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Monotherapy or Polytherapy for Epilepsy Revisited: A Quantitative Assessment


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Summary: Some investigators argue that treating epilepsy with several antiepileptic drugs (AEDs) simultaneously (polytherapy) may give rise to more adverse effects than monotherapy, but this argument lacks supporting quantitative data. To reexamine this issue, we recruited a cohort of patients from the outpatients of the Special Centres for Epilepsy in The Netherlands and from the outpatients of the Department of Neurology, Nijmegen University, The Netherlands. Two tools were used for analysis. All daily doses of antiepileptic drugs (AEDs) were standardized by the ratio of prescribed daily dose to defined daily dose (PDD/DDD). The DDD is the assumed average effective daily dose for a drug used for its main indication in adults. The assignment of DDD values is the task of the World Health Organization (WHO) Collaborating Centre for Drugs Statistics Methodology and Nordic Council on Medicines, which regularly publishes Guidelines for Defined Daily Doses. The severity of adverse effects (AE) was assessed by using the Neurotoxicity Index and the Systemic Toxicity Index as developed by the VA Cooperative Study Group for their recent studies comparing the efficacy and tolerability of AEDs. One hundred sixty-one patients received monotherapy; all had a PDD/DDD ratio ≤2/day; 128 of 262 patients receiving polytherapy also had ≤2 PDD/DDD ratios/day. The mono- and polytherapy groups were stratified according to the PDD/DDD ratio. The prevalence of neurological AE for patients with similar PDD/DDD ratios was 50–80% for monotherapy patients and 50–82% for polytherapy patients. The difference between the mono- and polytherapy groups was not significant. The prevalence of neurological AE for patients receiving polytherapy with a PDD/DDD ratio >2.0 was 71–100%, whereas all patients with a PDD/DDD ratio >4.0 had neurological AE. This difference between patients with a PDD/DDD ratio ≤2.0 and those with >2.0 was statistically significant; p < 0.05. The severity of neurological AE also increased with dose, but appeared to peak at ~3.5 PDD/DDD ratio. Our study underscores the usefulness of applying quantitative methods to the analysis of drug AE. Comparison of monotherapy and polytherapy showed no difference for equipotent doses. Because distribution of the AED doses was uneven between the groups receiving mono- and polytherapy, our study permits only a tentative statement that the frequency and severity of AE is independent of the use of either. In addition, frequency and intensity of AE apparently are not very sensitive to changes in dose. An experimental prospective study is planned to verify or refute the conclusions of this observational pilot study. Key Words: Epilepsy—Antiepileptic drugs—Adverse effects—Monotherapy—Polytherapy—Clinimetrics.

Remaining seizure-free is sufficiently important for many patients with epilepsy for them to accept the adverse effects (AE) of continual use of antiepileptic drugs (AEDs). The problem of toxicity of AEDs has been reviewed repeatedly (1–4). There is a long tradition of using several AEDs simultaneously for the treatment of epilepsy (polytherapy). Reynolds and Shorvon (5), however, signaled three major problems associated with this practice: (a) chronic toxicity, (b) exacerbation of seizures, and (c) drug interactions. The evidence lacks quantitative support, however.

A few years ago, three special centers for epilepsy in The Netherlands and the subdepartment of Epileptology of Nijmegen University decided to determine whether further quantification of symptoms and signs could improve optimal management of epilepsy. Feinstein (6) has been a strong advocate of quantification. He recommends the use of the term clinimetric indices as the term for the rating scales that have been developed for clinical phenomena. To advance these studies of the feasibility and profitability of using quantitative data, we examined
whether the incidence and/or severity of AE was affected by the use of one AED (monotherapy) or several AEDs (polytherapy) to control seizures.

USE OF DEFINED DAILY DOSES (DDD)

We hypothesized that there should be no difference in either the frequency or the severity of AE if equipotent doses of AEDs are used. To compare the effect of one drug with the effect of a combination of several drugs a measure of equipotency must be determined. Therefore, all daily doses were standardized by using the ratio of prescribed daily dose to DDD (PDD/DDD). The PDD is the dose prescribed by the physician for the individual patient and because only compliant patients were admitted to the study the PDD equals the actual daily dose. The DDD is the assumed average effective daily dose for the drug used for its main indication in adults and is expressed in amount of the active substance. DDD values are assigned by the World Health Organization (WHO) Collaborating Centre for Drugs Statistics Methodology and Nordic Council on Medicines and are published in Guidelines for Defined Daily Doses, a publication based on dose documentations per drug as prepared by WHO-Oslo based on international textbooks, journals, and documentation approved by drug control authorities. These dose documentations are available on request from Oslo (7). Table 1 shows the published DDD of AEDs.

The rationale for summating PDD/DDD ratios of different AEDs is found in the definition of DDD as the average maintenance dose of a particular drug for its main indication in adults. According to DDD methodology of the WHO, half of a DDD of AED-I plus half of a DDD of AED-II should be as effective as a full dose of either, e.g., 750 mg valproate (VPA) plus 500 mg carbamazepine (CBZ) should be as effective as 1,500 mg VPA or 1,000 mg CBZ.

Because we were interested only in comparing AE in monotherapy and polytherapy, efficacy of monotherapy and polytherapy was not assessed in this study. Efficacy would be related to the severity of the epilepsy. There is no a priori reason to expect that sensitivity to toxic effects of AEDs is related to the severity of the epilepsy.

QUANTIFICATION OF AE

Studies of AEDs rarely use quantitative data to describe the clinical AE. Quantitative data have been largely restricted to laboratory findings or the results of psychological tests, both of which are intrinsically quantified. When semiquantification is used, categories are usually poorly defined and terms such as mild, moderate, or severe are used, with no explanation of their precise meaning (8). Recently, however, the use of a clinimetric approach to epilepsy management has been increasing. In previous studies of clinimetrics and epilepsy care (9–12), we noted that the rating scales developed by the VA Cooperative Study Group are a suitable tool for this purpose (13,14).

MATERIALS AND METHODS

Population

The Netherlands is exceptional in that it has a long tradition of tertiary care. Three special centers provide both intramural and extramural tertiary care nationwide for persons with difficult-to-treat epilepsies. The country has a national network of 16 outpatient clinics associated with these centers (approximately one clinic for each 1 million inhabitants). Patients attending these clinics are always examined by the same physician, and there is a high level of compliance.

For the present study, the data on medication and AE recorded at the first assessment of the patients recruited in the years 1991 through 1993 for previous studies of the use of quantitative data (10–12) were collected in toto. All patients were either attending an outpatient clinic of one of the special centres for epilepsy or of a university hospital neurology department. The study was approved by the ethical committees of the participating institutes: Patients aged ≥15 years whose seizures could be defined accurately according to the International
Classification of the International League Against Epilepsy (ILAE) were included in the study. Patients with factors that were believed to complicate the evaluation of whether a clinimetric approach has added value over present patient management were excluded from the study; these factors included progressive brain disorders, obvious non-compliance in drug usage or seizure registration, pseudoseizures, and severe mental retardation.

Indexes

The Indexes used in this study were first described by Cramer et al. (13) for use in the evaluation of AED therapy. Subsequently, Wijsman et al. (9) made minor adaptations to enable their routine use in epilepsy management. These indexes consisted of the Index of Seizures (IS) measuring the seizure frequency modulated by seizure type. The Seizure Activity Index (SA), which is a further modulation takes into account the possible presence of an aura, seizure-provoking factors, clustering of seizures, occurrence of seizures only during sleep or at awakening, and the interval for complete recovery after the seizure. The Neurotoxicity Index (NTX) rates the presence and severity of common neurological symptoms commonly considered AE associated with AED use. The Systemic Toxicity Index (STX) rates the presence and severity of disturbances in different organs, some due to idiosyncratic reactions. The scores per symptom range from 0 to 50 (Table 2). The Composite Index of Impairments (CII) is the sum of the SA and toxicity ratings.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Scoring range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurotoxicity</td>
<td></td>
</tr>
<tr>
<td>Diplopia</td>
<td>15-30</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>5-10</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>5-30</td>
</tr>
<tr>
<td>Ataxia</td>
<td>5-50</td>
</tr>
<tr>
<td>Dysdiadochokinesis</td>
<td>15</td>
</tr>
<tr>
<td>Tremor</td>
<td>10-50</td>
</tr>
<tr>
<td>Sedation</td>
<td>5-50</td>
</tr>
<tr>
<td>Affect and mood disturbances</td>
<td>5-50</td>
</tr>
<tr>
<td>Cognitive impairments</td>
<td>5-50</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3-50</td>
</tr>
<tr>
<td>Headache</td>
<td>3-50</td>
</tr>
<tr>
<td>Systemic toxicity</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal problems</td>
<td>3-50</td>
</tr>
<tr>
<td>Haematopoietic problems</td>
<td>50</td>
</tr>
<tr>
<td>Dermatologic problems</td>
<td>20-50</td>
</tr>
<tr>
<td>Impotence</td>
<td>20-50</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>50</td>
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<tr>
<td>Liver disease</td>
<td>25-50</td>
</tr>
<tr>
<td>Weight gain</td>
<td>3-20</td>
</tr>
<tr>
<td>Changes in hair/hair loss</td>
<td>5-50</td>
</tr>
</tbody>
</table>

Patient data collection

Before the start of the study, patients meeting the inclusion criteria were informed about the purpose and the procedure of the study and asked to collaborate. None refused. On the day of their regular visit the patients were interviewed and examined for ~30 min by the investigator to obtain data necessary to determine the value of the indexes. Data from all patients receiving monotherapy (n = 161) and also from patients receiving polytherapy with a PDD/DDD ratio in the same range (n = 128) were examined. Therefore, 289 patients entered the main arm of the study; the maximum PDD/DDD ratio was 2.0. All patients with a PDD/DDD ratio >2.0 (n = 134) were in the polytherapy group. The polytherapy group as a whole (n = 262) was also studied separately in comparisons of patients receiving polytherapy with a PDD/DDD ratio ≤2.0 and >2.0. The patients were stratified according to the PDD/DDD ratio with intervals of 0.33 PDD/DDD ratio and the prevalence and severity (NTX, STX) of AE was studied in each stratum (Tables 3 and 4). Although serum levels of AEDs were available, they were not included in this study because AE might be due to metabolites, the entire spectrum of which was not measurable.

Statistical analysis

Because of the size of the strata, Fisher's exact test (two-tailed) was applied for the assessment of differences in gender, for the study of the overall prevalence of AE, and for the prevalence per stratum of PDD/DDD ratios. The Kruskal-Wallis test was used for the assessment of differences in the severity of AE. Differences were considered statistically significant at p < 0.05. Multiple-regression analysis was used to investigate whether gender, age, duration of epilepsy, or the use of either mono- or polytherapy in themselves or combined could explain the variance in outcome of the toxicity scores. However, no factor reached significance.

RESULTS

Population

Of 289 patients entering the main study, 124 were men (43%) and 165 were women (57%). No statistically significant difference was noted in the gender distribution between patients receiving monotherapy and those receiving polytherapy with a PDD/DDD ratio ≤2.0.

The mean age of the patients receiving monotherapy was 37 years (range 15-76 years); of patients receiving polytherapy was 43 years (range 15-75 years). This difference in mean ages between
patients treated with monotherapy and polytherapy was statistically significant ($p = 0.0001$).

A statistically significant difference was also noted for the mean duration of epilepsy between patients receiving monotherapy (18 years, range 1–64 years) and those receiving polytherapy (26 years, range 1–70 years) ($p = 0.0001$). For the patients receiving polytherapy with a PDD/DDD ratio $>$2.0, the mean age was 44 years (range 15–80 years) and the duration of epilepsy was 27.5 years (range 2–70 years). No statistical difference was noted in age and duration of epilepsy between this group and the group of patients receiving polytherapy with a PDD/DDD ratio $\leq$2.0.

### Number of AEDs prescribed in polytherapy

The distribution of the number of AEDs over the various PDD/DDD ratios for all patients is shown in Table 5. Sufficient numbers were available in only two classes to allow comparison of the neurotoxic and systemic toxic effects according to the number of drugs used in polytherapy. Respectively, 38 patients with a PDD/DDD ratio of 1.67–2.00 used two drugs and 10 patients used three drugs, whereas 11 patients with a PDD/DDD ratio of 2.34–2.66 used two drugs and 14 patients used three drugs.

### AE prevalence and severity

Overall, no significant differences in the prevalence of AE was noted between patients receiving monotherapy and polytherapy who had similar PDD/DDD ratios (Tables 3 and 4). Separate determinations of neurotoxicity and systemic toxicity did not change that finding. When specific AE were considered, the only significant differences in prevalence were sedation (37% in those receiving monotherapy and 52% in those receiving polytherapy, $p < 0.05$) and cognitive impairment (27% in those receiving monotherapy and 34% in those receiving polytherapy, $p < 0.05$) (Table 6). In both groups, sedation was the most common AE. The prevalence of individual systemic AE did not differ between the groups.

Neither the cumulated scores nor the median scores for intensity of each specific AE differed significantly between patients treated with monotherapy and those treated with polytherapy. Neither did the distribution of the severity scores for the AE separately differ between patients treated with monotherapy and those treated with polytherapy.

### AE prevalence and severity for PDD/DDD ratio $>$2.0

The prevalence of AE in patients receiving polytherapy with a PDD/DDD ratio $>$2.0 was greater than that in patients receiving polytherapy with a PDD/DDD ratio $\leq$2.0: 91 and 78%, respectively. This difference was statistically significant ($p < 0.05$). The prevalence of neurological AE effects showed some increase with higher doses of AEDs, although this finding was not statistically signifi-

## Table 3. Prevalence and severity of neurological AE per dose for patients receiving monotherapy and polytherapy

<table>
<thead>
<tr>
<th>PDD/DDD ratio</th>
<th>Monotherapy NCS</th>
<th>Polytherapy NCS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>0.01–0.33</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>0.34–0.66</td>
<td>62</td>
<td>60</td>
</tr>
<tr>
<td>0.67–1.00</td>
<td>64</td>
<td>72</td>
</tr>
<tr>
<td>1.01–1.33</td>
<td>18</td>
<td>78</td>
</tr>
<tr>
<td>1.34–1.66</td>
<td>4</td>
<td>75</td>
</tr>
<tr>
<td>1.67–2.00</td>
<td>3</td>
<td>67</td>
</tr>
</tbody>
</table>

AE, adverse effects; NCS, neurotoxicity cumulative score; n, number of patients per stratum; %, percentage of patients with AE per stratum.

## Table 4. Prevalence and severity of systemic AE per dose for patients on monotherapy and polytherapy

<table>
<thead>
<tr>
<th>PDD/DDD ratio</th>
<th>Monotherapy SCS</th>
<th>Polytherapy SCS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>0.01–0.33</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>0.34–0.66</td>
<td>62</td>
<td>23</td>
</tr>
<tr>
<td>0.67–1.00</td>
<td>64</td>
<td>22</td>
</tr>
<tr>
<td>1.01–1.33</td>
<td>18</td>
<td>33</td>
</tr>
<tr>
<td>1.34–1.66</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>1.67–2.00</td>
<td>3</td>
<td>33</td>
</tr>
</tbody>
</table>

SCS, systemic toxicity cumulative score; other abbreviations as in Table 3.
TABLE 5. Distribution of the number of AEDs over the various PDD/DDD ratios

<table>
<thead>
<tr>
<th>PDD/DDD ratio</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01-0.33</td>
<td>10</td>
<td>—</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>0.34-0.66</td>
<td>62</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>0.67-1.00</td>
<td>64</td>
<td>16</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1.01-1.33</td>
<td>18</td>
<td>17</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1.34-1.66</td>
<td>4</td>
<td>42</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>1.67-2.00</td>
<td>3</td>
<td>38</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>2.01-2.33</td>
<td>23</td>
<td>5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2.34-2.66</td>
<td>11</td>
<td>14</td>
<td>5</td>
<td>—</td>
</tr>
<tr>
<td>2.67-3.00</td>
<td>9</td>
<td>14</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3.01-3.33</td>
<td>1</td>
<td>13</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3.34-3.66</td>
<td>—</td>
<td>—</td>
<td>8</td>
<td>2</td>
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<td>4</td>
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<td>4.34-4.66</td>
<td>—</td>
<td>—</td>
<td>7</td>
<td>—</td>
</tr>
<tr>
<td>4.67-5.00</td>
<td>—</td>
<td>—</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5.01-5.33</td>
<td>—</td>
<td>—</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>5.34-5.66</td>
<td>—</td>
<td>—</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

PDD, prescribed daily dose; other abbreviations as in Table 1.

significant. The severity of neurological AE also increased with higher doses, but appeared to peak at a PDD/DDD ratio level of 3.67-4.00 (Table 7).

AE and number of AEDs

No statistically significant difference was noted between the patients receiving two AEDs and three AEDs with respect to the prevalence and severity of neurological AE. Systemic AE occurred more frequently in the patients using three AEDs, although the severity did not differ.

DISCUSSION

Prevalence of polytherapy

Reynolds and Shorvon (5) remarked that "There seems little doubt that polytherapy has characterized the treatment of epilepsy throughout the ages..." Textbooks over the years contain little evidence that the use of polytherapy has been based solely on rational choice. Guelen et al. (15) collected data on plasma concentrations of AEDs from 11 institutions in The Netherlands, Norway, England, Germany, and the U.S., obtaining information on 11,720 patients from 1969 to 1974. The average number of AEDs prescribed per patient in that period was 3.2, of which 85% consisted of AEDs and 15% of stimulants such as amphetamines or caffeine, and/or vitamins and/or neuroleptic drugs. Only 4.2% were treated with single drug. Thanks to the advocacy of Reynolds and Shorvon (5) and other epileptologists, most physicians who now treat epilepsy initiate treatment with a single AED. In a previous study, we examined 225 patients from the special centers for epilepsy and noted an average use of 2.0 AED per patient, but only 28% were receiving monotherapy (10). Those treated with polytherapy received an average of 2.4 AEDs per patient. One hundred twenty patients from the University Hospital Nijmegen received an average of 1.4 AED/patient and 62.5% were treated with monotherapy. Those treated with polytherapy received an average of 2.1 AEDs per patient. Polytherapy is therefore still an issue. In the present study we examined pooled data from the epilepsy centers and Nijmegen University. Of the 423 patients, 38% received monotherapy. Those treated with polytherapy received 2.45 AEDs on the average.

Possible confounders

The data from our patients have been standardized in two respects. AE of AEDs were assessed quantitatively with respect to both the prevalence of the AE and their severity. The scores are presumed to be independent of the type of the drug responsible. The AED doses were standardized by the PDD/DDD ratio. The concept of adding fractions of the DDD as a measure of drug exposure obviously does not take into account linearity of dose-effect relationships of metabolic or dynamic interactions of the drugs in individuals, but the concept has been used extensively in pharmacoepidemiological studies (16).

Because our study is a prospective observational study, it has an inherent weakness: The parameters could not be set according to the demands of the study. All patients visiting the outpatient clinic who met the entry criteria were studied. The patients receiving monotherapy and those receiving polytherapy did not differ with respect to gender but differed significantly with respect to mean age and mean duration of epilepsy. Patients receiving monotherapy were on average, younger and had had epilepsy for a shorter time. Whether this difference influences the occurrence of AE cannot be judged from our study. When the results were assessed by multiple-regression analysis, age and duration did not explain the variance in frequency and severity of AE. The patients treated with polytherapy with a PDD/DDD ratio ≤2.0 and those with a PDD/DDD ratio >2.0 did not differ significantly either in gender, age, or duration of epilepsy.

In the main arm of the study (n = 289), 71% of patients receiving monotherapy and 79% receiving polytherapy had AE. This result from a prospective study contrasts with the results obtained in a retrospective study (9): 20.9% of patients receiving monotherapy and 20.5% receiving polytherapy had AE. Our results are more in agreement with those...
TABLE 6. Distribution of AE in monotherapy and polytherapy

<table>
<thead>
<tr>
<th>Effects</th>
<th>Monotherapy (n = 161)</th>
<th>Polytherapy (n = 128)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>Median score (25-75%)</td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diplopia</td>
<td>5.0</td>
<td>15 (15-15)</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>6.2</td>
<td>5 (5-10)</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>6.8</td>
<td>5 (5-5)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>11.8</td>
<td>5 (5-15)</td>
</tr>
<tr>
<td>Dysdiadochokinesis</td>
<td>1.2</td>
<td>15 (15-15)</td>
</tr>
<tr>
<td>Tremor</td>
<td>18.0</td>
<td>10 (10-10)</td>
</tr>
<tr>
<td>Sedation</td>
<td>37.3</td>
<td>5 (5-5)</td>
</tr>
<tr>
<td>Affect and mood disturbances</td>
<td>6.2</td>
<td>5 (5-5)</td>
</tr>
<tr>
<td>Cognitive impairments</td>
<td>26.7</td>
<td>5 (5-5)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7.5</td>
<td>5 (3-7.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>9.3</td>
<td>5 (5-10)</td>
</tr>
<tr>
<td>Systemic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal problems</td>
<td>5.0</td>
<td>4 (3-7.5)</td>
</tr>
<tr>
<td>Hematopoietic problems</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Dermatological problems</td>
<td>1.9</td>
<td>15 (15-15)</td>
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<td>Impotence</td>
<td>0.6</td>
<td>50 (50-50)</td>
</tr>
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<td>Kidney disease</td>
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<td>Liver disease</td>
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<tr>
<td>Weight gain</td>
<td>11.2</td>
<td>10 (3-10)</td>
</tr>
<tr>
<td>Change in hair/hair loss</td>
<td>12.4</td>
<td>5 (5-5)</td>
</tr>
</tbody>
</table>

n, number of patients per therapy group; %, percentage of patients with adverse effects [(AE); some had multiple AE].

of the prospective study of Keyser et al (17), in which 57.3% of the patients reported AE and that of the Collaborative Group of Epidemiology of Epilepsy (18) of Milan, Italy, in which 41.6% of the patients had AE. The selection of patients for these two studies does not allow detailed comparison.

Comparison of patients receiving monotherapy and those receiving polytherapy with similar PDD/DDD ratios showed no overall difference in either prevalence or severity of neurological and systemic AE. It is remarkable that on stratification neither the frequency nor the severity increased notably per stratum, although they tended toward increase. Because ours was an observational study, our results may well reflect the practice not to increase dose beyond a tolerable level. The dose tolerated may differ from person to person, however. Analysis of the data of patients receiving polytherapy showed an increase in frequency of AE to 100% when the PDD/DDD ratio increased to >3.0. The severity of AE increased at a PDD/DDD ratio of 3.67-4.00, followed by a decrease at higher doses. We attribute this to the practice of administering such high doses only to patients who are relatively insensitive to AE. Patients receiving polytherapy had a significantly longer duration of epilepsy, which may have led to the development of tolerance to some AE, and thus to a lower prevalence and

TABLE 7. Prevalence and severity of neurological and systemic AE for PDD/DDD ratio >2.0

<table>
<thead>
<tr>
<th>PDD/DDD ratio</th>
<th>NTX</th>
<th>Polytherapy (n = 134)</th>
<th>STX</th>
<th>Polytherapy (n = 134)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>Median NCS</td>
<td>n</td>
</tr>
<tr>
<td>2.01-2.33</td>
<td>28</td>
<td>71</td>
<td>20.0</td>
<td>28</td>
</tr>
<tr>
<td>2.34-2.66</td>
<td>30</td>
<td>83</td>
<td>15.0</td>
<td>30</td>
</tr>
<tr>
<td>2.67-3.00</td>
<td>23</td>
<td>83</td>
<td>19.0</td>
<td>23</td>
</tr>
<tr>
<td>3.01-3.33</td>
<td>14</td>
<td>93</td>
<td>20.0</td>
<td>14</td>
</tr>
<tr>
<td>3.34-3.66</td>
<td>10</td>
<td>100</td>
<td>21.5</td>
<td>10</td>
</tr>
<tr>
<td>3.67-4.00</td>
<td>10</td>
<td>90</td>
<td>35.0</td>
<td>10</td>
</tr>
<tr>
<td>4.01-4.33</td>
<td>10</td>
<td>100</td>
<td>25.5</td>
<td>10</td>
</tr>
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<td>25.0</td>
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</tr>
<tr>
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<td>15.0</td>
<td>3</td>
</tr>
<tr>
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<td>5.34-5.66</td>
<td>2</td>
<td>100</td>
<td>13.0</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviations as in Tables 1, 3, and 4.
severity. This possibility could not be confirmed in the context of this study and will require further investigation.

Lack of correlation

The prevalence of AE in the group receiving polytherapy (n = 262) was greater for patients with a PDD/DDD ratio of >2.0. No correlation was noted between the number of AEDs and prevalence of neurological AE which again suggests that the occurrence and the severity of AE are influenced by the total dose and not by the number of AEDs prescribed. Keyser et al. (17) showed that patients treated with polytherapy had a higher prevalence of AE than did patients treated with monotherapy. In that study, all patients were compared, irrespective of the dose of medication, in contrast to the patients in the main arm of the present study in which only patients with similar PDD/DDD ratios were compared.

Sedation and cognitive impairment were the two more frequent neurological AE in patients receiving polytherapy. However, there was no difference in the intensity (median level of NTX score) of these AE between the two groups. There is no prima facie explanation for this finding, which obviously requires further study.

Our results underscore the feasibility of applying clinimetric methods to the analysis of AE of drugs. Frequency and intensity of AE apparently are not very sensitive to changes in dose. Neither was any difference noted between monotherapy and polytherapy. Because the distribution of the dose of AEDs was uneven between the groups receiving mono- and polytherapy, our study permits only a tentative conclusion that the frequency and severity of AE is independent of the use of either. Longer duration of epilepsy in the cohort on polytherapy, might be supposed a complicating factor but this possibility was not confirmed by the statistical analysis. An experimental study is planned to verify or refute the conclusions of this observational study.

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