the active substance of the drug used in its main indication in adults. A written dose document is prepared on the basis of international textbooks, journals, and documentation approved by drug-control authorities. The dose documentations are available on request from the WHO in Oslo.

AEDs included in our study were carbamazepine (CBZ), clonazepam (CZP), ethosuximide (ESM), phenobarbital (PB), phenytoin (PHT), methsuximide (MSM), methylphenobarbital (MPB), oxcarbazepine (OCB), primidone (PRM), valproate (VPA), and vigabatrin (VGB). Diazepam (DZP), oxazepam (OZP), nitrazepam (NZP), clobazam (CLB), flunarizine (FNR), and acetazolamide (AZM) were excluded even though these drugs were present in the prescriptions of the UH and EC populations, as confusion with chronic administration for other disorders was apt to occur.

To evaluate the use of a newly introduced drug, the dispensing histories of the patients using VGB in 1992 were assessed separately from 1989 until 1992.

Patients who used one or more of the AEDs during a period longer than 180 days were defined as patients having epilepsy. This period was considered sufficient for the elimination of those patients who used these drugs incidentally for indications other than epilepsy. However, in addition to the long-term use of AEDs in the treatment of epilepsy, there is a tendency to use AEDs also for longer periods in certain psychiatric disorders and trigeminal neuralgia. We shall come back to this point in the Discussion.

The percentage of patients in the population of 1992 using one or more AEDs according to the aforementioned criterion was considered to be the period prevalence of epilepsy. The data were compared with the 1980 data from Rochester, Minnesota, reported by Hauser et al.[11]

Statistical analysis. In the analysis of AED distribution or number of AEDs used from 1989 to 1992 and for the analysis of prevalence across the age groups, the χ^2 test was applied. For the analysis of prevalence by gender, the combination of the χ^2 tests over the age categories was applied. Statistical significance was defined at $p < 0.05$.

Results. *Antiepileptic drugs used.* According to the Dutch Central Bureau for Statistics, the total population of the six cities on January 1, 1992, was 302,149; there were 149,647 men (49.5%) and 152,502 women (50.5%).[12] In this population, 2,696 people (0.89%) used one or more AEDs. The use of AEDs increased with age by a statistically significant degree for both men and women. The highest prevalence was observed among men 75 years of age and older. No statistically significant difference in prevalence was observed between men and women in any age group (table 1).

Approximately 80% of the patients were treated with monotherapy. Two AEDs were used by 16%, three by 4%, four by 0.4%, and five by 0.04%.

The use of individual AEDs by the PHARMO population in 1992 is detailed in table 2; information about the use of these drugs in the UH and EC populations is presented for comparison.

In the PHARMO population, a statistically significant ($p < 0.05$) decrease was seen during 1989–1992 in the

Table 2 *Use of antiepileptic drugs (AEDs) in the PHARMO population as compared with published data on prescriptions from UH and EC populations*

	PH 1992 n = 2,467 PDD/DDD		UH n = 120 PDD/DDD		EC n = 559 PDD/DDD		PH 1992 n = 2,467 (%)	UH n = 120 (%)	EC n = 559 (%)
	M	A	M	A	M	A			
CBZ	0.60	0.55	0.60	0.66	0.80	0.93	49.4	56.7	70.1
VPA	0.60	0.65	0.63	0.75	0.80	0.90	24.6	27.5	42.4
PHT	0.61	0.69	1.00	0.90	1.10	1.15	24.3	26.7	27.5
PB	0.90	0.96	1.15	1.25	0.50	0.71	12.1	18.3	9.8
CZP	0.19	0.26	0.50	0.50	0.13	0.17	9.3	1.7	2.3
VGB	0.50	0.70	0.00	0.00	0.75	0.72	3.3	0.0	12.5
CLB	n.r.	n.r.	0.00	0.00	1.00	0.87	n.r.	0.00	15.4
PRM	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	1.6	3.3	3.0
ESM	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	1.2	0.8	4.5
MPB	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.7	0.0	0.0
MSM	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.2	0.0	0.0
OCB	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.2	0.0	2.9
DZP	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.8	0.5
OZP	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.8	0.0
FNR	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.0	0.7
AZM	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.0	1.3
NZP	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.0	0.4
Cumul. PDD/DDD	0.60	0.82	1.00	1.55	1.60	1.74	—	—	—
Total*	—	—	—	—	—	—	126.9	136.6	193.3

* Some patients used more than one AED.

For abbreviations of drug names see text. PH = population in PHARMO database; UH = university hospital; EC = epilepsy centers (Wijsman et al, 1993[1]); PDD/DDD = ratio of the prescribed daily dose to the defined daily dose; n = number of patients older than 15 years of age; M = median value; A = average (mean) value; n.r. = not registered (see text); Cumul. PDD/DDD = median and average of the sums of the ratios of each AED and its proper defined daily dose prescribed per patient; % = percentage of patients using a particular AED.

percentage of patients using MPB (2.1% to 0.7%) and PB (14.8% to 12.1%). There was also a statistically significant ($p < 0.05$) increase in the percentage of patients using CZP (7.1% to 9.3%).

New drugs on the market. VGB was registered in 1990 and OCB in 1991; however, until 1995 OCB was only partly reimbursed by insurance companies. The percentage of patients using OCB increased from 0.1% in 1991 to 0.2% in 1992. Those patients who used VGB in 1992 were studied separately as of 1989 as the "VGB group." The percentage of patients in the VGB group receiving monotherapy declined from 46% in 1989 to 11% in 1992. Over a period of three years, the percentage of patients using VGB increased from 0.2% to 3.3%. In 1992, 16 of the 90 patients (17.7%) stopped using VGB. No patients stopped using VGB during 1990 or 1991. In 1990, when VGB was registered in The Netherlands, no patient in the VGB group used this AED as monotherapy. In 1992, 11% of these patients used VGB as monotherapy, compared with an 80% use of monotherapy overall.

When another AED was prescribed with VGB, the most frequently used was CBZ, followed by VPA. In triple therapy, VGB was most frequently prescribed in combination with CBZ and VPA.

Most frequently prescribed drugs. In all years CBZ was the most frequently prescribed AED used as monotherapy, followed by VPA and PHT.

When two AEDs were used, the combination of CBZ with VPA occurred most often, followed by the combination of CBZ with PHT.

The percentage of patients on monotherapy differed considerably between the three populations studied. Monotherapy was used by only 35% of the patients from the EC and by 65.2% of the patients from the UH, while almost 80% of the PHARMO population was treated with monotherapy ($p < 0.05$). The average number of drugs prescribed per patient was 1.3 in the PHARMO group, 1.4 in the UH population, and 1.9 in the EC population (table 2). As in the PHARMO population, CBZ was the drug most often prescribed as monotherapy in both the EC and the UH populations. Also, when two AEDs were prescribed the combination most frequently used was CBZ with VPA, followed by the combination of CBZ with PHT.

Dosing. In table 2 the median and average PDD/DDD ratios are presented for the drugs used in over 5% of the respective cohorts. Instances in which the PDD/DDD ratio was 0.00 or >6.00 were considered inaccuracies and were excluded from the assessment. Also, patients under 15

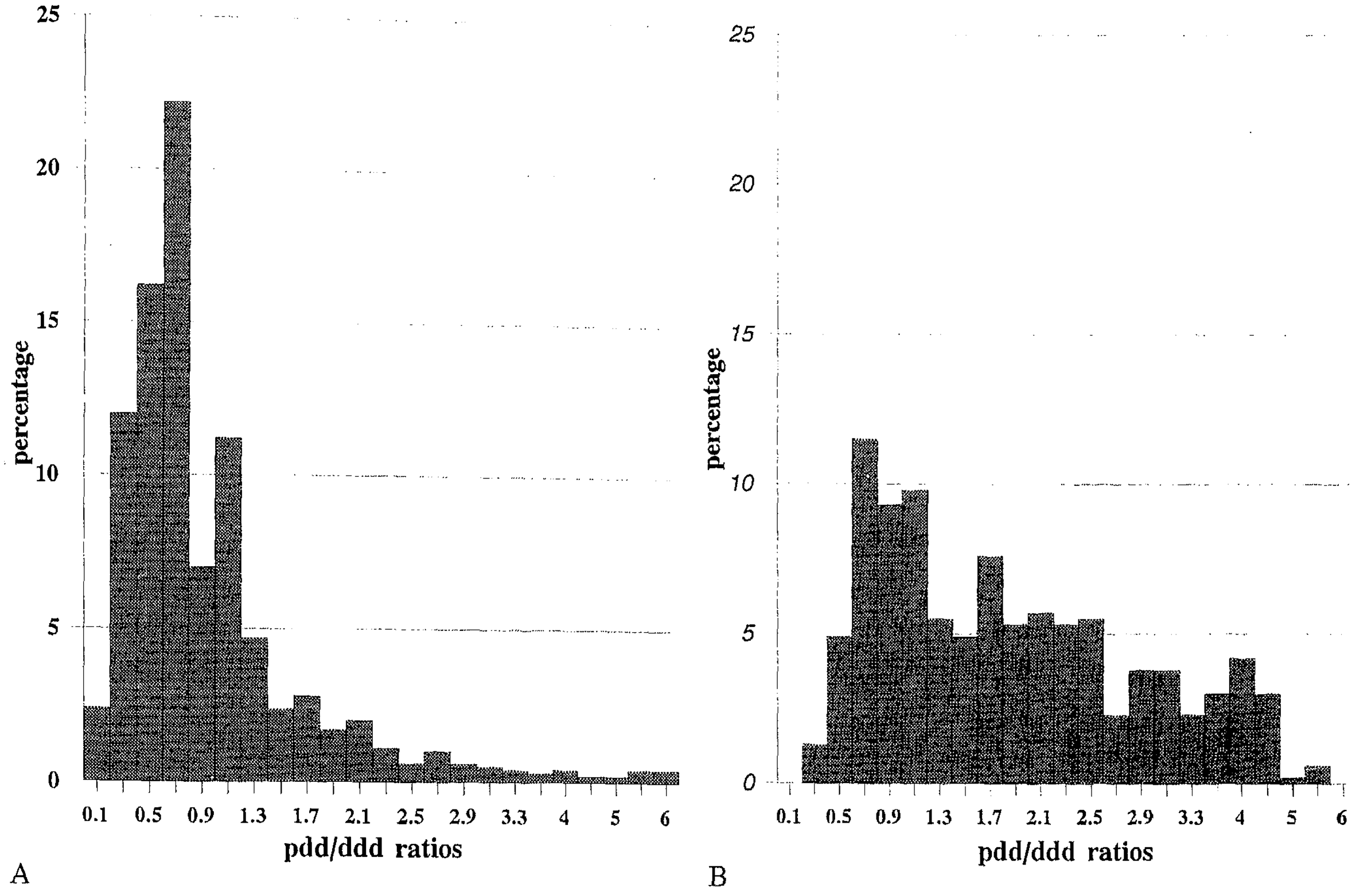

Figure. Distribution of the total dose per day of antiepileptic drugs prescribed to patients registered in the PHARMO database (N = 2,467) (A) and to patients attending outpatient departments of epilepsy centers (N = 559) (B), expressed as prescribed daily dose/defined daily dose ratios (pdd/ddd).

years were excluded in the PDD/DDD analysis in order to allow comparison with the UH and EC data.

In the PHARMO population, the median and average PDD/DDD ratios were all lower than 1.00. This was also the case in the UH and EC populations, except for PHT. PB was close to unity in the PHARMO population, higher than unity in the UH, but much less than unity in the EC, where it was also used much less frequently. CLB was used in only 15.4% of the EC patients, with a median PDD/DDD ratio of 1.0.

The frequency of use of CZP in the PHARMO population is surprising; however, the median and average PDD/DDD ratios for CZP were relatively low.

The highest doses per drug were used by patients under the care of the EC, while those who attended the UH hold an intermediate position. This is also reflected in the comparison of the total dose, whether it be of patients using monotherapy or polytherapy (cumulated PDD/DDD ratios).

The distribution of the cumulated PDD/DDD ratios per patient is illustrated for the PHARMO population in 1992 and the EC population in the figure.

Discussion. The results of this study show that 0.89% of a Dutch community of 302,149 people used AEDs longer than 180 days and therefore likely had epilepsy. Although reasons of privacy prevented us from verifying that assumption, comparison of the assumed number of epileptics found in this study with the epilepsy prevalence in Rochester, Minnesota,[11] shows them to be remarkably close, especially for the age group 5 to 44 years old (table 1) (PHARMO prevalence = 0.72%; Rochester prevalence = 0.65%; difference is not significant [$p > 0.1$]). The difference between the average prevalence estimated for all age groups in the PHARMO population (0.89%) and that in Rochester (0.68%), however, is highly significant ($p < 0.001$). The deviation, for which the age groups >44 years old are mainly responsible, may be explained by our study's using as the only criterion for the diagnosis of epilepsy the use of AEDs for more than 180 days. It may be argued that nowadays some patients with trigeminal neuralgia or mania are also treated for prolonged periods with at least one of the AEDs, ie, CBZ. In a recent population-based door-to-door study of all elderly people living in Ommoord, a suburb of Rotterdam, The Netherlands, 5,559 persons aged 55 to 95 were interviewed.[13] Ninety-seven reported epilepsy, and 24 used AEDs without reporting epilepsy. Of these 24, four had epilepsy but had not been told or had not understood that such was the case; seven used CBZ for trigeminal or hypoglossal neuralgia, two for polyneuropathy, and one for manic-depressive psychosis; five were long-term barbiturate users with nervous disorders; three were prescribed CZP for restless legs; one was prescribed VPA after an

attack of herpes encephalitis (without clinical or EEG evidence of epilepsy); and in one person verification was impossible. Thus, a risk of overreporting of 20% could be inherent in our method. The type of disorders AEDs are used for apart from epilepsy increases the likelihood of contamination, chiefly from middle age onwards. Even after correction by 20%, the differences in the prevalence of epilepsy between this study and the Rochester study remain significant ($p < 0.01$) for the age groups from 45 to 74 years old; the difference for the age group 74+ is not significant due to the steep increase in the Rochester data. The higher prevalence of epilepsy in these Dutch towns cannot be explained by a selection bias, as the patients in the PHARMO population were all outpatients who collected their own medication from one of the pharmacies in the database. The six towns covered by the study do not have institutions for mentally retarded or epilepsy centers, both of which would have attracted patients from outside the region, thus influencing the prevalence. As the Rochester data covered the period 1940–1980 and the PHARMO drug database covered 1989–1992, the difference may depend on differences in diagnosis or in the composition of the population older than forty-five.

The percentage of patients on monotherapy was almost 80% in the PHARMO population, in agreement with Reynolds and Shorvon,[14] who showed that 72% of epileptics can be well controlled with monotherapy. The percentage of patients on monotherapy in studies performed over the years shows a definite tendency toward monotherapy for the treatment of epilepsy.[15-19]

There were few changes in the AEDs prescribed over the years, with only MPB and PB showing a distinct decrease. MPB was most likely used by older patients, and the decrease in use could be explained by increased mortality among the elderly patients and by MPB's not being prescribed for newly diagnosed patients.

The number of users of CZP is surprising because patients may develop a tolerance for this drug, making it less advantageous for chronic treatment.

For most AEDs the median PDD/DDD ratio was well under 1.00, the reason possibly being that the DDD, as recommended by the WHO, is too high. The WHO Collaborating Center for Drugs Statistics in Oslo presents the DDD of OCB as being equal to the DDD of CBZ, while clinical trials show that the DDD of OCB should be 1½ times the DDD of CBZ.[20-22] Further studies normalizing the dosages using PDD/DDD ratios may require more accurate assessment of equipotence of the AEDs at several dose levels.

The percentage of prescriptions of VGB increased rapidly after its introduction in 1990, and the percentage of patients using VGB as monotherapy also increased considerably during the 3-year period, although VGB was primarily registered as add-on therapy for partial seizures. That the overall percentage of patients on monotherapy decreased and the average number of AEDs per patient increased in the VGB group is explained by VGB's mostly being used for patients with intractable seizures and not those with well-controlled epilepsy. The pattern of drug use in the PHARMO group resembled that of a secondary referral center since patients with epilepsy are usually referred to a secondary referral center for confirmation of diagnosis and regulation of therapy.

In the EC, a greater variety of AEDs were used and more patients used a larger amount of antiepileptic medication, as expressed in the sum of PDD/DDD ratios per patient. That about 27% of the patients at the EC are treated with less than 1.00 PDD/DDD probably reflects that not only therapy-resistant patients are referred to tertiary care centers but also patients with psychosocial problems.

We conclude that prescription data of AEDs used for over 180 days can be used as an indicator for the prevalence of epilepsy, although for the middle-aged and elderly a correction factor has to be applied. The concept of normalizing prescriptions on the basis of DDDs facilitates comparison of treatment policies and treatment outcomes. However, the DDDs of AEDs should be refined; in particular, there is a need to obtain complete dose-response curves of equivalent AEDs.

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