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Sustained Release Valproate in the Treatment of Epilepsy

– Experience with Sustained Release Minitablets (Orfiril® long) in a Once-Daily Evening Dosage

Hermann Stefan
Epilepsy Center, Erlangen

Address of the author:

Professor Dr. med. Hermann Stefan
Neurological University Hospital with Policlinic
Epilepsy Center Erlangen (ZEE)
Schwabachanlage 6
91054 Erlangen, Germany
Tel.: 09131/ 853 9116
Fax: 09131/ 6469
Hermann.Stefan@neuro.imed.uni-erlangen.de

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– Experience with Sustained Release Minitablets (Orfiril® long) in a Once-Daily Evening Dosage

Summary:

In an observational study under routine clinical setting data after administration of once daily evening dosing of valproate sustained release minitablets* were recorded in 359 patients with epilepsy aged between 12 and 86 years. Patients were either newly treated with valproate sustained release minitablets (N=58) or switched from conventional valproate (N=124) or from sustained release valproate (N=138) to the once daily evening dosing. In 39 patients other antiepileptic drugs were replaced. At the end of the 7-week observational period most patients (65.4%) received a daily dose of 10 to less than 18 mg/kg body weight followed by 17.4% receiving doses in the therapeutically recommended range of 18-24 mg/kg. 8.6% and 7.4% of patients received more than 24 mg/kg or less than 10 mg/kg body weight, respectively. As expected, in both groups with valproate pre-treatment the mean morning valproate plasma levels increased by approximately 10 µg/ml after switch to once evening dosing with sustained release minitablets. The mean seizure frequency decreased from 2.1 to 0.5 in the 318 patients with data before the beginning and at the end of the investigation. At the final examination 137 patients (62.3%) were seizure free, and further 60 patients (27.3%) experienced a seizure reduction of more than 50% (responders) of those 220 patients who experienced seizures in the last 7 weeks before the study. The efficacy and tolerability was rated in more than 95% of the cases by the patient and the investigator as good or very good. The compliance/acceptance of the valproate sustained release minitablets was rated as good or very good in almost all patients. These results confirm the excellent risk-benefit ratio of the valproate sustained release minitablets and underline the importance of a simple compliance-improving dose regimen for effective seizure control.

1 Introduction

Valproate belongs to the classical first line anti-epileptic drugs - its anti-convulsive properties have been known since 1963 [1]. It possesses the broadest spectrum of activity of all anti-epileptics and is reliably effective against both generalised as well as focal seizures [2]. Furthermore, anti-manic and mood-stabilising properties of valproate have also been demonstrated [3,4,5]. The substance is meanwhile established as a therapeutic option in bipolar affective disorders [6]. Valproate has also been available in sustained release form for about twenty years. On the one hand, the patient profits from the better tolerability due to more constant plasma concentrations. Not only the risk of dose-dependent side-effects, for example neurological disorders, is reduced by avoiding peak levels of the active substance, but also the risk of teratogenic effects, as animal experimental investigations have shown [7]. Furthermore treatment is made easier by a simplified dosage scheme, as the administration of sustained release valproate can be divided into 1-2 single doses per day. This aspect is not to be underestimated for success of treatment, as the compliance of epilepsy patients is higher the fewer the number of single doses per day, according to recent findings [8,9].

Sustained release valproate in the form of sustained release minitablets has been available since 1998. In a recent study, it was shown by circadian measurements of valproate serum levels after administration of the sustained release mini-

* Orfiril® long 150 mg, 300 mg, 500 mg, 1000 mg

tablets once in the evening that levels are not exceeded or fall short of the therapeutic range (50-100 µg/ml) in a preferred daily dose range of 18-24 mg/kg bodyweight and that the evening single dose in patients from 12 years of age can be considered as an effective and safe therapy option [10]. Altogether, the advantages of a modern valproate sustained release therapy increase the patient's compliance and the chance of success of long-term treatment.

The aim of the present study was to collect data on the use of valproate sustained release minitablets *(Orfiril® long)* in a once daily evening dosage in patients newly adjusted to the drug or switched from other anti-epileptics, under conditions which are close to those in routine clinical practice. The seizure protection, the dosage and, if applicable, the valproate plasma level measurements were of particular interest as well as assessment of the reliability of taking the medication with this simplified therapeutic regimen.

2 Patients and Method

General practitioners from throughout Germany participated in this post-marketing surveillance study. This surveillance study was a prospective, open and uncontrolled trial without any change being made in routine diagnosis and therapy, i.e. patients and prescription habits corresponded to those under normal practice conditions. Children below 12 years of age were excluded from participating. The Physicians received a folder with the documentation sheets, and electronic documentation was carried out in parallel via the internet. The content of both versions was identical. A total of 370 patients (conventional documentation: 333 patients, internet: 37 patients) were enrolled by 165 physicians.

The documentation sheet included questions on anamnesis, seizure type and frequency of seizures in the past 7 weeks, anti-epileptic co-medication at the enrolment examination and, if available, the valproate plasma levels were to be collected indicated. All changes in anti-epileptic medication were documented during the observation period. A termination visit took place after 7 weeks at which details of the final dosage, the number of seizures in the observation period and possible adverse drug reactions, and the valproate plasma levels (if determined), were requested. In addition, the physicians and patients gave a global assessment of efficacy, tolerability, handling and compliance/acceptance of the single evening dosage.

The following patients were treated from the physicians with the valproate sustained release minitablets:

- Newly adjusted to the once daily evening dosage as well as
- Switch from immediate release valproate to once daily evening dosage of sustained release valproate minitablets,
- Switch from other valproate sustained release preparations as well as from valproate sustained release minitablets 2 x daily to once daily in the evening,
- Switch from another anti-epileptic substance to the once daily evening dosage.

The new adjustment or switch from another active substance was made as a stepwise increase with the once daily evening dosage until the optimum effective dose was reached. The dose of the other anti-epileptic was reduced slowly in parallel to this. According to the summary of product characteristics, the initial dose of valproate in monotherapy is 5-10 mg/kg bodyweight, which should be increased every 4-7 days by about 5 mg/kg. Patients who were already receiving valproate-containing preparations in the intended dose range of 18-24 mg/kg could be switched from the previous total daily dose 1:1 to the once daily evening dosage with the sustained release minitablets. The dose could be taken before, with or after meals or fasting. The 150 mg and 300 mg capsules should be taken without chewing and with plenty of liquid. Alternatively, the sustained release minitablets could be taken in a loose form after pulling the capsules apart, likewise for the sustained release minitablets from the 500 mg and 1000 mg minipacks, e.g. also in a preferred carbonated drink or sprinkled into yoghurt/soft food.

Statistical evaluation was undertaken by the company GKM, Munich. Data was collected using two independent entries. All statistical calculations were carried out with the statistical program SAS (Version 8.02). Descriptive statistical details were given as the mean ± standard deviation.

3 Results

Eleven cases were excluded from the evaluation of the 370

documented patients (3 patients received valproate sustained release minitablets several times daily, in 2 patients no data was documented und six others were younger than 12 years of age). The demographic and clinical baseline data are shown in *Table 1*. In 27 patients (7.5%), the first seizure had taken place in the previous 3 months, in 67 cases (18.7%) this had been 20 years earlier or even longer. The mean time difference to the first seizure was 11 years (median 7.4 years). 118 patients (32.9%) and 255 patients (71.0%) had focal seizures or generalised seizures, respectively.

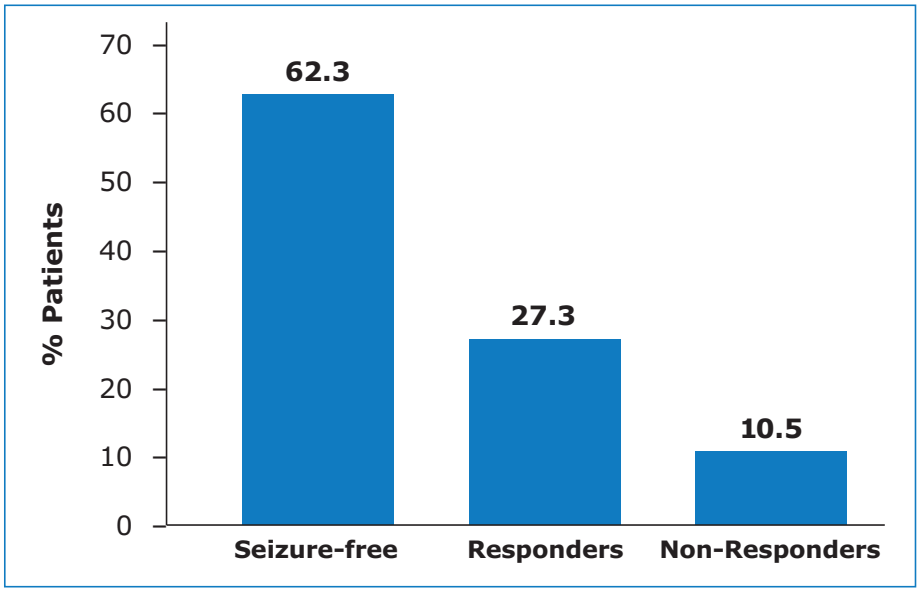
Table 1: Demographic and clinical baseline data of the patient collective (N=359)

Age		37.5 years (mean)	Range 12 – 86 years
Sex		175 females	184 males
Period of illness		7.4 years (median)	Range 0-71 years
Aetiology		Symptomatic 95 Idiopathic 217 Cryptogenic 39 No details 8	(26.5%) (60.4%) (10.9%) (2.2%)
Diagnosis of epilepsy*		**N=359**	**%**
Focal	Simple focal	20	5.6
	Complex focal	47	13.1
	Secondary generalised	74	20.6
Generalised	Absences	66	18.4
	Tonic-clonic	193	53.8
	Myoclonic	15	4.2
	Tonic	10	2.8
	Atonic	2	0.6
	Other	7	1.9
Number of seizures (in the last 7 weeks)			
None		100	27.9
1-2		161	44.8
3-5		63	17.5
More than 5		28	7.9
No details		7	1.9
Newly adjusted or switched to the once daily evening dosage			
Newly adjusted patients		58	16.2
Switch from immediate release valproate		124	34.5
Switch from sustained release valproate		84	23.4
Switch from Orfiril® long 2 x daily		54	15.0
Switch from another anti-epileptic drug		39	10.9
Pre-treatment prior to switch		**N=301**	**%**
Valproate		262	87.0
Carbamazepine		24	8.0
Oxcarbazepine		4	1.3
Phenytoin		4	1.3
Topiramate		2	0.7
Other (respective single entries)		5	1.5
Patients with anti-epileptic co-medication**		53	17.6
Number of anti-epileptic drugs per patient		1.2	Range 1-3

* = multiple entries possible
** = in addition to the medication from which the switch was made

The majority of pre-treated patients (87%) had been receiving valproate previously, followed by carbamazepine (8%) as single drug therapy. The newer anti-epileptics of the second generation were only used in altogether 8 cases (2.6%). A total of 55 patients (15.3%) received an anti-epileptic co-medication apart from valproate sustained release minitablets at least for a part of the observation period, in 6 cases two preparations were documented. Carbamazepine was mentioned most frequently (20 patients), followed by lamotrigine in 9 cases and levetiracetam in 5 cases.

Figure 1: Percentage of seizure-free patients, at least 50% reduction of seizures (responders) and non-responders at the final examination (only patients with seizures in the last 7 weeks prior to the start of observation n = 220)



After adjustment or switch was made to the once daily evening dosage of sustained release valproate, the median daily dose at the time of the initial examination as well as at the end of the trial amounted to 1000 mg. As expected, there was hardly any change in dosing in the valproate pre-treated patients after switching to the once daily evening dosage. Altogether, only 6.4% received less than 1000 mg at study completion, 69.6% of patients 1000 mg, 14.5% received more than 1000 mg to less than 2000 mg and 8.4% of patients 2000 mg and more valproate per day (no data for 1.1% of patients). In 65.4% of cases, most patients were within the daily dose range of 10 to less than 18 mg/kg bodyweight, followed by 17.4% of patients in the recommended range of 18-24 mg/kg, 8.6% above 24 mg/kg and 7.4% below 10 mg/kg bodyweight. The mean daily dose thus remained below the recommended daily dose range of 18-24 mg valproate/kg bodyweight over the entire observation period.

For 120 of the total 262 patients pre-treated with valproate, valproate plasma levels were available prior to and after the switch to the once daily evening regimen. In both collectives with valproate pre-treatment, the mean valproate plasma level measured in the mornings rose as expected by about 10 µg/mL after the switch to the once daily evening dosage *(Table 2)*.

Table 2: Plasma levels (mean ± standard deviation) before and after switch to once daily evening dosage of valproate sustained release minitablets in valproate pre-treated patients

Pre-treatment prior to switch		Plasma levels (µg/ml)	
		Prior to start of treatment	During therapy*
Immediate release valproate	(N=62)	65.1 ± 17.0	74.4 ± 14.6
Sustained release valproate**	(N=58)	63.1 ± 21.3	74.7 ± 16.4

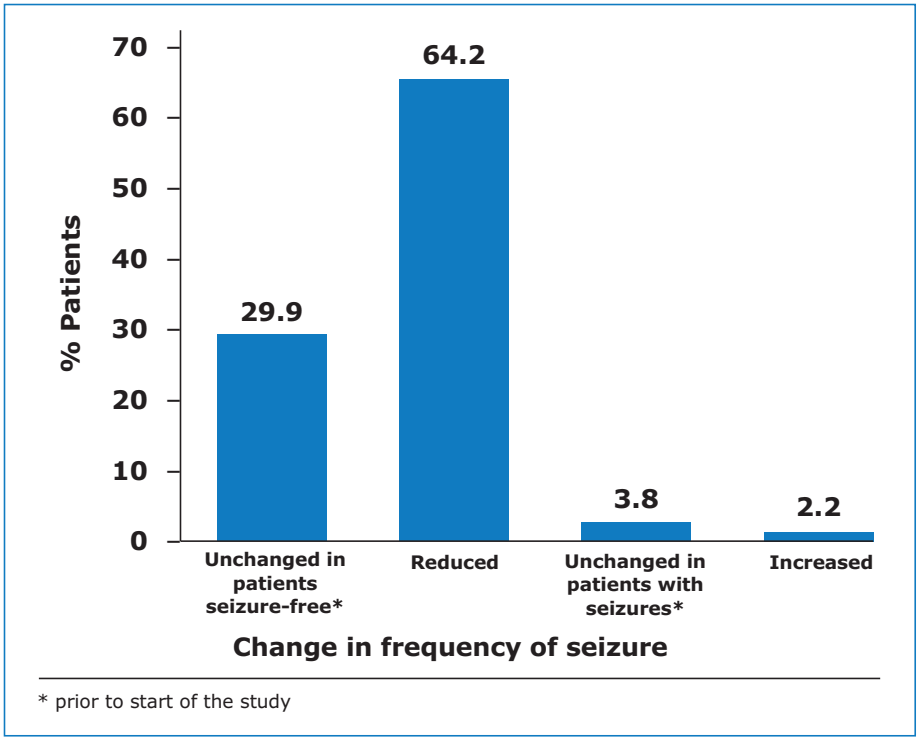
*=last observed value
**=including the sub-group with valproate sustained release minitablets 2 x daily

The mean frequency of seizures declined from 2.1 to 0.5 in the 318 evaluable patients. Seizures were less frequent in a total of 204 patients (64.2%). The proportion of seizure-free patients rose from 98 patients (30.8%) to 232 patients (73.0%). Of these, 95 patients had neither a seizure in the 7 weeks before starting nor during the observation period. Of the 220 patients, in whom seizures had been documented in the last 7 weeks prior to the surveillance period, 137 (62.3%) patients were seizure-free after 7 weeks of treatment, in 60 further patients (27.3%) the reduction in the frequency of seizures was at

least 50% (responders, but not seizure-free patients) *(Figure 1)*. The change in the number of seizures for the total group according to the type of pre-treatment is shown in Figures 2 and 3.

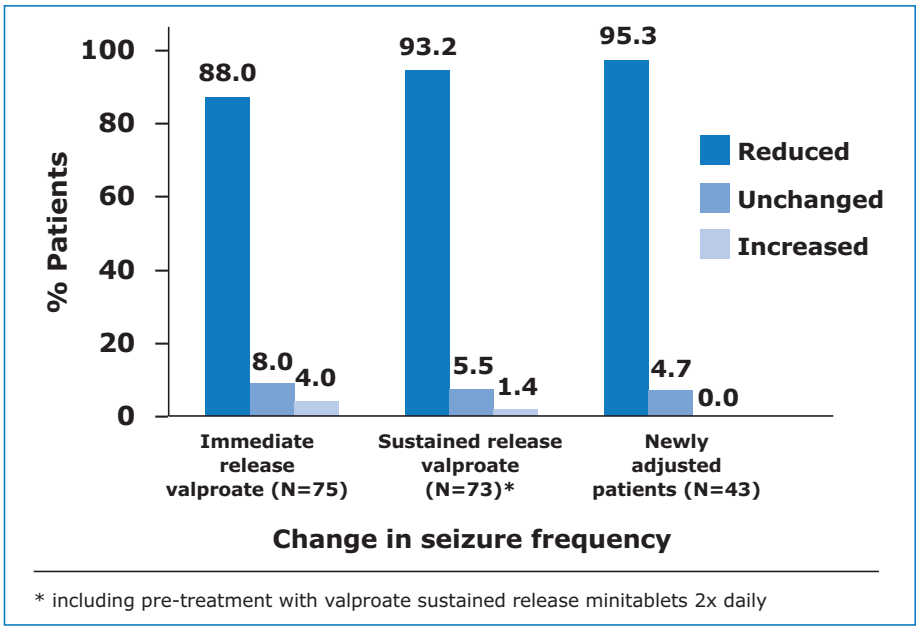
Twenty adverse drug reactions (ADR) were reported in a total of 14 patients (3.9%). Disturbances of the central and peripheral nervous system were most frequent – 3 patients reported tiredness/somnolence and tremor occurred in 2 patients. Only three patients discontinued treatment due to adverse drug reactions.

Figure 2: Percentage of patients with changes in the number of seizures (n = 318)



* prior to start of the study

Figure 3: Percentage of patients with changes in the number of seizures according to type of pre-treatment (only patients with seizures in the last 7 weeks prior to the start of observation n = 191)



* including pre-treatment with valproate sustained release minitablets 2x daily

At the overall assessment during the final examination, patients considered the efficacy and tolerability of the sustained release minitablets to be very good or good in more than 95% of cases. Handling of the once daily evening dosage was judged to be very good or good by almost all patients (99.1%). The attending physicians also assessed the efficacy and tolerability of Orfiril® long to be very good or good in more than 95% of cases, the compliance and the acceptance of the once daily evening dosage were similarly adjusted.

Discussion

When discussing the results, the methodical limits of an open trial have to be considered. For this reason, a surveillance study is not suitable to demonstrate strict proof of efficacy especially because of the lack of a control. This is, however, in the case of valproate not necessarily essential. The decisive advantage of open prospective clinical observations is that they reflect routine clinical practice in patients with epilepsy. For this reason, the focus of this investigation was put on assessing a simplified treatment regimen of valproate sustained release minitablets with administration of the entire dose once daily in the evening.

Valproate as a first line antiepileptic drug was already used in the majority of the pre-treated patients, in more than two-thirds of patients with gene-

ralised seizures and in about a third of patients with focal seizures. Half of these patients respectively received conventional valproate-based preparations or sustained release preparations. The switch to the once daily evening dosage of valproate sustained release minitablets could be made immediately without risk, i.e. ad-hoc at the same daily dose. Also, effective plasma levels were quickly achieved with the recommended dose scheme in the case of newly adjusted patients according to the Orfiril® long summary of product characteristics.

In the meantime, faster titration of the valproate dose, e.g. 300 mg increases every 3 days, is quite often practiced [11]. Besides the practicability, the once daily evening dosage proved to be effective and well tolerated. It was very well accepted by patients, as shown by the assessment of the patients themselves and the evaluation of compliance by physicians. It is to be emphasized that the number of seizures with the once daily evening dosage of valproate sustained release minitablets declined on average from 2.1 to 0.5. The number of seizures was reduced not only in the group of newly adjusted patients, but also in the pre-treated patients. It is notable that the number of seizures in more than 90% of patients who were already being treated with sustained release valproate was reduced still further by the switch to the once daily evening dosage regimen. This is presumably due to better compliance [8,9]. The valproate sustained release mini-tablets, which were already provided in the low doses in hard gelatine capsules and in minipacks in the higher doses, offer particular advantages with regard to their application: The capsules with the sustained release minitablets can be taken whole or after pulling the capsules apart or opening of the minipacks in loose form, e.g. in a preferred carbonated drink or sprinkled over soft food such as yoghurt. An additional advantage of the minitablets is that they can be taken independently of mealtimes. In contrast to monolithic tablets, they are able to pass the stomach quickly thanks to their small diameter of only 2 mm, so that they can be taken flexibly before, with, or after meals or fasting [12,13].

It is normal in the treatment of epilepsy to check plasma levels when patients are newly adjusted or switched to another medication. In the 120 patients with documented plasma levels, a distinct correlation was seen between the change in the frequency of taking valproate and valproate plasma levels. The distinct increase in the mean valproate plasma levels measured in the morning after switching to the once daily evening dosage both in the group which had previously received immediate release valproate, as well as in the group which had already received sustained release valproate preparations, was to be expected-considering the once daily intake of the entire daily dose and that normal blood samples for valproate level assays are taken in the morning. It is important to know the significance of the morning plasma level following adjustment or switch to the once daily evening dosage and whether the valproate level at the end of the dosing interval, i.e. in the early evening prior to taking the next dosage, still lies reliably within the therapeutic range. These questions were answered in a controlled trial in which the plasma levels were determined during the day following once daily evening dosage of valproate sustained release minitablets. 27 patients received daily doses between 600 and 1500 mg valproate sustained release minitablets. In almost 60% of patients, the level measured at 9:00 a.m. was the maximum value. Maximum negative deviations from this value of between 32% and 46% were measured during the day. Positive deviations between 1% and 21% were seen. Negative deviations can lead in particular in the lower dose range to plasma levels below the therapeutic window (50-100 µg/ml). With daily doses of between 18-24 mg/kg, levels did not fall below the therapeutic range, in the case of daily doses between 10-17 mg/kg a maximum shortfall of 43 µg/ml was observed; the seizure frequency did not increase [10]. Daily doses in this surveillance study were on average between 16-17 mg/kg and thus in the low dose range described by Fraunberger and colleagues. Nevertheless, reliable protection against seizures was ensured by the once daily evening dosage. In a further study in patients with acute mania, the once daily dosage of valproate sustained release minitablets proved to be effective and well tolerated. Therapeutic levels could be established within a short period, and 7 out of 11 patients were responders. In maintenance therapy, it was possible to stablish a continuous improvement in persisting hypomanic symptoms without

a relapse in a new manic episode or depression [14].

The once daily evening dosage is an important therapeutic option, which together with the above-mentioned advantages of valproate sustained release minitablets leads to greater freedom and improved quality of life for patients. Switching patients already pre-treated with valproate can be easily made 1:1 without a problem to the once daily evening dosage without a risk of possible increase in the number of seizures. Instead a further improvement of the control of episodes was achieved, which is probably due on the one hand to a simplification of the treatment regimen, on the other to more stable serum concentrations. To what extent sub-optimal therapeutic success with non-sustained release valproate preparations is a consequence of pronounced serum concentration variations, still needs to be further clarified. The results of this post-marketing surveillance study also show the outstanding risk-benefit ratio of valproate sustained release minitablets in a once daily evening dosage regimen and underline the importance of compliance-promoting therapeutic regimens for the effective seizure control.

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References

1 Moinier H, Carraz G, Moinier Y, et al.: Propriété pharmacodynamique de l'acide N-dipropylacétique. Thérapie 1963; 18: 435 – 438

2 Bourgeois BFD.: Valproic acid: Clinical efficacy and use in epilepsy. In: Levy RH, Mattson BS, Meldrum BS, et al. (eds). Antiepileptic Drugs, 5th ed. Philadelphia (PA): Lippincott Williams and Wilkens, 2002: 808 – 817

3 Emrich HM, Zerssen v D, Kissling W, Möller HJ et al.: Effect of sodium valproate on mania. The GABA-hypothesis of affective disorders. Arch Psychiat Nervenkr 1980; 229: 1 – 16

4 Brennan MJW, Sandyk R, Borsook D.: Anticonvulsants in Affective Disorders. Use of sodium valproate in the management of affective disorders: Basic and clinical aspects. In: Emrich HM, Okuma T, Müller AA (eds). EXCERPTA MEDICA, International Congress Series 626, Elsevier Science Publishers BV 1984: 56 – 65

5 Müller-Oerlinghausen B, Retzow A, Henn FA, Giedke H, Walden J.: Valproate as an adjunct to neuroleptic medication for the treatment of acute episodes of mania: a prospective, randomized, double-blind, placebo-controlled, multicenter study. J Clin Psychopharmacol 2000; 20: 195 – 203

6 Grunze H, Walden J, Dittmann S, Berger M, Bergmann A, Bräuning P, Dose M, Emrich HM, Gastpar M, Greil W, Krüger S, Uebelhack R.: Psychopharmacotherapy of bipolar affective diseases. Nervenarzt 2002; 73: 4 – 19

7 Nau H, Ralf-Siegbert H, Ehlers K.: Valproic acid-induced neural tube defects in mouse and human: aspects of chirality, alternative drug development, pharmacokinetics and possible mechanisms. Pharmacol Toxicol 1991; 69: 310 – 321

8 Cramer JA, Glassman M, Rienzi V.: The relationship between poor medication compliance and seizures. Epilepsy & Behavior 2002; 3: 338 – 342

9 Claxton AJ, Cramer J, Pierce C.: A systematic review of the associations between dose regimens and medication compliance. Clin Therapeutics 2001; 23: 1296 – 1310

10 Fraunberger, B.; Kirchner, A.; Kerling, F.; Pauli, E.; Stefan, H.: Wirksamkeit und Verträglichkeit von Valproat-Retard-Minitabletten nach abendlicher Einmalgabe in Monotherapie unter Berücksichtigung zirkadianer Serumspiegelmessungen bei Patienten mit Epilepsie. Aktuelle Neurologie (2006); 33: 195-199

11 Schmidt D, Elger CE.: Kapitel 7. Antiepileptika auf einen Blick. In: Schmidt D, Elger CE. Praktische Epilepsiebehandlung, 2. Auflage, Thieme Verlag 2002; 53

12 Retzow A, Vens-Cappell B, Wangemann M.: Influence of food on the pharmacokinetics of a new multiple unit sustained release sodium valproate formulation. Arzneim-Forsch 1997; 47: 1347 – 1350

13 Wangemann M, Retzow A, Vens-Cappell B.: Pharmacokinetic characteristics of a new multiple unit sustained release formulation of sodium valproate. Int J Clin Pharmacol Therap 1999; 37: 100 – 108

14 Grunze H, Amann B, Schäfer M, Sterr A, Schaerer L, Wild E, Walden J.: Effectiveness, safety and practicality of delayed-release minitablets of valproate in bipolar affective disorders. Fortschr Neurol Psychiat 2000; 68: 496 – 502

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