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Newer Anticonvulsants

Comparative Review of Drug Interactions and Adverse Effects

Anne Sabers and *Lennart Gram*[1]

Dianalund Epilepsy Hospital, Dianalund, Denmark

Contents

Abstract

The tolerability and drug interaction profiles of 6 new anticonvulsants: oxcarbazepine, vigabatrin, lamotrigine, gabapentin, tiagabine and topiramate, are reviewed. In general, these new anticonvulsants are well tolerated and drug interaction problems are minor with the exception of the risk of failure of oral contraceptives during treatment with oxcarbazepine or topiramate.

In this review, the clinical implications of the tolerability of these drugs are discussed for different patient groups. The choice of which new anticonvulsant for which patient depends upon individual factors, in particular, seizure type, tolerability and practical administration factors.

Treating elderly patients may be complicated by an increased sensitivity to adverse effects as these patients very often receive polytherapy for accompanying diseases. Drugs with very simple pharmacokinetic properties may be preferred in this group. Women of childbearing age face specific problems related to the epilepsy and to treatment with anticonvulsants. These include impaired fertility, failure of oral contraceptives and the risk of birth defects. Some new anticonvulsants may be suggested in preference to classical drugs to avoid these problems, but the human experience with newer anticonvulsants is still limited and, therefore, so is knowledge of the risk of congenital malformations in the offspring of

1 Editor's note: Dr Gram died before the completion of this article. His contribution is gratefully acknowledged.

mothers taking anticonvulsants. Psychiatric and behavioural changes frequently complicate treatment of patients with mental retardation. Some of the new anticonvulsants, in particular those affecting the γ-aminobutyric acid (GABA) system such as vigabatrin, seem to exacerbate this problem and should be used with caution in these patients.

Six new antiepileptic drugs, namely oxcarbazepine, vigabatrin, lamotrigine, gabapentin, tiagabine and topiramate, have been marketed in a significant number of countries within the last 10 years. Only oxcarbazepine and lamotrigine are licensed for use as monotherapy in Denmark.

In everyday clinical practice, polytherapy is prescribed in a significant proportion of patients with epilepsy and these patients may experience complicated pharmacokinetic and pharmacodynamic drug interactions. Most of the new anticonvulsants have relatively simple pharmacokinetic properties and favourable toxicity profiles compared with older drugs [phenobarbital, phenytoin, carbamazepine and valproic acid (valproate sodium)]. In particular, induction and inhibition of the hepatic enzyme system may result in important changes in serum concentrations of anticonvulsants. Unlike most of the older agents, vigabatrin, lamotrigine, gabapentin and tiagabine are devoid of significant enzyme inducing or inhibiting properties.[1-4] Oxcarbazepine and topiramate induce selectively specific hepatic enzymes.[5,6] The most commonly observed pharmacokinetic interactions by induction or inhibition of hepatic enzymes, therefore, in general are related to co-medication with the older drugs and are almost negligibly induced by the newer drugs.

Comparative clinical trials of tolerability between new anticonvulsants do not exist. A systematic review of placebo-controlled, randomised controlled trials of new anticonvulsants as add-on therapy in refractory partial epilepsy demonstrated that patients are more likely to withdraw from vigabatrin or topiramate therapy because of tolerability problems than from lamotrigine or gabapentin.[7] A meta-analyses of 29 randomised placebo-controlled add-on trials of new anticonvulsants demonstrated no significant differences in the incidence of ataxia, dizziness, fatigue, nausea or somnolence with lamotrigine, vigabatrin, gabapentin or topiramate.[8] Symptoms of depression were significantly more likely to occur in patients taking vigabatrin.

This review evaluates the tolerability of oxcarbazepine, vigabatrin, lamotrigine, gabapentin, tiagabine and topiramate, and clinically significant interactions between these newer anticonvulsants and other anticonvulsants and drugs used for the treatment of unrelated medical conditions in adult patients.

1. Interactions and Tolerability of New Anticonvulsants

1.1 Oxcarbazepine

Oxcarbazepine is a prodrug, rapidly metabolised to the pharmacologically active mono-hydroxy derivative (MHD). Oxcarbazepine has a significantly lower level of enzyme induction compared with, for example, carbamazepine[9] and treatment with oxcarbazepine, in general, causes only minor pharmacokinetic interaction problems. However, co-administration of oxcarbazepine with lamotrigine reduces lamotrigine concentrations by 29%[10] and phenytoin concentrations may be increased by high doses of oxcarbazepine.[11] Co-administration of carbamazepine, phenobarbital or phenytoin with oxcarbazepine decreases the mean plasma MHD concentration.[11] Interactions with other anticonvulsants involving pharmacodynamic actions are not well documented. However, it is our clinical experience that dizziness frequently emerges when lamotrigine is added to oxcarbazepine treatment. This adverse effect disappears upon reduction of the oxcarbazepine dosage.

Oxcarbazepine induces specific isoenzymes of the cytochrome P-450 (CYP) 3A group, responsible for the metabolism of dihydropyridine calcium antagonists[12] and oral contraceptives.[5,13]

The most commonly reported adverse effects are tiredness, headache, dizziness and ataxia.[9,14,15] The nature of adverse effects is very similar during oxcarbazepine and carbamazepine treatment but the number of adverse effects seems to be more frequent during carbamazepine treatment compared with oxcarbazepine in the majority of comparative studies.[15,16] Neuropsychological assessments reveal no measurable impairment of cognitive functions following 4 months and 1 year of oxcarbazepine monotherapy, respectively.[17,18]

Oxcarbazepine therapy is frequently associated with the occurrence of 'asymptomatic' hyponatraemia.[19,20] However, hyponatraemia as a cause for discontinuation of oxcarbazepine is only occasionally reported.[21] Water intoxication in one patient due to oxcarbazepine treatment showed complete reversibility upon discontinuation of the drug.[22] Some abnormal haematological parameters including decreased erythrocyte folate concentration observed during carbamazepine treatment are normalised after replacing carbamazepine with oxcarbazepine,[23] which is probably as a result of the elimination of liver enzyme induction.

Allergic skin rashes seem to occur in about 10% of patients during oxcarbazepine treatment, which appears to be less frequent than with carbamazepine treatment.[9,15] Cross-allergy between oxcarbazepine and carbamazepine takes place in about 25 to 31% of patients.[16]

1.2 Vigabatrin

Interactions between vigabatrin and other drugs should not be expected since vigabatrin is not bound to plasma protein and is excreted largely unchanged in the urine. However, several reports have demonstrated a reduction (about 20 to 30%) of the plasma concentrations of phenytoin after adding vigabatrin to the therapy.[1,24]

Adverse events are usually mild and transient, and most commonly include drowsiness, dizziness, fatigue and bodyweight gain.[1,25-27] Severe drowsiness, progressing to a state of stupor has been described.[28] Development of mood disturbances is described in a significant proportion of patients during vigabatrin treatment.[29] The most severe adverse effects of vigabatrin include depression[30] and psychotic reactions.[31] Confusion and psychotic symptoms may be associated with a dramatic decrease in seizure frequency[31] and/or a history of psychosis.[32] The psychiatric symptoms seem to be fully reversible after dose reduction or drug withdrawal. Psychosis following abrupt discontinuation of vigabatrin has also been reported.[33,34]

The effect of vigabatrin on cognitive functions in adults seems minimal or absent.[35-37]

Vigabatrin may induce myoclonus in some patients with partial epilepsy.[38] In addition, reversible motor disturbances such as tremor, athetosis and dystonia have been described during vigabatrin treatment.[39]

Peripheral visual field defects in relation to vigabatrin were reported for the first time by Eke et al.[40] This neurotoxic effect is predominantly asymptomatic and was present for 8 years before being disclosed. In the recent report from Kälviäinen et al.,[41] 40% of patients receiving vigabatrin monotherapy had concentrically constricted visual fields compared with no patients in a carbamazepine control group. All patients were subjectively asymptomatic and had received vigabatrin for 32 to 108 months. Males seem to be significantly more frequently affected than females.[42,43] At the moment it is not known if this adverse effect is related to duration of vigabatrin exposure, if there is an adverse synergism with other drugs or if these visual defects are reversible on withdrawal of vigabatrin. It is suggested by Arndt et al.,[44] that the toxicity of vigabatrin is exacerbated by valproic acid. Manuchehri et al.[45] found a significant correlation between the severity of visual field defect and the total dose of vigabatrin ≥1500mg. Anecdotal reports describe that progression of visual field defects was halted after reducing the vigabatrin dose[46] and that the field defects were completely reversible after vigabatrin was withdrawn.[47] However, the reversibility of the visual field defects remains unsolved and necessitates that visual field testing should be performed before treatment with vigabatrin and during routine follow-up.

Allergic skin reactions do not seem to occur with vigabatrin.

1.3 Lamotrigine

Lamotrigine is mainly eliminated by hepatic metabolism through glucuronidation processes.[2] The glucuronide formation of lamotrigine is acutely inhibited by valproic acid, which approximately doubles the plasma elimination half-life ($t_{½\beta}$) of lamotrigine.[48-50] Co-medication with enzyme-inducers increases metabolism and almost doubles the plasma clearance of lamotrigine.[48,49] The addition of oxcarbazepine to lamotrigine decreases lamotrigine concentrations by 29%.[10] Felbamate does not seem to affect the $t_{½\beta}$ of lamotrigine.[51] In patients taking both enzyme-inducing drugs and valproic acid the plasma $t_{½\beta}$ is close to that of seen with lamotrigine monotherapy.[52] Lamotrigine does not affect the metabolism of other anticonvulsants, nor that of oral contraceptives.[53] Development of nausea, ataxia and dizziness is frequently observed following the addition of lamotrigine to carbamazepine. An increased serum concentration of carbamazepine 10,11-epoxide following the addition of lamotrigine to carbamazepine has been reported by Warner[54] but this is not confirmed by others.[55-57]. These signs of neurotoxicity are more likely explained by a pharmacodynamic interaction between these drugs.[57] A similar pharmacodynamic interaction seems to exist with oxcarbazepine and lamotrigine.

Concomitant treatment with some selective serotonin re-uptake inhibitors may reduce the elimination of lamotrigine.[58]

In general, lamotrigine is very well tolerated. During monotherapy the most commonly reported adverse experiences are dizziness, somnolence, nausea, asthenia, and headache in 8 to 20% of the patients. Lamotrigine monotherapy is discontinued because of adverse events in less than half the number of patients compared with carbamazepine and phenytoin monotherapy.[59] Insomnia is associated with lamotrigine treatment in some patients.[60] In most patients, a dose reduction or administration of lamotrigine in one daily morning dose may eliminate the problem. It is our personal experience that hair loss is occasionally associated with lamotrigine therapy.

The adverse effect which most frequently requires withdrawal of lamotrigine is allergic skin reactions.[59] Rashes develop in about 12% of patients and typically within the first 8 weeks of lamotrigine administration. Rarely, severe cutaneous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, have been described.[61] The risk of serious rashes is approximately 3 times greater in children compared with adults.[62] The risk of allergic reaction is correlated to the initial plasma concentration of lamotrigine. Low starting dose and slow titration should therefore always be used, especially in patients also receiving valproic acid.

Case reports of severe leucopenia,[63] agranulocytosis,[64] fulminant hepatic failure[65] and multiorgan failure[66] induced by lamotrigine have been reported.

Lamotrigine does not appear to have a negative influence on cognitive function[67] but might have some favourable effects on mood and well-being.[67,68]

1.4 Gabapentin

As gabapentin is not metabolised, does not influence hepatic enzymes and is not bound to plasma proteins, interactions with other anticonvulsants or other drugs should not be expected. However, the bioavailability of gabapentin is decreased by 20% by concomitant use of an aluminium/magnesium hydroxide antacids.[3]

Gabapentin is fairly well tolerated in most patients. As the intestinal absorption of gabapentin has a saturable transport mechanism, the risk of overdosing should be negligible. Adverse effects are primarily CNS-related, of mild to moderate severity and usually transient during continued therapy. The most frequent adverse effects, occurring in about 10% to 20% of patients, are somnolence, dizziness, ataxia, nystagmus, tremor,[69-72] and headache.[73] A clear relationship between dose and adverse effects does not seem to exist[61-73] besides dizziness and somnolence, which may show a dose-related trend.[73] Gabapentin monotherapy is better tolerated

than carbamazepine monotherapy.[74] Bodyweight gain is described in some patients.[75,76] Myoclonus may be precipitated by gabapentin[77,78] but it may be difficult to ascertain whether the symptom reflects an epileptic phenomenon or a movement disorder.[79] In 3 cases of gabapentin-induced myoclonus, the jerks showed no electroencephalogram (EEG) correlation, suggesting a subcortical mechanism. Case reports of choreo-athetosis as an adverse effect of gabapentin has also been described.[80]

Gabapentin does not seem to have a negative influence on cognitive functions.[81,82]

Rashes are very rarely associated with gabapentin treatment.[74]

1.5 Tiagabine

Tiagabine is extensively metabolised in the liver and the rate of elimination is more than doubled during concomitant treatment with hepatic enzyme-inducing anticonvulsants.[83,84] The metabolism of other anticonvulsants is not affected by tiagabine.[4]

Tiagabine is generally well tolerated and adverse effects are most often CNS related.[85] The most common significant adverse effects are dizziness,[85,86] asthenia, amnesia, nervousness, and abdominal pain.[87] Insomnia and abnormal thinking (difficulty in concentration or slowness of thought) have also been described during tiagabine monotherapy.[85]

Development of nonconvulsive status epilepticus has been observed in a few patients with partial epilepsy treated with tiagabine and followed by complete electroclinical remission after discontinuation of tiagabine.[88] It is our clinical experience that remission of this condition can be obtained even by reduction of tiagabine dose.

Tiagabine does not seem to affect neuropsychological performances.[89-91]

Visual field deficiencies have not been demonstrated during tiagabine treatment.[92]

Rash is a very unusual occurrence and, when seen, is probably not related to tiagabine.

1.6 Topiramate

Topiramate is mainly eliminated by renal excretion and has minimal protein binding. However, the metabolism of topiramate is increased approximately 50% when it is administrated with enzyme-inducing drugs.[93,94] Topiramate does not significantly affect the metabolism of other anticonvulsants with the exception of the elimination of phenytoin, which may be reduced in some patients after the addition of topiramate.[94] Topiramate is a weak inducer of CYP enzymes and so its use is associated with the risk of failure of oral contraceptives.[6]

Adverse events seen during topiramate treatment are predominantly CNS-related and include dizziness, difficulty with concentration and speech, somnolence, ataxia, and fatigue.[95] Word finding difficulties seems to be a fairly specific problem with topiramate and is reported as a adverse effect in up to one-third of patients.[96,97] Psychotic symptoms have been observed in 12% of patients, which was significantly higher than for patients treated with gabapentin or lamotrigine.[97] The adverse events are minimised by initiating treatment with a low dosage followed by slow titration.

Specific adverse effects probably related to the carbonic anhydrase activity of topiramate include acroparesthesia and an increased risk of developing renal stones. The paraesthesia seems to decrease with time or dosage reduction. Nephrolithiasis has been observed in (1.5%) of patients treated with topiramate, which is 2 to 4 times the incidence expected in the general population.[96,98] Sufficient daily fluid intake may reduce this problem.

Bodyweight loss is frequently observed during long term treatment with topiramate with an average of approximately 4kg.[99] The risk of bodyweight reduction seems to be dose-related and is more common in heavier patients.[96]

Topiramate may impair attention with a dose-related fashion in some patients.[100]

2. Which Drug for Which Patient?

2.1 Patients with Partial Seizures

Treatment of patients with partial epileptic seizures has always been difficult, producing a group of patients whose 'optimum' treatment results in insufficient efficacy and/or intolerable toxicity. Consequently, in this group of patients there is always a need for introducing more effective or less toxic new anticonvulsants. In fact, it is this group of patients who very often participate in the initial clinical testing of potential new anticonvulsants. All the new anticonvulsants have demonstrated their efficacy, compared with placebo, as add-on treatment in this group of rather therapy-resistant patients. The placebo-controlled trials, resulting in registration of all these new anticonvulsants, except oxcarbazepine, have been reviewed in a meta-analysis.[8,101] Although these trials were not directly comparative, the trials selected for this analysis exhibited very similar designs and on this basis an attempt to compare the results obtained for the individual drug has been performed. The result was that because of wide overlapping confidence intervals no significant differences in clinical efficacy or tolerability could be identified. When odds-ratio analysis for 50% seizure reduction and drug discontinuation was used, it was probable that lamotrigine and gabapentin were less effective and better tolerated than vigabatrin, tiagabine and topiramate. The overall message from this analysis seems to be that apparently the most effective drugs involve more toxicity/tolerability problems than less effective new anticonvulsants. However, these findings were inconclusive because gabapentin and lamotrigine were probably not tested at their optimal doses. In addition, summarisation of data into a single odds-ratio may not be the most optimal approach for comparisons among trials.[102-104] Calculating the number needed to treat to get one responder, instead of using odds ratios, indicates differences in efficacy of the anticonvulsants with vigabatrin and topiramate as the most effective ones.[105]

Monotherapy studies, comparing the efficacy and tolerability of new anticonvulsants with carbamazepine as the standard reference drug for partial seizures, demonstrate that oxcarbazepine,[15] lamotrigine,[106] vigabatrin[107] and probably gabapentin[74] have a similar efficacy and are better tolerated than carbamazepine. Topiramate was also found to be effective as monotherapy in the treatment of partial seizures.[108]

2.2 Patients with Generalised Seizures

Until recently, treatment options of patients with generalised seizures were rather limited. The only anticonvulsants with a wide spectrum of activity available were valproic acid and the benzodiazepines. However, with the introduction of the new generation of anticonvulsants, it is becoming increasingly clear that two of these agents seem to be drugs with a wide spectrum of activity, namely lamotrigine and topiramate.

Today, there is increasing evidence that lamotrigine is effective in the treatment of idiopathic generalised epilepsy, even involving tonic-clonic convulsions such as juvenile myoclonic epilepsy.[109] Several reports describe the effect of lamotrigine in the treatment of Lennox-Gastaut syndrome[110,111] as well as in the treatment of absences.[112,113] However, one should be aware that lamotrigine may aggravate severe myoclonic epilepsy.[114,115] In our experience, lamotrigine is playing an increasingly important role in the treatment of idiopathic generalised epilepsy because of excellent efficacy and in many instances because of superior tolerability, for example compared with valproic acid, which may frequently cause significant problems with body-weight gain.

Like the other new anticonvulsants, topiramate was introduced for the treatment of partial seizures with or without secondary generalisation. However, as time goes by we have learned that, apart from being very effective in the treatment of partial seizures, this drug also exhibits efficacy against idiopathic generalised epilepsy[116] as well as in the treatment of drop attacks and tonic-clonic seizures in patients with Lennox-Gastaut syndrome.[117] However, there is no evidence that topiramate is effective against absences. It is becoming increas-

ingly clear, that topiramate is one of the most effective drugs, with a broad spectrum indication within epilepsy treatment, which has emerged for a number of years.

2.3 Elderly Patients

Physiological changes that occur with aging may influence drug pharmacokinetics and tolerability. Treatment of elderly patients is further complicated by comorbid illness, which necessitates multiple drug therapy. In many elderly patients serum albumin concentrations are decreased and the biotransformation of drugs may be slowed as a result of declining hepatic and renal function. Some of the new drugs may, therefore, have a theoretical advantage over older drugs. With the exception of tiagabine, the new anticonvulsants have low or negligible protein binding. Vigabatrin, lamotrigine, gabapentin and tiagabine do not affect the hepatic enzyme system, and the enzyme-inducing properties of oxcarbazepine and topiramate are selective and less pronounced compared with older drugs.

The choice of anticonvulsant for elderly patients calls for specific considerations. Many older patients live alone and memory disturbances may interfere with optimal compliance. Drugs, which can be administrated once daily, may be preferred in these patients. In some patients, for example in those with new-onset epilepsy after stroke, it may be mandatory to achieve early therapeutic plasma concentrations of anticonvulsants to prevent repetitive seizures which may jeopardise rehabilitation.

Gabapentin may be a good choice for partial epilepsy in elderly patients because of the absence of drug interactions and a favourable tolerability profile. Therapeutic serum concentrations can be achieved within a few days but the necessity for three-times-daily administration may be limiting for some elderly patients. Lamotrigine is in general well tolerated and can be administrated once or twice daily. A recent study by Brodie et al.[118] demonstrates that lamotrigine is as effective and significantly better tolerated than carbamazepine in elderly patients. However, the slow dose escalation of lamotrigine constitutes a theoretical disadvantage for new-onset epilepsy. Clinical data as well as our own experience of vigabatrin, tiagabine and topiramate are too limited to make recommendations for use of these drugs in the elderly population.

It is our experience that oxcarbazepine treatment is frequently associated with dizziness in the elderly population. Lowering the dosage may solve the problem.

2.4 Women of Childbearing Age

The rate of failure of oral contraceptives is high among women taking enzyme-inducing anticonvulsants. This includes the selectively enzyme-inducing effect of oxcarbazepine and topiramate. Vigabatrin, lamotrigine, gabapentin and tiagabine do not reduce the effect of oral contraceptives.[53,119]

The choice of anticonvulsant in women who wish to conceive is more controversial. Menstrual disturbances and reduced fertility are frequent among women with epilepsy[120] and may, at least partly, be caused by treatment with anticonvulsants. The metabolism of sex hormones can be altered by anticonvulsants with enzyme-inducing properties which probably also includes oxcarbazepine and topiramate. Polycystic ovaries are significantly more frequent in women with epilepsy and is especially related to treatment with valproic acid.[121] It has been demonstrated that replacing valproic acid with lamotrigine is followed by reversal of polycystic ovaries in 70% of patients.[122] Therefore, from a theoretical point of view, new anticonvulsants without enzyme-inducing properties and with simple pharmacokinetics could be favoured in women with reduced fertility. On the other hand, the teratogenic potential of newer anticonvulsants is not known. Except for topiramate, which is associated with limb agenesis in rodents, the newer anticonvulsants do not appear to be teratogenic in animals when given in subtoxic doses. In addition, clinical experience in humans are still very limited. Occurrence of fetal malformations in the infants of women with epilepsy may be associated with low serum folate levels during pregnancy. Enzyme-inducing anticonvulsants reduce

serum folate levels[123] and alterations of folate metabolism seem to be associated with valproic acid.[124] Oxcarbazepine does not interfere with folate metabolism[23] and lamotrigine has no significant antifolate properties in humans.[125]

2.5 Patients With Mental Retardation

Mental retardation is often associated with severe and intractable epilepsy. A substantial proportion of these patients receive polytherapy for epilepsy and often in combination with other drugs. Since many patients with mental handicaps are unable to speak or express subjective sensations, an important problem in treating these patients is assessment and recognition of possible adverse effects of anticonvulsants. Careful attention and observation of the patient's mood, functioning and behaviour may therefore be the best guidance for evaluating the treatment. However, absence of seizures following effective therapy or replacing drugs with sedative adverse effects with nonsedative drugs, sometimes unmasks the underlying personality, which may induce behavioural problems. In addition, tapering off some anticonvulsants may be associated with reappearance of psychotic phenomena in some patients.

Comparative clinical controlled studies of the tolerability of new anticonvulsants in patients with mental retardation do not exist.

Lamotrigine is associated with improved functioning, mood and well-being in many patients with mental retardation[67,68,126] while aggressive behaviour, violence and hyperactivity seems to be provoked by lamotrigine in some patients.[126,127] The reason for this disparate effect is not clear. Lamotrigine therapy in patients with Lennox-Gastaut syndrome is associated with improved behaviour and quality of life in most studies.[110,128,129] The same may be the case for patients with Rett syndrome.[130]

Behavioural adverse effects are described with gabapentin especially in children with mental retardation.[131,132] It is our experience that vigabatrin causes behavioural problems in a significant number of patients and that these problems are more frequently associated with vigabatrin than with other anticonvulsants. This is in agreement with the results of Bhaumik et al.[133] who found behavioural problems during treatment with vigabatrin, lamotrigine and gabapentin but with the highest incidence during vigabatrin treatment.

Topiramate must be used with caution regarding specific problems in this patient group. Acroparestesias may not be recognised. In patients with changed behaviour or self-mutilation, examination for blood in the urine should be considered. Changes in bodyweight and the requirement for sufficient fluid intake is often a problem in these patients, who cannot be expected to adhere to diets.

3. Conclusions

Compared with previously available anticonvulsants the reviewed new generation of anticonvulsants represents progress with regard to a number of issues:

- The new generation of anticonvulsants exhibit far fewer drug interactions compared with classical anticonvulsants, where this aspect is sometimes quite overwhelming, e.g. for phenytoin.
- The tolerability profiles of several of the new anticonvulsants represent much progress compared with older anticonvulsants. This is represented in a better retention time on trial drug compared with reference treatment, as was seen in the comparative trial of carbamazepine and lamotrigine.[106]
- A number of the new anticonvulsants are devoid of enzyme-inducing properties, which can be a problem with the majority of already available anticonvulsants.

These advantages, combined with the fact that several comparative trials show no detectable differences in efficacy between the new drugs and older agents, makes using the new generation of anticonvulsants tempting.

Selection of which new anticonvulsant for which patient depends upon individual factors, such as the need for treatment effect combined with consideration of the patient's sensitivity towards drug toxicity.

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Correspondence and offprints: Dr *Anne Sabers*, Dianalund Epilepsy Hospital, DK-4293, Dianalund, Denmark.
E-mail: kfansa@vestamt.dk