Epilepsia, 52(7):1303–1310, 2011
doi: 10.1111/j.1528-1167.2011.03075.x

FULL-LENGTH ORIGINAL RESEARCH

Long-term control of epileptic drop attacks with the combination of valproate, lamotrigine, and a benzodiazepine: A "proof of concept," open label study

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Summary

Purpose: Long-term medical management of epileptic drop attacks is usually unsatisfactory and more effective antiepileptic drug (AED) regimens are needed. The present study aimed at providing *proof of concept* that previously refractory epileptic drop attacks could be significantly and safely controlled by the specific combination of valproate, lamotrigine, and a benzodiazepine.

Methods: An open label trial providing class IV evidence of efficacy, including 32 patients with cryptogenic/symptomatic, generalized or multifocal epilepsies, and refractory drop attacks. Following baseline, the combination under study was introduced and patients followed for 12 months. Frequency of drop attacks was compared at 3-month intervals with that during baseline and correlated with clinical, electroencephalography (EEG), and imaging variables. A list of putative side effects was read to patients and caregivers at each visit.

Key Findings: Four patients were excluded, one due to a Stevens-Johnson syndrome (SJS). Median number of drop attacks decreased 96% between baseline and the fourth trimester of the study (from 50 to 2; $p < 0,001$). Intention-to-treat (ITT) analysis showed that 15 patients (47%) had complete control, 7 (21%) had a 75% and 5 (15%) had a 50–74% reduction in the frequency of falls in the fourth trimester. Twenty-two patients (68%) had side effects, but except for the three excluded because of early rash, caregivers did not consider discontinuation. Mean final dose of valproate was 35.9 mg/kg/day and that of lamotrigine 4.9 mg/kg/day. Twenty patients used clobazam, eight nitrazepam, and the other four clonazepam as the elected benzodiazepine. Outcome did not correlate with clinical, EEG, and imaging variables.

Significance: This open label study suggests that the combination of valproate, lamotrigine, and a benzodiazepine can markedly reduce the frequency of epileptic drop attacks in patients with generalized or multifocal epilepsies. Careful clinical monitoring for early signs of SJS is needed.

KEY WORDS: Severe epilepsies, Drop attacks, AED, Valproate, Lamotrigine, Benzodiazepines.

The efficacy of antiepileptic drugs (AEDs) to control epileptic drop attacks is limited. Several AED regimens have been tested (Schuele & Lüders, 2008; Vining, 2009) but alleviation is only partial for the majority of patients. Furthermore, most clinical trials provide only short-term efficacy data (Ritter et al., 1993; Motte et al., 1997; Sachdeo et al., 1999; Glauser et al., 2008; Conry et al., 2009), and studies testing specific AED regimens for longer periods are needed. Because valproate, lamotrigine, and benzodiazepines are used for treatment of generalized seizures (Sherard et al., 1980; Brodie, 1996; Donaldson et al., 1997; French et al., 2004), and accepting that the mechanisms of epileptic drop attacks involve generalized interference with motor systems (Tassinari & Ambrosetto, 1988), we hypothesized that the combination of these three AEDs could be useful to control these falls. There are no monotherapy studies with these medications for treatment of drop attacks in severe epilepsies, and the few studies in which combinations of two of these AEDs were tested have yielded unsatisfactory results (Thomé-Souza et al., 2003; Arzimanoglou et al., 2009). Therefore, we decided to evaluate the effectiveness of the combination of these three drugs for patients with generalized or multifocal epilepsies seriously disabled by drop attacks, in an open trial, ''proof of concept'' design.

Accepted February 22, 2011; Early View publication April 19, 2011.
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Prof. Dr. Mario Wagner, a consultant in epidemiology and biostatistics, performed the statistical analyses.

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Patients and Methods

From January 2007 to January 2009, we followed a consecutive series of 32 patients with cryptogenic/symptomatic generalized or multifocal epilepsies and refractory drop attacks attending the Epilepsy Outpatient Clinic of the Neurology Service, Hospital São Lucas da PUCRS, in Porto Alegre. All underwent laboratory, epileptologic, electroencephalographic, and neuroimaging evaluation. Caregivers were instructed to fill a seizure diary registering drop attacks, considered as episodes of *sudden fall*, either to the ground or to a chair, sofa, or bed. Patients had to have at least three drop attacks per month during the 2 months of baseline. Seven patients had Lennox-Gastaut syndrome (LGS), in that they also had tonic seizures during slow sleep with bursts of bilateral trains of fast spikes (10 Hz or more), generalized spike-slow wave complexes at 1.5–2.5 Hz, and cognitive disability (Arzimanoglou et al., 2009). No patient was using or had previously received the specific combination of valproate, lamotrigine, and a benzodiazepine (Table 1). Following baseline, patients were progressively switched to the regimen proposed by the study with adjustments as needed. The target dosage of valproate was 30–80 mg/kg/day for children and a maximum of 3,000 mg/day for adults. Starting doses were 5–10 mg/kg/day for children up to age 16 years and 250 mg for adults, with increases every 3 days. The target doses of lamotrigine were 4–12 mg/kg/day. Lamotrigine was introduced at a dose of 12.5 mg/day (0.17–0.6 mg/kg/day), with similar increments every second week. When patients were already using lamotrigine, dosages were also increased at 12.5 mg and adjusted according to efficacy. Clobazam, clonazepam, and nitrazepam were started at the following respective daily doses: 2.5, 0.5, and 2.5 mg for children, and 10, 1.0, and 5 mg for adults. When side effects ensued, doses were transiently reduced. All adjustments were clinically based and we did not use data on serum levels. Blood chemistry and hematologic tests were performed during baseline and again between 6 and 9 months into the study.

Parents were informed about the objectives and risks of the study, particularly of severe rash and other immunologic reactions, and patients were included only after their formal agreement and written consent, according to the rules of resolution 196/96 of the National Health Council of the Ministry of Health of Brazil. The study was also approved by the Ethics Committee of our Institution.

Follow-up visits were at 3-month intervals, when the frequency of epileptic drop attacks from the previous 3 months was entered into a database and a list of potential AED side effects was read to patients and caregivers. We emphasized the presence of rash, gastric intolerance, somnolence, dizziness, ataxia, tremor, alopecia, and weight gain. Tonic–clonic, generalized tonic and absences, and typical and atypical were the most frequent other seizure types in this sample. We did not ask caregivers to keep record of the frequency of these other seizure types. However, at each visit, we did ask whether it was noticeable that any of these had worsened in comparison with the previous 3-month interval. At least two outpatient 30-min EEG recordings were performed, one at enrollment and the other 6–9 months later. Discharges were classified as generalized or multifocal and their frequency noted before and after institution of the three-drug regimen. This was an outpatient study and patients did not undergo long-term video-EEG. Magnetic resonance imaging (MRI) was performed in all with a 1.5-T Siemens Magneton (Siemens, Erlangen, Germany). Presence and severity of mental retardation were evaluated with a battery of neuropsychological tests (Wechsler, 2005).

The diagnosis of the epilepsy syndrome and presumed etiology was based on clinical evaluation, EEG, and MRI. A hypoxic–ischemic etiology was considered when parents reported perinatal cyanosis, need for oxygen immediately after delivery, and Apgar score ≤7. Eleven patients (34%) had cryptogenic and the others had variable etiologies of symptomatic generalized or multifocal epilepsies (Table 1). Mean IQ of the 23 patients tested was 63.9 [standard deviation (SD): 14.5; range 32–82; Table 1].

The median frequency of epileptic drop attacks at baseline was the comparator to establish the efficacy of the new AED regimen. With the exception of four patients who discontinued the combination early, the other 28 received the study medication for 12 months. The adjustment of AED dosages was dynamic, dictated by titration schedule, efficacy, and tolerability. Therefore, the final, stabilized doses of the three AEDs were reached at month 3 in 4 patients, between months 3 and 6 in 6 patients, and between 6 and 12 months in the other 18 patients. The efficacy of the treatment was assessed as percent reduction of the frequency of epileptic drop attacks in each 3-month period compared to baseline: 100% (free of drop attacks), 75–99%, 50–74%, 25–49%, and <25% reduction. Finally, clinical, cognitive, etiological, demographic, and EEG data were correlated with degree of control of drop attacks.

The primary efficacy end point was percent reduction in the median number of epileptic drop attacks in the fourth trimester after institution of the study medication regimen in comparison with the median number of drop attacks in the 2 months of baseline. One secondary outcome was the percentage reduction in the median number of drop attacks at each 3-month interval compared with the median number of drop attacks at baseline. This secondary outcome established the timing of improvement and the stability of the results over time. Another secondary outcome was the correlation between epileptologic and imaging variables with response to treatment. All outcome analyses included the 32 patients originally enrolled in an intention-to-treat design.

To describe the occurrence of drop attacks we used median, minimum, and maximum values. To evaluate the statistical significance of reductions in the frequency of drop attacks during the period of observation, we used a

Table 1. Clinical data on 32 patients with epileptic drop attacks previously refractory to AED

Patient	Age	Sex	Duration of epilepsy (years)	Abnormalities neurological exam	IQ	Mean frequency of DA at baseline	Medication at baseline	EEG	Presumed etiology	MRI
1	16	M	13	N/A	81	30	CBZ, TPM	GPSW	CCT	L post atrophy
2	24	M	17	N/A	82	300	VPA, PHT, CZP	GSSW	Midline Cyst	Midline cyst
3	18	M	18	Dev dysphasia	52	195	CBZ, VPA, LTG	MED, FPS	Hypoxia	Normal
4	7	M	6,5	N/A	68	20	CBZ, VPA, CLB	Normal	Cryptogenic	Normal
5	23	F	17	Dev dysphasia	54	300	CBZ, PB, VPA	GPSW	Hypoxia	Normal
6	8	M	4, 5	Dev dysphasia	N/A	60	VPA, LTG, PB	GPSW	Radiotherapy	Diff ctx atrophy
7	10	M	7	Dev dysphasia	69	120	OXC, CLB	GSSW, FPS	Cryptogenic	Normal
8	48	M	46	Normal	N/A	76	CBZ, VPZ, FNT, CLB	MED	Meningitides	Normal
9	11	M	10	Dev dysphasia	N/A	4	PB, VPA, LTG	GPSW	Cryptogenic	Normal
10	10	M	9, 5	N/A	65	150	VPA, PB, CLB	GSSW, FPS	MCD	Multiple tuberous
11	18	F	15, 5	N/A	55	20	CBZ, VPA, PB, LTG	GSSW	MCD	Bilat double cortex
12	12	M	9	N/A	43	150	CBZ, PHT, AZM	GSSW	Cryptogenic	Normal
13	20	F	17	N/A	73	5	CBZ, PRM, VPA, CLB	GPSW	Hypoxia	Normal
14	14	M	11	N/A	62	40	CBZ, VGB, CLB	MED	Cryptogenic	Normal
15	29	M	22	Dysphasia	N/A	12	CBZ, TPM	GS	Cryptogenic	Normal
16	12	M	3	R hemiparesis	71	350	PB, VPA, CBZ	GSSW	Meningitides	L encephalomalacia
17	9	M	7	Dev dysphasia, ataxia	59	150	VPA, LTG	GPSW, FPS	Hypoxia	Hippocampal atrophy
18	20	M	12	R hemiparesis	81	20	CBZ, PHT, PB, VPA	Normal	MCD	Perisylvian PMG
19	18	F	16	Dysphasia	N/A	20	VPA, PB	Normal	Cryptogenic	Normal
20	10	F	10	N/A	65	30	PB, VPA, CBZ, CLB	GSSW	MCD	Cortical dysplasia
21	26	M	26	N/A	72	3	CBZ, NZP	GSSW	Hypoxia	Normal
22	34	F	29, 5	L hemiparesis	80	30	CBZ, VPA, CZP	MED	MCD	R polymicrogyria
23	44	M	30	N/A	69	12	OXC, VPA	Bifrontal Spikes	Cryptogenic	Cerebellar atrophy
24	15	M	15	Dev dysphasia	47	150	PB, VPA, CZP	MED, FPS	Hypoxia	Normal
25	32	M	31, 5	Dev dysphasia	80	3	CBZ, VPA	MED	Hypoxia	Normal
26	5	M	3	Dev dysphasia, ataxia	N/A	120	CBZ, VPA, CLB	GPSW, FPS	Hypoxia	Normal
27	15	M	11	Ataxia	N/A	90	CBZ, PB, VPA	GPSW, FPS	Cryptogenic	Cerebellar atrophy
28	9	M	8, 5	Dev dysphasia	32	60	VGB, NTZ	GSSW	MCD	Multiple tuberous
29	17	F	7	N/A	77	20	VPA, OXC	Normal	MCD	Bilat double cortex
30	6	M	3	Dev dysphasia, ataxia	N/A	900	TPM, PB	GSSW	Hypoxia	Diff ctx atrophy
31	9	F	13	Normal	N/A	25	CBZ, VPA, TPM, NZP	GSSW	Cryptogenic	Normal
32	18	M	13	N/A	34	150	CBZ, VPA, ACTZ	GPSW	Cryptogenic	Normal

MCD, malformation of cortical development; CCT, craniocerebral trauma; GE, generalized slowing; GPSW, generalized polyspike slow waves; GSSW, generalized spike slow waves; MED, multifocal epileptiform discharges; FPS, fast polyspikes; Dev, development; R, right; L, left; Diff ctx, diffuse cortical; PMG, polymicrogyria; AZM, acetazolamide; CBZ, carbamazepine; CZP, clonazepam; CLB, clobazam; ETX, ethosuximide; LTG, lamotrigine; NZP, nitrazepam; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; PRM, primidone; TPM, topiramate; VPA, valproate; VGB, vigabatrin.

nonparametric analysis of variance (ANOVA) for repeated measures (Friedman's test). The percent reduction of drop attacks between visits was obtained according to a simple formula: First, we subtracted the median frequency of drop attacks at each visit (representing the previous 3-month interval) from the median frequency of drop attacks at baseline. The result was then divided by the median frequency of drop attacks at baseline and multiplied by 100. Therefore, the larger the median reduction of drop attacks at each visit compared to baseline, the larger the numerator of the final equation and, therefore, the larger the percent reduction of drop attacks. Data were analyzed using SPSS version 17.0 (IBM Corporation, Somers, NY, U.S.A.).

Results

Demographic and clinical data are summarized in Table 1. Twenty-eight patients (22 male) aged 5–44 years (mean 16.5) were followed for 12 months. Four were excluded: three had rash at the first 3 months of treatment—one of whom progressed to Stevens-Johnson syndrome (SJS), which resolved with treatment discontinuation—and a fourth was lost to follow-up after the first visit.

Twenty-two of the 32 patients (68%) originally included, and 18 of the 28 who completed the study, had side effects that caregivers considered relevant to report, most commonly gastric intolerance, tremor, sedation, and hair loss. Table 2 details the side effects and provides the dosage of each medication associated with each side effect. Mean final dosage of valproate was 35.9 mg/kg/day (range 10.4–76.9, SD: 14.48) and that of lamotrigine was 4.9 mg/kg/day (range 0.8–11.5, SD: 2.5). Twenty patients used clobazam, eight nitrazepam, and the other four clonazepam as the benzodiazepine of the regimen under study. Clobazam, clonazepam, and nitrazepam were used at the following respective mean doses: 0.45 mg/kg/day (range 0.12–0.9, SD: 0.22), 0.05 mg/kg/day (range 0.03–0.09, SD: 0.03), and 0.25 mg/kg/day (range 0.06–0.5, SD: 0.14).

Seven patients had electrical decrement, following irregular spike and wave complexes and bursts of fast activities, as seen in LGS. These abnormalities were significantly reduced on the follow-up EEG, after institution of the study AED regimen. Twenty patients had predominantly generalized and six multifocal EEG discharges. One other had bifrontal spikes and one other generalized slowing. For four patients, the first EEG was completely normal. The two EEG studies performed in three patients did not show epileptic discharges, despite unequivocal diagnosis of epilepsy and previously epileptogenic EEG recording. One had "double cortex," another bilateral perisylvian polymicrogyria, and the third had a normal MRI. In five patients, the second EEG recording 6 months into the study showed disappearance of the epileptic discharges.

Figure 1 displays the evolution of the median frequency of drop attacks at 3-month intervals in the group of patients.

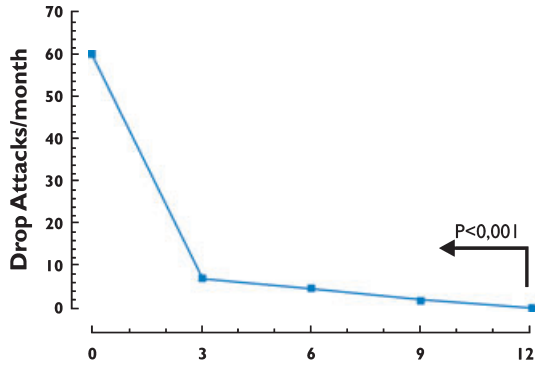
Table 2. Side effects during treatment with the AED combination under study

Patient	Side effects	Drugs (mg/kg/day) VPA	LTG	BZD
1	Tremors	38.8	3.5	0.35 CLB
2	Weight gain	32.3	6.6	0.06 NZP
3	Gastric intolerance, sedation, hair loss	24.0	4.8	0.14 CLB
4	NR	56.2	9.4	0.31 CLB
5	NR	58.8	4.9	0.2 NZP
6	Gastric intolerance, sedation	10.4	8.3	0.4 NZP
7	Gastric intolerance, sedation, hair loss, ataxia	22.2	5.8	0.8 CLB
8	Rash	37.4	2.3	0.15 CLB
9	Gastric intolerance	36.0	7.5	0.6 CLB
10	Gastric intolerance, sedation	68.2	6.8	0.5 NZP
11	Tremors, weight gain	40.0	3.0	0.4 CLB
12	NR	16.9	4.2	0.16 CLB
13	NR	27.1	6.5	0.6 CLB
14	NR	26.8	2.7	0.5 CLB
15	Rash	42.3	3.1	0.4 CLB
16	Gastric intolerance, hair loss	40.5	0.8	0.5 CLB
17	Gastric intolerance, ataxia	20.2	7.4	0.3 NZP
18	Sedation	28.1	3.8	0.09 CZP
19	SJS	31.5	1.4	0.13 NZP
20	NR	33.3	2.9	0.3 CLB
21	Gastric intolerance	40.0	4.0	0.03 CZP
22	Tremors, hair loss	28.8	2.9	0.6 CLB
23	Tremors	23.4	3.9	0.5 CLB
24	NR	33.3	2.5	0.25 NZP
25	Hair loss, weight gain	28.6	1.8	0.4 CLB
26	NR	54.5	9.1	0.9 CLB
27	Weight gain, sedation	33.3	3.3	0.06 CZP
28	Gastric intolerance	27.5	5.6	0.75 CLB
29	Hair loss, weight gain	26.6	2.7	0.03 CZP
30	NR	76.9	11.5	0.12 CLB
31	NR	45.0	5.0	0.4 CLB
32	NR	41.0	6.7	0.22 NZP

AED, antiepileptic drugs; NR, none relevant; CLB, clobazam; CZP, clonazepam; NZP, nitrazepam; SJS, Steven-Johnson syndrome.

It shows that the most impressive improvement occurred during the first 3 months after the institution of the treatment with valproate, lamotrigine, and a benzodiazepine, with posterior stabilization. Baseline median frequency of drop attacks in the seven patients with LGS was 120 (range, 3–900), whereas it was 30 (range, 4–195) in the other 25 patients ($p = 0.19$). The median number of drop attacks in the fourth trimester of the study in patients with LGS was reduced to 3 (0–51), and in the 21 non-LGS patients continuing in the study it was 0 (0–90). The magnitude of the reduction was not related to the presence of an LGS ($p = 0.79$) (Fig. 2).

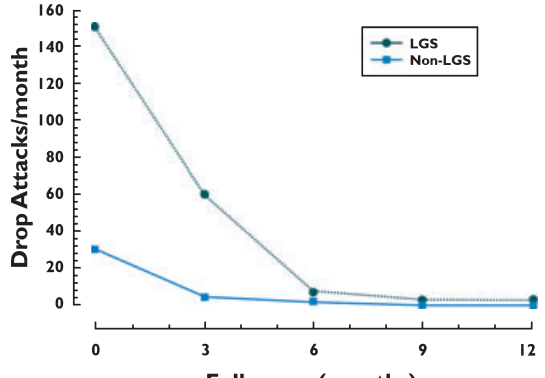
For the whole group, the median number of drop attacks during the 2 months of baseline was 50 (3–900). In the fourth trimester with the AED regimen under study, the median number of epileptic falls was two, representing a reduction of (96%) ($p < 0.001$). More specifically, 15



DA	n=	32*		30		28		28		28
median		50		7		6		3		2
minimum		3		0		0		0		0
maximum		900		229		109		202		204
%CCDA		0		22		22		41		47

%CCDA: Complete control of drop attacks
* ITT: Intention to treat patients

Figure 1.
Median frequency of drop attacks during the 12 months of treatment in the 28 patients who completed at least 1 year into the study.
Epilepsia © ILAE



LG	n=	7		7		7		7		7
median		120		83		10		3		3
nLG	n=	25		23		21		21		21
median		30		5		5		3		0
P		0.19		<0.01		0.46		0.96		0.79

LG, Lennox-Gastaut; nLG, non-Lennox-Gastaut

Figure 2.
Median frequency of drop attacks during treatment in patients with and without Lennox-Gastaut syndrome.
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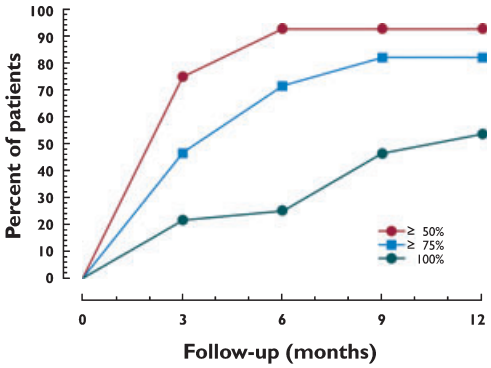

DA	n=		32		30		28		28		28
Percent reduction of Drop Attacks		≥ 50	0		72		81		81		84
		≥ 75	0		47		63		72		72
		100	0		22		22		41		47

Figure 3.
Percent reduction in the frequency of drop attacks at each three-month period compared to baseline.
Epilepsia © ILAE

patients (47%) were free of drop attacks, 7 (21%) had 75%, and 5 others had a 50–74% reduction in the frequency of falls in the fourth trimester (percent data relate to the original sample of 32 patients in the ITT design). Only one of the 28 patients completing the study had a reduction of <25% (Fig. 3). Half the patients who were free from drop attacks at month 12 were already fully controlled at month 6, although some adjustments in medication were necessary between months 6 and 12.

Figure 3 illustrates the variation in the median frequency of drop attacks during the 12 months of treatment. At different points in time, several patients had transient worsening in comparison to the previous 3-month period, leading to adjustments in the dosage of the AED combination under study. However, none of these aggravations were close to the baseline frequency of drop attacks. Two patients transiently worsened at month 3, still during the institution of the AED combination under study. Five others had a transitory aggravation of their drop attacks at the second trimester, and four at the third trimester. Caregivers did not report a noticeable increase in the frequency of any of the other seizure types throughout the study.

Finally, there were no significant correlations between IQ, demographic, IQ, etiologic, and EEG features and degree of control of drop attacks with the medication regimen under study (data not shown).

Discussion

Open label, uncontrolled trials have inherent biases and provide information of a limited scope, that is, class IV evidence (Engel et al., 2003). In particular, the possibility of spontaneous amelioration due to a "regression to the mean phenomenon" is not directly assessed and, therefore, the improvement we observed in the control of epileptic drop attacks could, theoretically, be related to the natural course of the disease. However, it is unlikely that the magnitude of the results before and after the intervention could be thus explained. Furthermore, all these patients had been

suffering from drop attacks for years before entering the baseline period, despite attempts with several different AED regimens in the same outpatient clinic. Therefore, it is unlikely that they would have improved spontaneously at the time of the study. Another important point is that the effectiveness of interventions evaluated in open trials may be overestimated due to a stronger engagement of patients and families with the investigators. Without a placebo group, we cannot rule out this possibility. Nevertheless, the significant reduction in the frequency of drop attacks sustained throughout the study provides ''proof of concept'' that the specific three-drug combination of valproate, lamotrigine, and a benzodiazepine may have a place in the treatment of epilepsies manifesting this malignant seizure type and should be further explored in controlled trials. The relevance of this finding is enhanced by the limited alleviation provided by other AED regimens tested over the years, as reviewed below.

It is known that the association of valproate and lamotrigine may increase the risk of SJS, a life-threatening disorder (Schlienger et al., 1998; Ertam et al., 2009). Indeed, we had to withdraw a 9-year-old boy because of SJS upon initiation of the AED combination we implemented, highlighting the importance of close surveillance of patients receiving this AED combination.

Median number of drop attacks decreased 96% between baseline and the fourth trimester of the study (from 50 to 2), and 47% of the patients had drop attacks completely controlled. Only one patient did not improve significantly, but because his drop attacks had been refractory to previous medications he was kept in the study while waiting for a corpus callosotomy. Furthermore, we believe one of the major strengths of these findings concerns the duration of the follow-up and the stable levels of control of drop attacks achieved with this regimen. Other studies addressing the control of epileptic drop attacks have followed patients for more limited periods, ranging from 11–16 weeks (Motte et al., 1997; Sachdeo et al., 1999; Glauser et al., 2008; Conry et al., 2009). Because there is a need for therapeutic studies mimicking patient management in real life, short-lasting studies may not address clinically relevant issues, such as the frequent loss of seizure control observed in patients with severe epilepsies after a few weeks or months of the institution of a given AED regimen initially thought to be effective (Schmidt & Löscher, 2005; Blume, 2006; Beleza, 2009).

Adverse side effects were reported by the caregivers of 22 of 32 patients (68%; Table 2). Except for the three patients who discontinued the study medication because of early rash, side effects were not a reason for discontinuation. However, our findings may underestimate the adverse events associated with the three-drug combination for at least two reasons. First, we assessed these symptoms clinically and did not use a standardized instrument. Second, because these patients had been treated over the years with many different AED polytherapy regimens, which led to a host of side effects, it is possible that caregivers had a higher threshold to both report side effects and to specifically attribute these to the particular AED combination we used.

Practitioners are well aware of the limitation of data informing the management of drop attacks in patients with symptomatic generalized or multifocal epilepsies. In a recent randomized, controlled study, Glauser et al. (2008) evaluated the efficacy of the addition of rufinamide in patients with LGS. They showed a reduction of 42.5% in the frequency of drop attacks during the 16 weeks of the trial. However, only 4.1% of the 74 patients receiving rufinamide became free of drop attacks, compared to 47% of the patients in our series, the latter result sustained up to 12 months. Although methodologic differences in study design may explain this discrepancy, the robustness and stability of our findings and the intensive follow-up of our patients suggest that practitioners should consider the possibility that the medication regimen reported here may be superior to the addition of rufinamide to the previous AEDs in patients with drop attacks. Nevertheless, because dose regimens were fixed, it is possible that a longer follow-up with adjustments in AED doses could have led to a more significant control of drop attacks in that study (Glauser et al., 2008), although 22% of our patients were already free of drop attacks after 12 weeks of follow-up. Another difference is that we asked caregivers to restrict their observation to epileptic drop attacks and to disregard other seizure types when filling seizure diaries. Because patients with severe symptomatic generalized or multifocal epilepsies usually have high frequencies of tonic–clonic, tonic, myoclonic, and/or absence seizures (Vossler et al., 1999; Arzimanoglou et al., 2009) keeping record of *all* these seizure types during any period of time may be a difficult task and could lead to less reliable records of specific seizure types such as drop attacks. The study of Glauser et al. (2008) and others addressing the control of drop attacks (Ritter et al., 1993; Sachdeo et al., 1999) have also assessed the effect of treatment in the other seizure types, which may have led to a less reliable specific counting of drop attacks.

The Felbamate Study Group in Lennox–Gastaut (Ritter et al., 1993) studied the efficacy of adding felbamate to the previous AED regimen in 73 patients and observed a reduction of 44% in the frequency of drop attacks, compared to 7% in the patients receiving placebo. However, the authors did not report the rate of complete control of drop attacks. Furthermore, felbamate was related to aplastic anemia (Pellock, 1999) and is only rarely used. Sachdeo et al. (Sachdeo et al., 1999) added topiramate or placebo to the previous AED regimen in 98 patients with LGS for 11 weeks and observed an overall 15% reduction in the frequency of drop attacks compared to baseline. Eleven percent had a complete control, 17% had a >75% reduction, and 28% of the patients had a 50–75% improvement in falls. Nevertheless, because dose regimens were predetermined

and fixed in the studies with felbamate and topiramate, in contrast to the real-life adjustments ''as needed'' used in the present study, direct comparison of efficacy is difficult.

Clobazam was evaluated during 14 weeks as add-on therapy in patients with LGS by Conry et al. (Conry et al., 2009). With doses of 0.25 mg/kg/day, 6%, 25%, and 38% of the patients had, respectively, a complete, >75%, and >50% reduction of epileptic drop attacks. With doses four times as high (1 mg/kg/day) reduction of attacks was, respectively, 22%, 67%, and 83%. The use of a benzodiazepine (more often clobazam) specifically associated with valproate and lamotrigine in our patients led to complete, >75%, and >50% control of drop attacks in 21%, 46%, and 75% of our patients at week 12 and in 54%, 82%, and 93% at 1 year, respectively. It is unknown whether the results reported by these authors would be maintained for longer periods. Furthermore, because the authors did not report which AEDs were in use before the introduction of clobazam, it is possible that some patients obtaining a good result were already on the combination of valproate and lamotrigine when clobazam was added. The percentage of treatment discontinuation due to the side effects was 12.5% and 16.6%, for low and high doses, respectively, compared to 12.5% in our study.

The role of lamotrigine in preventing falls has been studied by several authors. Motte et al. (1997) showed a reduction of at least 50% in the frequency of drop attacks in 34% of 75 patients with LGS when adding lamotrigine, and Faught (1999) observed that four patients controlled their falls using lamotrigine. Bisulli et al. (Bisulli et al., 2001) added lamotrigine to other AEDs in patients with drop attacks and partial epilepsy and observed a reduction of about 50% in the frequency of epileptic falls. In none of these studies was lamotrigine specifically associated with valproate and a benzodiazepine and followed closely for prolonged periods. Finally, Thome-Souza et al. (2003) designed a study similar to ours. They combined valproate and lamotrigine in 28 children with refractory epilepsy, 8 of whom had drop attacks. Five of the latter improved, however, with a <50% reduction in the frequency of drop attacks. Their AED regimen did not include a benzodiazepine. Four patients discontinued treatment: two with rash and the other two because of loss of efficacy or worsening of seizure control.

Because we chose to evaluate the three-drug combination of valproate, lamotrigine, and a benzodiazepine, we are not able to determine whether monotherapy with any of these AEDs or a two-drug combination would produce the same results. These alternative regimens, however, had been previously tested in these patients and also in other patients reported in the literature, with unsatisfactory control of drop attacks (Thomé-Souza et al., 2003; Arzimanoglou et al., 2009). Unquestionably, this three-drug regimen entails higher costs and increases the risk of untoward side effects. The fact that most of patients completed at least 1 year of treatment suggests that close surveillance may mitigate much of the adverse effects of this combination.

There are additional potential limitations in our study. We did not perform long-term video-EEG polygraphic recordings and we did not systematically measure the serum levels of lamotrigine, valproate, and the benzodiazepine. Therefore, we were not able to determine whether any specific pathophysiology of drop attacks is more prone to be controlled by our AED regimen and cannot provide data on effective or ineffective serum levels. We believe these limitations can be viewed from different angles in the sense that they mirror the outpatient practice in our epilepsy clinic and perhaps the epilepsy clinics of most developing countries clinics. Furthermore, there is no evidence that different mechanisms of epileptic drop attacks may respond differently to medication (Gambardella et al., 1994; Guerrini et al., 1998). Finally, because we did not ask caregivers to record the frequency of seizures other than drop attacks, we do not have a quantifiable measure of the impact of the combination of valproate, lamotrigine, and a benzodiazepine in those seizures. However, in no occasion did caregivers report a noticeable increase in the frequency of any of the other seizure types each patient presented. This is hardly unexpected, because the three medications we used have proven efficacy against other generalized and partial seizures (Sherard et al., 1980; Brodie, 1996; French et al., 2004). Nonetheless, the possibility that these caregiver reports might have been biased by the almost uniform reduction in the frequency of the more worrisome drop attacks should also be entertained. Therefore, the role of the AED regimen under study on the treatment of the whole spectrum of seizure types of symptomatic generalized and multifocal epilepsies should be formally studied in the future.

Finally, our results favorably compare with those reported for callosotomies and vagus nerve stimulation (Rychlicki et al., 2006; Sunaga et al., 2009). These invasive procedures are associated with inherent risks and much higher costs.

In conclusion, despite unquestionable methodologic limitations, we have shown a significant potential for the association of valproate, lamotrigine, and a benzodiazepine to significantly reduce or completely control epileptic drop attacks in patients with symptomatic generalized or multifocal epilepsies. The fact that the effect was sustained for long periods and that most patients tolerated the AED regimen should encourage trials to replicate these findings. Careful monitoring for severe side effects is, however, mandatory, because one patient developed an SJS.

Acknowledgments

We are indebted to our colleagues, both staff and residents, at the Severe Epilepsies Outpatient Clinic, for continued support during the study. This study was self-funded and performed in the context of the Graduate Courses in Health Sciences of PUCRS as part of Dr. Machado's doctorate degree.

Authors Contributions

Vitor Machado collected the data, actively participated in the design of the study and interpretation of the findings, and provided a first draft of the manuscript. Rosana Rotert and Fernanda Bastos performed the IQ evaluations and participated in group discussions that led to the final format of the manuscript. Andre Palmini supervised the study and wrote the manuscript.

Disclosure

Andre Palmini has received support from, and has served as a paid consultant for Abbott Laboratories, Novartis, and Janssen-Cilag. The remaining authors have no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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