

Improving the Effectiveness of Drugs in Epilepsy Through Concordance



**Professor
Hermann Stefan**

is Director of the Epilepsy Centre in Erlangen.

Correspondence to:
Professor Hermann Stefan
Neurological University Hospital
Epilepsy Centre
Schwabachanlage 6
91054 Erlangen, Germany

Statement of financial support:
The post-marketing surveillance study on sustained release valproate was carried out and financed by the company Desitin Arzneimittel GmbH, Hamburg.

Compliance with a prescribed medicine regimen is a ubiquitous problem not confined to the treatment of asymptomatic conditions. Despite this, the poor compliance in patients with epilepsy is somewhat surprising given that patients are aware of the serious consequences in terms of seizures and even death. In this context it is important that we look for ways to improve epilepsy patients' adherence to the prescribed medication as a way of improving outcome.

Compliance in Epilepsy

A survey undertaken by Neurologists (n=661) in the USA¹ revealed that 71% of patients with epilepsy forgot to take their AED (anti-epileptic drug) at least once per month and it was evident that the chance of a patient missing a dose increased with the number of tablets prescribed. Of patients that missed a dose 45% reported a seizure. Patients taking a larger number of tablets/capsules increased their odds of having a seizure after a missed dose by 43%.

Similar results were reported in a recent UK study² which revealed that 59% of epilepsy patients had poor compliance and that this was related to an increased frequency of seizures.

A study in Germany³ measured post-ictal serum levels of anti-epileptic medications and confirmed that in at least 44% of cases the seizure was related to poor compliance.

A review of 10,892 epilepsy patients in a USA managed care system⁴ revealed that poor adherence was associated with a 11% increase in hospitalisation and a 47% increase in emergency admissions and as a consequence there was significantly increased healthcare costs.

It is evident that if a patient's seizures are not controlled by one AED there may be no point changing to another if the reason for lack of efficacy is non-compliance. Key conclusions from these studies are that the assessment of compliance should be a routine part of the management of epilepsy and physicians should consider prescribing the simplest regimen with the fewest daily doses and tablets.

The importance of seizure control

With optimal AED therapy up to 70% of people with epilepsy can expect to become seizure free⁵ but inadequate management results in uncontrolled seizures, drug side effects, psychological and physical morbidity and an increased risk of premature death.^{6,7}

In the UK more than 1000 people die each year because of epilepsy and most of these deaths are associated with seizures.⁶ Sudden unexpected death in epilepsy (SUDEP) is the principal cause of death in people with chronic epilepsy.⁶ Patients with a history of seizure in the previous year have a 23-fold increased risk of SUDEP compared to people with fully controlled seizures, and the risks increase with increasing seizure frequency.⁸

Non-compliance significantly increases the risk of seizure, A&E visits, hospitalisation, road traffic accidents, fractures and death⁹ and is therefore a key contributor to suboptimal management.

Issues related to poor compliance

There are many factors that influence compliance in people with epilepsy but the frequency, type and severity of seizures do not in themselves

Adherence is an important precondition for efficacy of long-term epilepsy treatment

Factors influencing medicine taking in children and young people with epilepsy (Adapted from WHO ¹⁴)		
Type of factor	Factors and their influence	
	Positive	Negative
Patients	satisfaction with medical care not feeling stigmatised by epilepsy feeling that it is important to take the medicine high levels of stressful life events	disbelief/denial of the diagnosis refusal to take any medication delusional thinking inconvenience of treatment lifestyle and health beliefs influence by relatives fear of addiction uncertainty about the need for drugs anxiety over the complexity of the regimen feeling stigmatised by the epilepsy
Epilepsy		forgetfulness due to impaired memory previous treatment failures frequent seizures
Treatment	single AED with simple dosing schedule	complex regimens misunderstanding how to take the AED side-effects
Health professionals/ healthcare system	good relationship between patient and physician	irregular drug supply lack of education about AEDs.
Socio-economic	parents report less education language barriers lower income recent immigrants	long distance from treatment centre teenager poverty local beliefs about the origins of illness
Note: Some factors identified by WHO have been omitted as not relevant in the UK setting		

appear to influence compliance rates.¹⁰ Irregular requests for repeat AED prescriptions, lack of response to appropriate therapy and an increase in seizure frequency may indicate non-compliance. It is, however, difficult to identify all patients who do not comply with their AED therapy. Health professionals should therefore be alert to the potential for non-compliance in all patients with epilepsy, enquiring non-judgementally about medicine taking at each consultation and being prepared to support patients in complying with their treatment. In addition to the diagnosis of epilepsy in a considerable number of patients depressive mood changes exist. In those patients rates of adherence is reduced and requires special strategies for continuous treatment.¹¹

The patients can have poor compliance if they do not understand the importance of taking their medication, if they experience side-effects, feel stigmatised by their condition, have difficulty in swallowing their medication or have multiple doses.¹² These issues can be multiplied if the patient is on multiple medications for concomitant conditions. Age can also be a factor with compliance being particularly poor in teenagers. Factors influencing compliance in children are highlighted in Table 1. Caring for a child with a learning disability is a major source of stress for parents, and the family situation can be made more difficult by children's behavioural and emo-

tional difficulties that require treatment with drugs that in themselves may increase the risk of seizure.¹³

Although non-compliance in epilepsy may be unintentional, most non-compliance with AEDs is intentional and results from conscious choices by patients.¹ These decisions are based on patients' beliefs about medicines in general that are affected by the experience of family and friends, culture, education, social circumstances, fears and anxieties and may be the result of an incomplete understanding of epilepsy and the proposed treatment. The result may be that patients are unsure that the benefits of AED treatment outweigh the perceived risks of taking medication.¹⁴

Swallowing difficulties

The incidence of patients who have swallowing difficulties may be much higher than generally realised and this can have implications in relation to compliance and subsequent lack of symptom control.¹⁶ The issues related to children may be more widely accepted but recent UK surveys have shown significant issues with dysphagia in the elderly and other patient groups, for example between 29 and 65% of stroke patients are reported to have swallowing difficulties.¹⁶ Swallowing difficulties are common in patients with epilepsy partly because they are exacerbated by concomitant conditions such as mental disability,

stroke or by additional medications (e.g. opioids, corticosteroids, diuretics etc) which may cause dry mouth.

A recent survey conducted by The School of Pharmacy, Bradford University¹⁷ in care homes (n=540) revealed that 22% of patients had swallowing difficulties and 11% regularly spat out medication. A similar audit conducted in elderly patients (n=182) in general practice¹⁸ in 2004 found that 11% of patients had dysphagia. The authors concluded that these findings are of concern and raise serious medicine management issues. There is a need for healthcare workers to enquire more about such issues and aim to provide medicines that are easier to take.

A move towards concordance

Making patients aware of the potential consequences of non-compliance is an important first step, but patient education and empowerment programmes may simply increase knowledge of epilepsy without improving compliance.¹⁹ The approach should not concentrate on instruction and direction about medicine taking, but rather to raise the patients' sense of achieving their own specific goal in dealing with their condition.¹² Adherence can be improved by the following general principles: 1) patient education, 2) improved dosing schedule, 3) increased patient contacts and 4) improved communication.

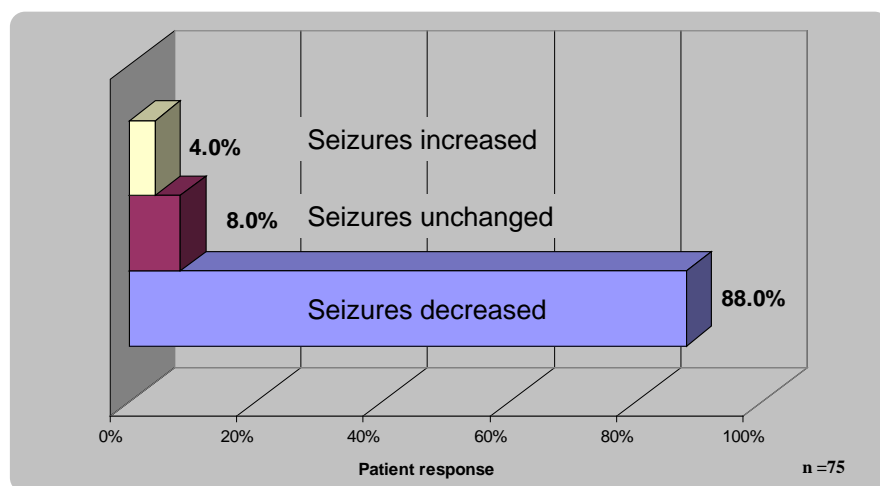


Figure 1: The change in the frequency of seizures in those patients who had seizures prior to being transferred from conventional valproate to valproate minitables (Episenta) taken once daily.

It is with this in mind that clinical guidelines recommend that healthcare professionals adopt a concordant consulting style that enables patients with epilepsy and, where appropriate, their family/carers, to participate as partners in decisions about their health care.²⁰ A two-way process respects the patients' experiences, beliefs and wishes, and enables a mutually agreed decision about medicine taking.

This concordant approach may be difficult to put into practice, but patients are more satisfied and adherent when they are encouraged to talk and perceive that professionals listen to their concerns.²¹

The choice of AED treatment

NICE recommends that AED treatment should be individualised according to each patient's seizure type, epilepsy syndrome, co-medication and comorbidity, lifestyle and preferences,²⁰ and that newer AEDs should only be used in people with epilepsy who have not benefited from or are unsuitable for established drugs such as sodium valproate and carbamazepine.²⁰

Poor compliance, drug interactions and long-term toxicity are all more likely if more than one AED is prescribed.⁵ Patients should therefore be treated with a single AED wherever possible and about 80% of patients can be controlled by a single drug,²⁰ so combination therapy should only be considered when

monotherapy has not resulted in freedom from seizures. If trials of combination therapy do not achieve worthwhile benefits, treatment should revert to the regimen that has proved most acceptable to the individual in terms of providing the best balance between effectiveness in reducing seizure frequency and tolerability of side effects.²⁰

Developing concordance with AEDs

Clinical guidelines provide detailed recommendations about the importance of ongoing counselling, education and support for people with epilepsy and it is essential to ask about practical problems that may reduce compliance, including any difficulties in taking the medicine, side effects or inconvenient AED dosing.

The aim should be to move towards an easy to take once daily medication whenever possible, but many drugs must be taken twice or three times daily. Sodium valproate is recommended and widely used as first-line for all types of seizure so, a means of improving concordance with this product should be welcomed.

Development of improved formulations

It had been recognised that valproate therapy could be limited by gastric intolerance and this led to the introduction of an enteric coated formulation (Epilim) in the 1970's. Sustained-release (SR) formulations enable

once or twice-daily dosing and have the additional advantage of being associated with fewer side-effects.²² In a comparative study (randomised cross over of conventional VPA BID; sustained release BID, once daily morning, once daily evening sustained release (study duration 16 months) patient preference was greatest for once daily evening sustained release VPA.²³

There are, for example, two SR formulations of sodium valproate: a conventional tablet (Epilim Chrono) using technology developed in the early 1990's and one developed to current regulatory guidelines containing many controlled release minitables (Episenta).

Some patients can find it difficult to swallow any conventional tablet, but most conventional sodium valproate SR formulations cannot be crushed because this destroys their prolonged-release effect.²² Liquid formulations are an option, but some young patients do not like the taste, especially if they are on high doses and need to take large volumes. However, with Episenta the capsules or sachets can be opened and the minitables sprinkled onto soft foods or taken with drinks. Each minitablet is a prolonged delivery unit containing 3mg of sodium valproate which can reliably ensure an effective once-a-day treatment to help enhance acceptability to patients with epilepsy. A single evening dose is suitable for most patients.

The eating habits of many patients may vary and this can have significant effects on the bioavailability of some formulations. Altered levels of sodium valproate can result in either more adverse reactions or ineffective treatment. In contrast, the minitables can be taken either before, during or after meals without any affect on absorption as they pass through the pylorus independent of food and do not get retained in the stomach to cause gastric irritation.¹⁰ This type of innovation can make a presentation that is easy to take and can fit into the patients lifestyle in order to improve concordance.

A simple dosage to improve effectiveness

Valproate is widely used as a first line antiepileptic drug in patients with generalised seizures as well as some with focal seizures and patients who may take either conventional or sustained release preparations on a twice

Simplification of drug uptake by once daily application using a slow release formulation supports treatment efficacy

or three times a day dosage. The launch of a version of valproate in an advanced drug delivery system gave us the opportunity of evaluating if patient outcome could be improved by switching to the once daily evening dosage of valproate sustained release minitabets (Episenta).

We conducted a study on 359 epilepsy patients (aged 12 to 86) in Germany;²⁴ the aim of which was to collect data on the use of valproate sustained release minitabets (Episenta) 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 effect on seizure frequency was of particular interest as well as assessment of adherence to the medication with this simplified therapeutic regimen.

There are methodical limits of an open trial, however, the decisive advantage of open prospective clinical observations is that they reflect routine clinical practice in patients with epilepsy.

Patients were either newly treated with valproate sustained release minitabets (N=58), switched from conventional valproate (N=124) or from sustained release valproate taken twice daily (N=138) to the once daily evening dosing. In 39 patients other antiepileptic drugs were replaced. Patients were entered at the end of a 7-week observational period and then observed for a further 7 weeks.

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 emphasised that the number of seizures with the once daily evening dosage of valproate sustained release minitabets 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 those pre-treated with valproate²⁴ (Figure 1). 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.¹

The valproate sustained release mini-tablets which are in capsules and in sachets, offer particular advantages with regard to their application. The capsules with the sustained release minitabets can be taken whole or after pulling the capsules apart or opening of the sachets in loose form, e.g. in a preferred carbonated drink or sprinkled over soft food such as yoghurt. An additional advantage of the minitabets in contrast to monolithic tablets is that they can be taken independently of meals.

The once daily evening dosage is an important therapeutic option, which together with the above-mentioned advantages of valproate sustained release minitabets leads to greater freedom and improved quality of life for patients. The incidence of seizures was reduced which is probably due to the one

hand to a simplification of the treatment regimen, on the other to more stable serum concentrations.

The results of this post-marketing surveillance study underline the importance of compliance-promoting therapeutic regimens for the effective seizure control. A more timely extended evaluation still is necessary to evaluate the amount and persistence of seizure control over a longer period. Medications that may be regarded as "patient friendly" can help move closer to the goal of concordance.

Conclusion

Non-compliance with AEDs is a major cause of seizures and healthcare professionals are tasked with the responsibility of finding ways to resolve this problem in order to protect patients with epilepsy from the consequences of seizure which include stigmatisation, social exclusion, disability, and increased risk of death.

Promoting long-term medicine taking is a complex task, involving combinations of more convenient care, information, reminders, self-monitoring, reinforcement, counselling, family therapy, psychological therapy, follow-up and supportive care. Individualised, patient-friendly treatment is an important first step and once daily regimens that are easy to swallow have been shown to improve outcomes, but no intervention will promote medicine taking in the absence of a supportive, concordant partnership between patients, carers and healthcare workers. ♦

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