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Reappraisal of Polytherapy in Epilepsy: A Critical Review of Drug Load and Adverse Effects

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Summary: *Purpose:* We reviewed the literature to determine whether an analysis of published data could clarify the relationship between antiepileptic drug (AED) polytherapy and adverse effects (AE). We highlight the problems encountered.

Methods: We made a Medline-search for articles published between 1974 and 1994 reporting the number of AE and doses or serum levels of every AED, per patient or treatment group, and used the PDD/DDD ratio to calculate AED load per patient from doses or the OSL/AToXL ratio to do so from serum levels of individual drugs. The PDD/DDD is the sum of ratios of the actual prescribed daily doses divided by the published average therapeutic dose of each drug. The OSL/AToXL is the sum of each observed serum level divided by its average toxic level.

Results: We retrieved 118 trial reports. Most had to be excluded because of incomplete reporting of concomitant medication or AE. The data of the 15 articles selected for further analysis indicate a relationship between drug load and number of AE. We noted no relationship between the number of AEDs administered and AE. In add-on studies,

the difference in neurotoxicity between the active and placebo arm may be obscured if the relative increase in drug load is small, as exemplified by the study of McGuire et al. (35).

Conclusions: Articles reporting add-on trials of new AEDs generally do not provide detailed information about the basic medication to which the new AED is added, which makes calculation of total drug load impossible. Furthermore, often only frequency of AE is reported, not severity or development of tolerance, making it difficult to judge the impact of AE. However, despite the paucity of available information, we present some evidence that toxicity in AED polytherapy may be related to total drug load, rather than to the number of drugs administered. Therefore, the present trend to reject polytherapy for fear of increased toxicity is not warranted, which removes one of the objections to initiating specific research to prove or disprove the value of AED combinations as long as the drug load is appropriate. **Key Words:** Polytherapy—Antiepileptic drugs—Adverse effects—Drug load—Epilepsy.

Antiepileptic drug (AED) pharmacotherapy is aimed at reducing seizure frequency and severity without producing adverse effects (AE). However, the reporting of AE in clinical trials lacks quantitative data because AE are often described in terms of frequency and rarely in terms of severity (1). Although the incidence of AE is important, the degree to which they occur also determines the acceptability of individual AEDs. When quantitative data are presented, a comparison is complicated because of the different rating scales used (2,3).

The risk of development of chronic toxicity has been one of the arguments against use of polypharmacy in epilepsy (4). Much of this toxicity is believed

to be directly related to the number of AEDs being consumed, as the number of AE is often reduced after the number of AEDs is reduced (5,6). Partly for this reason, monotherapy has long been advocated by leading epileptologists (7).

However, the total AED load of a multiple drug regimen rather than the number of AEDs may determine toxicity. High-level duotherapy is more likely to be associated with more AE than is the same combination of drugs at low serum levels (8). To compare the total AED load between patients receiving monotherapy and polytherapy, the prescribed daily dose/defined daily dose (PDD/DDD) ratio and the observed serum level/average therapeutic level (OSL/ATL) ratio can be used. These are ratios of the actual dose or serum level divided by the average therapeutic dose or level, respectively. The total drug load in polytherapy patients is calculated by summing the PDD/DDDs or the OSL/ATLs of the individual drugs. Lammers et al. (9) evaluated patients with

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epilepsy using this method combined with a method to quantify the incidence and severity of both seizures and AE. When the AED load of both groups was equal, patients receiving polytherapy did not necessarily have higher toxicity than patients receiving monotherapy.

Because, the pharmacodynamic action of seizure control does not necessarily correlate with neurotoxicity, however, the DDD may not correlate well with AE. Instead of the DDD, ideally a defined toxic dose should be used in determining drug loads in relation to AE. Using serum levels instead of doses has an advantage in that average toxic serum levels have been published. Instead of the ATL, the average toxic level (AToxL) must be substituted in the denominator, thus creating an OSL/AToxL ratio. Serum levels, contrary to the PDD/DDD ratio, furthermore reflect differences in pharmacokinetics between different AEDs, although metabolites and brain concentrations are not accounted for.

In the present study, we surveyed the literature, using the PDD/DDD ratio and the OSL/AToxL ratio to evaluate the reporting of AE in relationship to AED load. We placed special emphasis on articles reporting use of polytherapy in one of the treatment groups.

METHODS

We used the Medline program to screen the literature from 1974 to 1994, using the search commands [epilepsy], [adverse or side effects or cognitive or toxicity], and [combination therapy or add-on or discontinuation]. Next, we made a further selection using the following requirements: (a) a multiple AED regimen administered in one of the treatment groups of a trial, (b) mention of the dose or serum level of every prescribed AED per patient or mean dose, respectively, serum level, and number of patients treated with each AED per treatment group; and (c) mention of incidence and specification of AE per patient or treatment group.

Total drug load

The DDD is based on the assumed average daily dose in its main indication in adults and is assigned by the World Health Organization for each drug. An analogous ratio for AED serum levels was developed in our institute. AToxL per drug were assessed from literature data (10–13). The DDD and AToxL were determined (Table 1) and were analyzed statistically, by Pearson's correlation coefficient and the *z*-transformation to test correlations between parameters. Dice were thrown to select one observation randomly per patient for statistical analysis.

TABLE 1. DDD and AToxL values for individual AEDs

AED	DDD (mg) ^a	AToxL (mg/L) ^b
Carbamazepine	1,000	12
Phenytoin	300	20
Valproate	1,500	120
Phenobarbital	100	40
Primidone	1,250	15
Ethosuximide	1,250	120
Clonazepam	8	—
Clobazam	20	—
Progabide	1,800 ^b	—
Vigabatrin	2,000	—
Flunarizine	30 ^b	—
Felbamate	2,700 ^b	80
Clorazepate	—	5 ^c

DDD, defined daily dose; AToxL, average toxic level; AEDs, antiepileptic drugs.

^a Assigned by the World Health Organization.

^b Assigned according to literature data.

^c Nordiazepam level.

RESULTS

Screening of the literature

Through the Medline search, we retrieved 661 articles, of which 118 were trial reports with a multiple drug regimen in at least one of the treatment groups. Next, we applied our requirements to select articles suitable for analysis. Three were not suitable because two of them compared differences in frequency of administration, e.g., a daily dose versus a three-times weekly dose; the third reported a study of a new drug for which no information was available about the average effective dose. Most articles were rejected for two reasons:

1. Eighty studies in which new drugs, multiple drug regimens, or a reduction in the number of AEDs in these regimens were evaluated were rejected because the researchers did not provide data on doses or serum levels of each drug or about the number of patients treated with the drug; a few representative examples are cited (14–19).
2. Twenty papers were rejected because AE were either not mentioned or were not adequately described. (One fourth of the articles were thus deficient). Seizure control was the only outcome measure in these cases (19–21).

Fifteen papers met the three requirements described in the Methods section. In these, drug toxicity was evaluated by listing of subjective complaints, by repeated neurological examinations, and/or by neuropsychological testing. Even in these articles, no systematic comments were made regarding the severity of the AE. We divided the selected articles into three groups: A, B, and C.

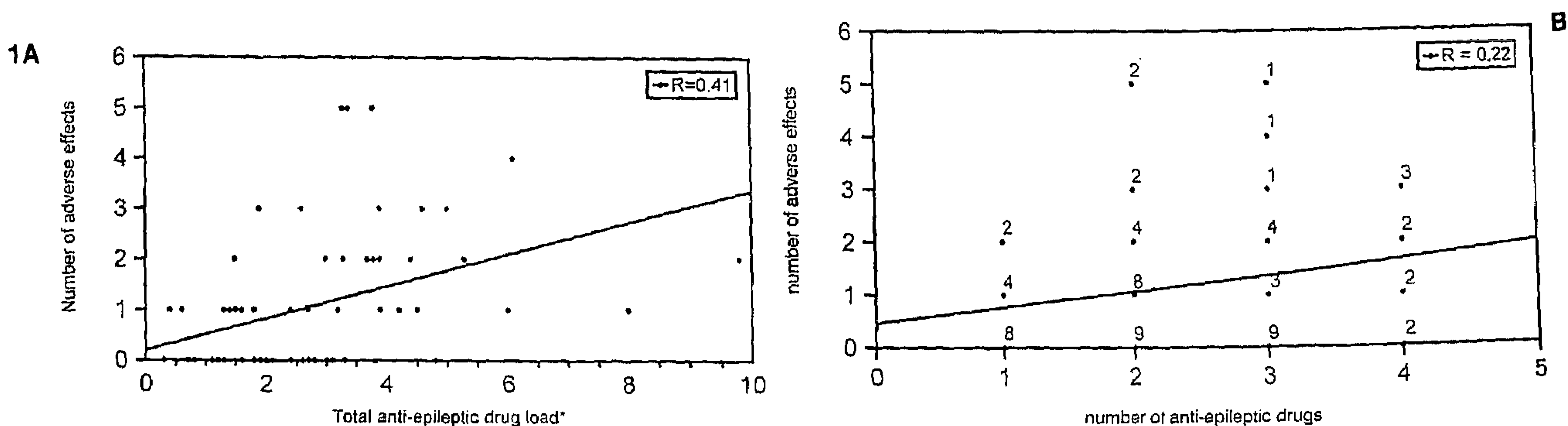


FIG. 1. **A:** Adverse effects in relation to total drug load in individual patients. Combined data from the studies cited (22–26). From the published data, one measurement per patient was taken at random. *Expressed in prescribed daily dose/defined daily dose. **B:** Adverse effects in relation to number of antiepileptic drugs in individual patients. Combined data from studies cited (22–26). From the published data, the same measurement per patient was taken as described in A. Numbered dots indicate number of patients having the same coordinates.

AE and dose/serum levels reported per individual patient

In five articles, the number and dose of all AEDs (but not serum levels) and AE were reported per patient (22–26). The total AED load in relation to the number of AE in individual patients is shown in Fig. 1A. Although the correlation coefficients vary between the trials, a weak positive association between these parameters does exist for the total group ($r = 0.41$). The number of AEDs in relation to the number of AE is shown in Fig. 1B. We did not note a significant association between these parameters.

AE and dose/serum levels reported per treatment group

In seven articles, two treatments were compared and the number of AE effects and the average dose or serum level of every AED was reported per treatment group (27–33). We calculated the mean total AED loads or OSL/AToxL ratio per treatment group (Table 2) with the respective number of AE reported. In all these studies, except that of Schmidt (27), a cross-over design was used. In all the studies, a higher

total AED load or a higher OSL/AToxL ratio was associated with an increase in AE (Table 2).

Drug toxicity evaluated by neuropsychological testing

Four articles described neuropsychological testing used to detect drug-related changes in cognitive functioning; doses or serum levels were adequately reported (8,33–35). The trial of Wilensky et al. (33) is also included in group B.

Different neuropsychological tests were applied by the various researchers, which complicated a detailed comparison. We calculated the mean total AED load or OSL/AToxL ratio per treatment group (Table 3). The tests the authors used are categorized according to cognitive functions and the results of the various trials in Table 3. Thus, for example, decision making and visual scanning are categorized as components of mental speed. Intellectual achievement was tested by arithmetic in three trials. Patients in treatment groups with higher drug loads or higher OSL/AToxL ratios performed as well as or worse, but not better,

TABLE 2. *Trials in which number of adverse effects was reported per treatment group*

Reference	Treatment groups	PDD/DDD ^a	No. of side effects
Loiseau et al. (28) (n = 23)	VGB versus placebo add-on	3.6 versus 2.1	18 versus 11
Loiseau et al. (29) (n = 23)	LTG versus placebo add-on	3.1 versus 2.2	50 versus 20
Tartara et al. (30) (n = 21)	VGB versus placebo add-on	3.5 versus 2.3	26 versus 9
Sander et al. (31) (n = 18)	LTG versus placebo add-on	3.3 versus 2.6	20 versus 14
	Treatment groups	OSL/AToxL ^a	No. of side effects
Leppik et al. (32) (n = 56)	FBM versus placebo add-on	1.7 versus 1.4	133 versus 16
Wilensky et al. (33) (n = 42)	PB versus CLZ both added to PHT	1.7 versus 1.5	32 versus 16
Schmidt (27) (n = 36)	Two-drug versus monotherapy	1.4 versus 0.9	41 versus 31

PDD, prescribed daily dose; OSL, observed serum level; VGB, vigabatrin; LTG, lamotrigine; FBM, felbamate; PB, phenobarbital; PHT, phenytoin; CLZ, clonazepam; other abbreviations as in Table 1.

^a Mean total antiepileptic drug load (PDD/DDD) or OSL/AToxL per treatment group is shown.

TABLE 3. Trials in which drug-related effects on cognitive functioning were measured

Reference	Treatment groups ^a	PDD/DDD ^b	Mental speed	Short-term memory	Attention/concentration	Visuomotor response	Intellectual level	Motor speed
McGuire et al. (35) (n = 30)	Adding vigabatrin versus placebo	3.0 versus 2.5	s		s	s	i or s	
	Treatment groups ^a	OSL/AToxL ^b						
Duncan et al. (34) (n = 23)	After removal of PHT from a multiple drug regimen	1.2 versus 0.9	s	s	i		s	i
Duncan et al. (34) (n = 24)	After removal of CBZ from a multiple drug regimen	0.9 versus 0.4	s	s	s		s	i
Duncan et al. (34) (n = 25)	After removal of VPA from a multiple drug regimen	0.9 versus 0.6	s	s	s		s	i
Wilensky et al. (33) (n = 42)	PB instead of CLZ in combination with PHT	1.7 versus 1.5			d		s	s
Thompson and Trimble (8) (n = 28)	A change from high-level to low-level multiple drug regimens	0.95 versus 0.63	i	i		i		s

CBZ, carbamazepine; VPA, valproate; d, deteriorated; i, improved; s, same; other abbreviations as in Tables 1 and 2.

Trial designs, total drug loads and conclusions regarding cognitive changes as described in different reports. The changes in the cognitive functions are those observed after the second treatment was substituted for the first (i.e., VGB vs. placebo—the condition while receiving placebo).

^a Characterization of groups: In trials by Wilensky et al. (28), Duncan et al. (30), and Thompson and Trimble (5), a cross-over design was used. In the trial by McGuire et al. (31), a parallel design was used.

^b Total antiepileptic drug-load (in PDD/DDD) or OSLA/AToxL is shown per treatment group.

on neuropsychological tests than patients in treatment groups with a lower drug load.

DISCUSSION

Critique of the literature

Methods of assessing AE, and in particular methods of reporting about the incidence, leave much to be desired. Very few of the articles we collected in this literature search satisfied the requirements for inclusion. Lack of information about the exact dosages or serum levels of individual AEDs, or about the frequency of AE, or both, was particularly frequent. The few articles selected would have been reduced even further if adequate quantification of the severity of AE had been a requirement. This further compromises the comparability of trials with regard to toxicity, because, if no use is made of validated scales, it is debatable whether one can weigh the impact of AE if 10% of patients in one group and 20% in another group report dizziness. It is equally unclear how one can compare five cases of nausea in one group with five cases of drowsiness in another group without measuring how the health-related quality of life is affected. Several rating lists for scoring AE quantitatively according to type and severity are now in use or are being developed (2,3). These lists will provide individual toxicity scores by which patients can be compared. Such potential extra information may be undermined by the use of different

tests in trials. This point is clearly evident when the articles used in this study are compared.

Relation between number of AEDs, total drug load, and AE

Only group A articles allowed comparison of toxicity in individual patients and could therefore be used to estimate the correlation coefficient between toxicity and drug load, respectively, and number of AEDs administered.

Comparison of the articles in group A shows that the correlation between incidence of AE and drug load is slightly stronger than that between AE and number of AEDs received, although both are weak and thus cannot be taken as proof. An inherent weakness of our analysis is that DDD are established only for the main indication of a drug, i.e., seizure control, and not for toxicity. Although correlations between serum levels and toxicity have been published, few articles retrieved in our study contained information about serum levels. This is regrettable because the PDD/DDD ratio does not account for possible pharmacokinetic interactions. In group B and C articles, we could not disentangle the cause of greater toxicity, which might just as well be due to the higher drug load as to use of multiple AEDs or to both. Although the information we report does not yet permit conclusions regarding the superiority of polytherapy to monotherapy, it does remove one of the objections

against renewing the study of relative efficacy of mono- and polytherapy, keeping the considerations of equal drug load in mind. That polytherapy may have its merits has been advocated, e.g., in hypertension and oncology therapy (36–38). A prospective randomized double-blind study is in progress to verify the advantages or disadvantages of polytherapy in the treatment of epilepsy.

Not all the results we obtained were in accordance with the hypothesis of an association between total drug load and number of AE. One study in group C showed that elimination of phenytoin did have a beneficial effect on attention and concentration, whereas discontinuation of valproate or carbamazepine did not (34). This finding is in accord with reports that different AEDs often have different effects on cognitive functioning (39,40). Barbiturates have a greater impact on mental speed than do phenytoin, carbamazepine, and valproate (41). These differing drug effects emphasize the need for information about the quality of toxicity and its relationship to dosages. Qualitative and quantitative knowledge of drug-related toxicity is essential for accurate insight into the potential therapeutic window and the consequent merits of a drug. Using drug loads in relationship to dosages allows comparison of single and/or multiple drug regimens and thus provides a better tool for interpretation and evaluation of differences in seizure control or toxicity. Having knowledge of both therapeutic and toxic serum levels, instead of dosages in evaluations of patients with difficult-to-treat epilepsy receiving multiple drug regimens allows one to become cognizant of individual differences in metabolism. The use of serum levels does increase the cost of therapeutic drug monitoring, however.

The advantages of using methods to calculate total AED load are illustrated by the study of McGuire et al. (35), in which total drug loads in the vigabatrin add-on group and the placebo control group were high. Adding vigabatrin changed the drug load only by 20%. Therefore, given the premises of this method calculating total drug load, the patients in the placebo group were exposed to only a slightly less toxic total drug load than that of the add-on group, from which the effect of vigabatrin on cognitive function had to be evaluated. This emphasizes the importance of reporting doses or serum levels of concomitantly administered drugs, particularly in parallel studies.

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