REVIEW ARTICLE

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Effect of Antiepileptic Drugs on Cognitive Function in Individuals with Epilepsy

A Comparative Review of Newer Versus Older Agents

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Contents

Abstract

Several 'new' antiepileptic drugs (AEDs), i.e. oxcarbazepine, vigabatrin, lamotrigine, zonisamide, gabapentin, tiagabine, topiramate and levetiracetam have been introduced into clinical practice within the last decade. Most of these new drugs are at least as effective as the 'old' AEDs [phenytoin, phenobarbital (phenobarbitone), valproic acid (sodium valproate) and carbamazepine] and, in general, they seem to be better tolerated than the old drugs. The new AEDs might have less influence on cognitive functions but the aspect has not been systematically studied.

Neuropsychological testing has been the major method of objectively examining cognitive function related to the use of AEDs but a number of methodological problems blur the results. Alteration of cognition might reflect a chronic adverse effect of AEDs but the negative effects of the drugs are only one of several factors that may influence cognition. In addition, subjective complaints about cognitive deficits (e.g. memory problems or attention) may also reflect other aspects of adverse effects than those concerning specific cognitive functions (e.g. mood and anxiety).

This review focuses on studies of the cognitive effects of the new AEDs, and in particular on studies that compare cognitive effects of the old and new drugs.

In general, the new AEDs seem to display no or minor negative cognitive effects. In studies in which new AEDs have been compared with old AEDs, there was a tendency in favour of the new AEDs in some of the studies.

Modern epilepsy research has resulted in considerable progress in antiepileptic drug (AED) development. Until the last decade of the 20th century, the major AEDs in clinical use were phenytoin, phenobarbital (phenobarbitone), valproic acid (sodium valproate) and carbamazepine, which are referred to in this review as 'old AEDs'. Since then, nine 'new AEDs', oxcarbazepine, vigabatrin, lamotrigine, felbamate, zonisamide, gabapentin, tiagabine, topiramate and levetiracetam, have been introduced into clinical practice. The major challenge of clinical epileptology today is how to choose between these new and old AEDs in order to ensure optimal treatment for the individual patient.

Monotherapy studies comparing the efficacy and tolerability of the new AEDs with carbamazepine (as the standard reference old drug) demonstrate that most new AEDs[1-4] have a similar efficacy and in general are better tolerated than carbamazepine. In addition, it has not been possible to point out significant differences in efficacy between the new AEDs, at least when evaluated in patients with refractory partial epilepsy.[5] This means that the choice of AED in many situations depends on the tolerability profile of the drug, avoidance of physical and psychiatric adverse effects, and prevention of cognitive decline in individual patients. The fact that a considerable number of patients need AED therapy for many years, or for a lifetime, emphasises the need to focus on long-term adverse effects of the drugs. Disturbance of cognitive function is one of the major factors influencing quality of life (QoL) in individuals with epilepsy.[6,7]

In this article, we have reviewed studies that focus specifically on the effects of AEDs on cognitive function. In general, the studies use cognitive test batteries. However, cognitive data on lamotrigine and levetiracetam are very sparse, and therefore we also included QoL measures to the cognitive domain in the review of these drugs. The new drug felbamate is not reviewed in this article because of lack of data on its effects on cognitive function and because our personal experience with this drug is very limited. In addition, we have intentionally highlighted studies that have been designed to evaluate a proper comparison of cognitive test scores between old and new AEDs, even though there are very few such studies (table I).

We searched Medline via PubMed for studies up to May 2001 using the above mentioned drugs, and cognition, neuropsychology and quality of life as search terms. We included published studies including cognitive measures, and excluded studies based on small numbers of patients or studies with other major methodological problems. The reviews on old drugs and methodology are based on selected reviews and studies.

1. Methodological Considerations

Cognitive functions in individuals with epilepsy may be influenced by several factors of which basic neuropathology, seizures and the detrimental effect of AEDs are probably the most critical factors. When focusing specifically on the cognitive aspects of AED treatment it is important to realise that it can be difficult to isolate this issue from other aspects. Cognition, defined as the ability to retain, process and act upon information, depends on many factors in the person's overall physical and mental status (e.g. pain, arousal, sensation and emotion). AEDs can act on all of these factors and thereby indirectly affect the cognitive process. It means that the subjective complaints about cognitive deficits (e.g. memory problems or attention) of patients, may also reflect other aspects of adverse effects than specific cognitive functions. Even in objective neuropsychological tests, these other aspects will influence the measures. The use of neuropsychological testing, however, has been the major method of objectively measuring cognitive function related to the use of AEDs and approximately

Table I. Comparative studies of old antiepileptic drugs (AEDs) versus new AEDs in patients with epilepsy (pts) or healthy volunteers (vols) using neuropsychological tests

Reference	Drug (design)	No.	No. cognitive variables measured	Results
Äikiä et al., 1992[8]	PHT *vs* OXC (monotherapy)	29 pts	7	No significant difference
Kälviäinen et al., 1995[9]	CBZ *vs* VGB (monotherapy)	49 pts	19	VGB: improved on memory, psychomotor speed and flexibility of mental processing
Sabers et al., 1995[10]	PHT/PB/VPA/CBZ *vs* OXC (monotherapy)	52 pts	19	No significant difference
Akaho R, 1996[11]	PHT/VPA/CBZ *vs* ZNS (monotherapy)	48 vols	5	ZNS: reduced scores on WMS attention index
Dodrill et al., 1998[12]	PHT/VPA/CBZ *vs* TGB (monotherapy)	92 pts	19	TGB: improved on motorspeed, speed of reading, attention and verbal fluency
Meador et al., 1999[13]	CBZ *vs* GBP (monotherapy)	35 vols	31	GBP: significantly better performance on 8 variables
Aldenkamp et al., 2000[14]	VPA *vs* TPM (add-on CBZ)	53 pts	10	TPM: worsening on 1 variable (short term memory)
Dodrill et al., 2000[15]	PHT/CBZ *vs* TGB (add-on CBZ or PHT)	277 pts	19	Overall no significant difference
Meador et al., 2001[16]	CBZ *vs* LTG (monotherapy)	25 vols	40	LTG: significant better performance on 19 variables

CBZ = carbamazepine; **GBP** = gabapentin; **LTG** = lamotrigine; **OXC** = oxcarbazepine; **PB** = phenobarbital (phenobarbitone); **PHT** = phenytoin; **TGB** = tiagabine; **TPM** = topiramate; **VGB** = vigabatrin; **VPA** = valproic acid (sodium valproate); **WMS** = Wechsler Memory Scale; **ZNS** = zonisamide.

100 studies on this issue have been published during the last 30 years.

Despite this voluminous work, much uncertainty still exists with regard to the degree of cognitive effects of AEDs and whether there are significant differences in cognitive effects between the major AEDs.[17] The reason for this uncertainty is a result of a number of methodological problems, which are dealt with in several previous reviews.[17-20] The following major problems have been encountered: selection of participants used in the studies; the neuropsychological tests which have been applied; the study designs; and statistical factors.

1. The selection of participants in the studies dealing with cognitive effects of AEDs has differed in many aspects, i.e. healthy volunteers, newly diagnosed patients, patients with refractory epilepsy, patients in different age groups and with different levels of cognitive functioning. Results from one group cannot necessarily be generalised or compared with other groups. Studies on healthy volunteers tend to be acute or of relatively short duration, and thus are not comparable with the clinical situation. In addition, in some of the chosen samples seizures during the study period are a confounding factor because cognitive function can improve as a result of seizure reduction or deteriorate if seizures increase.[17]

2. The choices of neuropsychological tests used in the studies have not been uniform. Many different test batteries have been used, and the administration of tests and reporting of test results differ across the studies, which makes it impossible to make a qualified comparison of the results.[20] In many studies the chosen tests have only covered a few aspects of cognition, leaving out other and maybe important aspects, e.g. memory function.[19-21]

3. The study design represents the most troublesome aspect of methodology problems in the studies. The ideal design for studies on total cognitive effects in AED treatment would be randomised, double-blind, placebo-controlled monotherapy in seizure-free individuals with epilepsy, tested after several months of steady state treatment. The existing studies do not fulfil these criteria. Problems relate to a lack of control groups and non-

randomisation of the treatment. In addition, for practical and ethical reasons many studies investigate the target drug as add-on to the established treatment, which means that the results are often blurred by the effect of polytherapy.[17]

4. The major statistical problem in the studies relates to sample size. Most studies involve only a small number of participants and consequently they lack statistical power. This means that the statement 'no significant differences' may be false because, as a result of the small sample size, only large effects can be detected.[17] On the other hand 'false' significant differences can be found if a large number of comparisons are used.[17,19] A thorough review and analysis of the methodological problems in studies of cognitive effects of AED treatment has been completed by Vermeulen and Aldenkamp.[17]

2. Studies on Cognition and Individual Antiepileptic Drugs

Looking at the reviews of the large number of studies, it seems that only minor differences exist between the established drugs with regard to the effect on cognitive function, but the methodological problems give rise to major uncertainty in this respect. In the older reviews, the four major drugs phenytoin, phenobarbital, carbamazepine and valproic acid have been rated such that phenytoin and phenobarbital should be the most detrimental to cognitive function, and carbamazepine and valproic acid the least.[22-24] Some reviews have suggested that there might be different cognitive effects associated with the individual drugs:[22,25] phenobarbital being associated with mental slowing, attention deficits and memory problems; phenytoin with reduction in motor speed, problem solving and attention deficits; and carbamazepine with impaired motor tasks. However, these observations reflect the specific tests that showed significant reductions and not necessarily the cognitive functions affected in the individuals investigated. Whether the cognitive effects are non-specific 'mental slowing' or more specific deficits related to the action of individual drugs remains unsolved. Later studies[17,19,20,26] and a critical review of the old studies[27] have raised the question of whether any cognitive adverse effect was actually proven in the studies. In addition, they point out that there is a lack of evidence for differentiation between the drugs with regard to cognitive effects. In general, however, there seems to be an agreement that polytherapy and high-dose treatment can produce cognitive adverse effects.[18,28,29]

2.1 Oxcarbazepine

Oxcarbazepine is a keto-analogue of carbamazepine developed by modification of the chemical formula of carbamazepine with the aim of improving the tolerability profile. Clinical use demonstrates that oxcarbazepine is generally better tolerated than carbamazepine with at least similar efficacy.[1] The most commonly reported central nervous system (CNS) adverse effects are tiredness, headache, dizziness and ataxia.

Oxcarbazepine has been marketed in Denmark and a few other countries for more than 10 years, but only recently has the registration of oxcarbazepine been completed on a larger scale worldwide. Maybe this is the reason why data on oxcarbazepine and cognition is very sparse. Only two small studies have been published.[8,10]

In the study by Äikiä et al.,[8] 37 newly diagnosed patients were randomised to either oxcarbazepine or phenytoin monotherapy. Neuropsychological assessment was performed at baseline and after 6 and 12 months, measuring verbal memory, sustained attention and simple psychomotor speed. Twenty-nine patients (14 were in the oxcarbazepine group) completed the 12-months follow up (plasma concentrations of 10-hydroxy-oxcarbazepine were 30 to 120 μmol/L and of phenytoin were 40 to 80 μmol/L). The neuropsychological test scores did not reveal any differences between baseline and after 6 and 12 months for either drug. The study did not control for practise effect but the authors suggested that lack of practise effect might be an indicator of a possible negative effect on cognition related to the drugs.

In another study, oxcarbazepine was compared with carbamazepine, valproic acid, phenytoin and

phenobarbital monotherapy in 52 newly diagnosed patients (10 in the oxcarbazepine group).[10] Dosages used were oxcarbazepine 900 to 1200 mg/day, carbamazepine 450 to 800 mg/day, valproic acid 750 to 2500 mg/day, phenobarbital 50 to 150 mg/day and phenytoin 250 to 450 mg/day. Neuropsychological testing was carried out measuring verbal learning and retention, visual learning and retention, digit span, sustained attention, simple psychomotor speed, executive functions and constructional ability. In this study, also, the neuropsychological test performances were in general unchanged in all groups from baseline to after 4 months treatment.

2.2 Vigabatrin

Vigabatrin increases brain γ-aminobutyric acid (GABA) levels through a selective and irreversible inhibition of GABA-transaminase, the key enzyme in the breakdown of GABA.[30]

Vigabatrin has shown a promising profile concerning efficacy and tolerability, but the use of the drug has been very limited since the first case reports of vigabatrin-induced visual field defects were published in 1999.[31] This neurotoxic effect of vigabatrin seems to be a selective retinal problem. The most frequent CNS-related adverse events reported with vigabatrin therapy are drowsiness, dizziness, headache and irritability.[32,33] The adverse events are usually mild and transient, and do not seem to have negative influence on cognitive test scores.[34-40]

In a monotherapy study, the cognitive effects of vigabatrin were compared with those of carbamazepine in 100 patients with newly diagnosed epilepsy.[9] Mean daily dose of vigabatrin was 50 mg/kg. The serum carbamazepine concentrations were 35 μmol/L or lower. Cognitive tests were performed at baseline, after 3 months and after 1 year of treatment, measuring verbal fluency, verbal learning and retention, digit span, visual span, sustained attention, flexibility of mental processing, psychomotor speed and executive functions. Forty-nine successfully treated patients completed the 12-month follow-up. Acceptable seizure control was achieved in 60% of the patients in each group. Only in the carbamazepine-treated group were the majority of the patients actually seizure-free, which is a confusing factor for the test results. Cognitive test results after 1 year of treatment were in favour of the vigabatrin-treated group, who showed improvements in tests of memory, psychomotor speed and flexibility of mental processing. The carbamazepine-treated group showed no differences compared with baseline.

Possible cognitive effects of different dose regimens of vigabatrin were studied in two large double-blind, randomised, placebo-controlled, multicentre studies including 314 patients with refractory epilepsy.[36,37] The first study[36] compared vigabatrin 3 g/day with placebo, and in the second study[37] three groups treated with 1 g/day, 3 g/day and 6 g/day were compared with placebo. The patients were evaluated with eight cognitive tests and three tests of mood and adjustment. Cognitive tests measured verbal fluency, verbal learning and retention, visual learning, sustained attention, psychomotor speed and executive functions. Results of these tests at baseline compared with results after 12 weeks of treatment showed no substantial change, apart from the Digit Cancellation Test (measuring sustained attention in visual scanning), which showed a decrease in performance with increasing dosage.[37]

2.3 Lamotrigine

Lamotrigine is a chemically novel AED that acts by blockade of sodium channels with the result of concomitant inhibition of glutamate release.[41] The efficacy of lamotrigine in patients with partial seizures is comparable to carbamazepine, but it seems to have a more attractive profile with regard to CNS-related adverse effects; ataxia, sleepiness, dizziness and nausea being less frequent during lamotrigine treatment.[2,42]

Although lamotrigine has been widely used around the world for several years, only limited study data exist on cognitive test performances.

In a randomised, placebo-controlled, double-blind, crossover, add-on study in patients with refractory epilepsy, 54 patients completed a small

cognitive test battery including three tests of concentration and psychomotor performance.[43] The lamotrigine dosage was 400 mg/day (patients receiving enzyme-inducing drugs only) or 200 mg/day (patients receiving an enzyme-inducing drug and valproic acid). Patients were tested at baseline and at the end of each treatment period with no significant difference between lamotrigine and placebo shown. The same result was found in a number of small studies.[44-46] A comparative study comparing lamotrigine 150 mg/day and carbamazepine (mean dosage 696 mg/day) was conducted on 25 healthy adults, using a double-blind, randomised crossover design with two 10-week treatment periods. Cognitive tests measured attention/vigilance, cognitive and motor speed, memory, executive functions and subjective behavioural measures. Differences in favour of lamotrigine were shown in a broad spectrum of measures (19 of 40 total variables).[16]

Several studies have used QoL assessment or subjective reports and demonstrated a lack of cognitive adverse effects or even positive 'psychotropic' effects during treatment with lamotrigine compared with the traditional AEDs (carbamazepine, phenytoin, valproic acid).[16,47-50] In the double-blind, parallel study by Steiner et al.,[49] 181 patients with newly diagnosed epilepsy were randomised into two groups receiving either lamotrigine or phenytoin. The dosages used were lamotrigine 150 to 400 mg/day and phenytoin 300 to 600 mg/day. Health related QoL was examined by the side effect and life satisfaction (SEALS) inventory at baseline and after 4, 12 and 24 weeks' treatment. A slight improvement in the lamotrigine group was seen, whereas the phenytoin group showed a slight deterioration. Similar results were found in another large randomised study comparing lamotrigine with carbamazepine in newly diagnosed patients who were evaluated with SEALS.[50] Dosages were adjusted according to efficacy, adverse events and plasma concentrations, the median daily doses were lamotrigine 150mg or carbamazepine 600mg.[2] Patients were evaluated at baseline and after 4, 12, 24 and 48 weeks of treatment. 133 patients completed the study (73 lamotrigine, 60 carbamazepine). The cognition subscale as well as other subscales showed improvements in the lamotrigine group at 48 weeks compared to baseline. Deterioration in the cognitive subscale was seen in the patients randomised to carbamazepine.

It has been reported in several studies in mentally retarded children and adults that lamotrigine is associated with improved behaviour and alertness.[48,51-53]

2.4 Gabapentin

Gabapentin is a widely used AED with several pharmacological actions, including modulation of GABA and glutamate synthesis.[54] The mechanism of action, however, is not fully understood at present. CNS-related adverse events (dizziness, headache, somnolence) of gabapentin are minor even at high doses and with fast dose escalation.[4]

The cognitive effects of gabapentin 2400 mg/day were compared with carbamazepine (mean dosage 731 mg/day) in a double-blind, randomised crossover study on 35 healthy volunteers.[13] A neuropsychological test battery was administered at baseline and after a 5-week treatment period. Neuropsychological variables were attention/vigilance, dual task, cognitive/motor speed, memory, and executive functions. After a 1-month non-drug washout period the participants were retested. The procedure was duplicated after the second treatment and washout period. Gabapentin showed superiority compared with carbamazepine on eight out of 31 neuropsychological measures; however, compared to the non-drug period, gabapentin was favoured in one measure (verbal memory) but was inferior in four measures (speed and attention).

In a study by Mortimore et al.,[55] the cognitive effect of gabapentin was studied in 15 patients with epilepsy where gabapentin 1600 mg/day was add-on to the established AEDs. Fifteen patients who remained on stable medication were used as controls. The cognitive tests were administered at baseline and after 1 to 2 months of treatment. Neuropsychological variables were attention, cognitive/motor speed, verbal memory, executive functions and 'central integrative ability' (critical flicker fusion). In one of ten cognitive test results, a significant

between-group difference was found in favour of gabapentin [Stroop Neuropsychological Screening Test (SNST) word reading]. The remaining nine test results showed no significant differences.

A possible dose-related impact of gabapentin on psychomotor and memory functions was investigated by Leach et al.[56] in a double-blind, add-on, dose-ranging (1200, 1800 and 2400 mg/day), placebo-controlled, crossover study, completed by 21 patients with refractory partial seizures. Patients were tested at baseline and at the end of a 4-week period on a given dose. No significant differences were found between gabapentin and placebo. Similar results were found in a large multicentre, randomised, double-blind, dose-controlled study.[57] Cognitive functions were evaluated in 201 adults with uncontrolled partial seizures converted from one or two old AEDs to gabapentin 600, 1200 or 2400mg/day monotherapy. A group of placebo-treated patients from another study was used as a control. Cognitive tests measured verbal fluency, verbal learning and retention, visual learning, sustained attention, psychomotor speed and executive functions. After a 26-week treatment period no differences were seen between gabapentin and placebo.

2.5 Tiagabine

Tiagabine is a GABA-uptake inhibitor designed to reduce neuronal excitability by increasing the availability of GABA in the synaptic space. Tiagabine is generally well tolerated and adverse effects are most often mild, transient and CNS-related (e.g. dizziness, asthenia, somnolence).[58]

In the first study on the effect of tiagabine on cognitive function, 22 adult patients were evaluated with neuropsychological tests in a non-blind add-on trial, followed by a double-blind, placebo-controlled, crossover add-on trial in 12 patients (showing a response to tiagabine). The tiagabine dosage range was 16 to 52 mg/day during the fixed dose period and 20 to 40 mg/day during the double-blind period. Eleven patients completed the study. The cognitive tests included verbal learning and memory, semantic processing, attention, motor speed and reaction time. The cognitive evaluation did not find any significant effect in either the non-blind or double-blind phase.[59]

The long-term cognitive effects of tiagabine were studied in 37 patients in a double-blind, placebo-controlled, parallel-group add-on study followed by a non-blind extension study.[60] The tiagabine dosage during the double-blind phase was 30 mg/day and during the non-blind extension study was 24 to 80 mg/day. The neuropsychological test battery was administered at baseline and after a 12-week period on fixed dose. Twenty-five patients continued in a non-blind extension study with a third cognitive evaluation at 6 to 12 months after baseline. Fourteen continued to a fourth evaluation at 18 to 24 months after baseline. Cognitive tests measured general intelligence, verbal fluency, verbal and visual learning, and memory and attention. No significant changes of test scores were found compared with baseline.

In two multicenter studies Dodrill et al.[12,61] studied a possible dose-related impact of tiagabine on cognition. In the first study,[61] an add-on parallel study in 162 patients with focal epilepsy, they evaluated cognitive and QoL effects of three different dosages of tiagabine (16 mg/day, 32 mg/day and 56 mg/day) compared with placebo. Cognitive tests used measured verbal fluency, verbal learning and retention, visual learning, sustained attention, psychomotor speed and executive functions. Neuropsychological evaluation was conducted at baseline and after a 12-week fixed-dose period, and no clinically important changes were found with the addition of tiagabine in the three dose regimens. The second study[12] evaluated dose-related impact on cognition and mood in 123 adult patients treated with tiagabine, using the same cognitive test battery as in the first study. The patients were randomised to tiagabine 6 mg/day or 36 mg/day. In total, 92 patients achieved tiagabine monotherapy. No control group was used. Results for the whole group showed modest improvements with tiagabine in the cognitive domain (motor speed, speed of reading, attention and verbal fluency) compared with the more traditional AEDs (carbamazepine, pheny-

toin, valproic acid) given at baseline. However, the tiagabine group also showed one unfavourable change in adjustment and mood (diminished vigour). The most favourable results were found in the group of patients who achieved tiagabine monotherapy.

A multicenter study using the same cognitive test battery compared tiagabine with carbamazepine and phenytoin add-on to either carbamazepine or phenytoin monotherapy.[15] 153 patients receiving carbamazepine monotherapy were randomised to add-on phenytoin (up to maximum 600 or 1000 mg/day) or tiagabine (up to maximum 80 mg/day), and 124 patients on phenytoin monotherapy were randomised to add-on carbamazepine (up to maximum 2000 mg/day) or tiagabine (up to maximum 80 mg/day). After a 16-week double-blind treatment period, few or no differences were seen with tiagabine compared with add-on carbamazepine and add-on phenytoin.

2.6 Topiramate

Topiramate is a new potent AED with antiepileptic activity mediated by multiple mechanisms, e.g. blockade of voltage-dependent sodium channels and glutamatergic mechanisms, and potentiation of GABAergic mechanisms.[62] Topiramate has been associated with adverse effects on cognitive function as well as other CNS-related adverse effects (dizziness, fatigue, confusion, somnolence, abnormal thinking, ataxia, impaired concentration),[63] but it is uncertain to what degree these adverse events are related to dosage and fast dose-escalation. Word finding difficulties seems to be a fairly specific problem with topiramate and is reported in up to one-third of the patients.[64]

Only a few studies describe neuropsychological test measurements of cognitive function during topiramate treatment. The possible impact of topiramate on attention was studied in ten patients with epilepsy over a 3-month period.[65] Attention was evaluated at weekly intervals, using digit span forwards and backwards. Add-on dosage of topiramate varied over the period according to clinical considerations but the average dosage for the ten participants was between 100 and 355 mg/day. In four of nine participants, higher topiramate dosage was associated with lower digit span forwards.

In a study on cognitive function in healthy volunteers, topiramate was compared to gabapentin and lamotrigine.[45] Seventeen participants were divided into three groups and received on average topiramate 2.8 mg/kg, gabapentin 17 mg/kg or lamotrigine 3.5mg/kg per day. Cognitive tests and Profile of Mood States (POMS) were administered at baseline, acutely (3 hours after medication), and after 2 and 4 weeks of receiving the drug. The cognitive tests used measured verbal fluency, verbal learning and retention, sustained attention, and psychomotor speed. Only the group treated with topiramate showed significant cognitive decline acutely and after 2 and 4 weeks. The study has been criticised for the small sample size, dosage size and administration, and the rather short test interval.[66,67]

In a recent multicentre study, topiramate was compared with valproic acid in 53 patients.[14] Both drugs were add-on to carbamazepine. To reduce the risk of adverse effects as a result of fast dosage escalation, topiramate was gradually introduced starting at 25 mg/day and was then increased weekly by 25 mg/day to a minimum of 200 mg/day. Target dosage of topiramate was 200 to 400 mg/day compared with valproic acid 1800 mg/day. Cognitive tests measured verbal learning and retention, simple and selective reaction time, sustained attention, visual searching task and psychomotor speed. The differences found between the two treatments were small from baseline to endpoint (20 weeks). Only one of ten cognitive test measures (a test on short-term verbal memory: Rey Auditory Verbal Learning) worsened with topiramate therapy. From baseline to end of titration (8 weeks), another test on short-term verbal memory (recognition of words) showed a change in negative direction with topiramate.

Thompson et al.[68] performed a retrospective study, evaluating neuropsychological test results from topiramate treatment in clinical practice. Eighteen patients were tested before and during steady state (minimum 3 months) topiramate treat-

ment and were matched with 18 controls. Cognitive tests measured intellect, verbal fluency, language, visual perception, and verbal and spatial learning and retention. The topiramate dosage was 125 to 600mg/day. In accordance with the patients' subjective complaints, the authors found a decline in verbal functions during topiramate treatment (verbal fluency most prominent). Retest on 8 patients after discontinuation or reduction of topiramate dosage showed improvement on all test measures. The retest effect was not compared with a control group. The authors stated that the study had considerable methodological limitations in not being a prospective, randomised, controlled trial.

2.7 Levetiracetam

Levetiracetam is a pyrrolidone derivative resembling piracetam, which is one of the 'nootropic' drugs, primarily investigated for a possible enhancing effect on cognition.[69] The antiepileptic mode of action has not been fully elucidated but the finding that levetiracetam only inhibits epileptiform burst firing without affecting normal synaptic transmission[70] makes it probable that this is an AED with no or minimal cognitive adverse effects. However, this issue needs to be more thoroughly investigated. Asthenia and somnolence are the most frequent CNS-related adverse effects reported from the clinical use of levetiracetam.[71]

At the present time, only one study has been published evaluating levetiracetam with the use of cognitive tests.[72] In this single-blind, add-on, dose-escalation study, 10 patients with chronic epilepsy were evaluated with cognitive tests after levetiracetam treatment. Examination on neuropsychological functions included subtests from the comprehensive neuropsychological test battery 'FePsy' measuring memory, attention and speed. Three examinations were performed: at baseline; after one week of levetiracetam 500 mg/day (followed by 2 weeks washout period); and finally after one week of levetiracetam 1000 to 1500 mg/day. Small improvements were seen on tapping rate nondominant hand, selective reaction time, and memory for simultaneously presented words. The study did not include a control group.

QoL during levetiracetam treatment was investigated by Cramer et al.[73] in a randomised, placebo-controlled, double-blind add-on trial, which included 246 patients without adequate seizure control. A self-administered questionnaire (qolie 31) was used to measure changes in QoL (including cognitive functions) after 18 weeks treatment with levetiracetam 1 g/day or 3 g/day, or placebo. At follow up, the sub-scale 'cognitive functions' showed a significant improvement in both levetiracetam treatment groups compared with placebo. This effect was mainly related to seizure reduction in the levetiracetam-treated groups, but a difference in favour of levetiracetam was still found comparing the non-responder groups, especially in the high dose group.

2.8 Zonisamide

Zonisamide is a synthetic benzisoxazole derivative which shows an antiepileptic profile with a broad spectrum of activity. The mechanism of action is not completely understood but it appears to act by reducing spread of seizure discharges, probably through suppressing T-type calcium and sodium channels.[74] In the Japanese clinical trials, the major CNS-related adverse events were drowsiness and ataxia.[75]

Cognitive effects of zonisamide were first investigated by Berent et al.[76] in a small pilot study in nine patients with refractory partial seizures. Zonisamide was administered as an add-on to the established treatment with either two or three standard AEDs, and the dosage adjusted to achieve a plasma concentration of 15 to 40 mg/L. Cognitive tests, measuring learning and retention (Wechsler Memory Scale; WMS), Wechsler Adult Intelligence Scale (WAIS) - Vocabulary and Arithmetic, simple and selective reaction time, sustained attention, strength of grip and psychomotor speed, were administered at baseline and after 12 and 24 weeks of treatment. Compared with baseline, four of 15 tests showed worsening after 12 weeks of zonisamide treatment, whereas after 24 weeks no significant

differences were found. The reduced test scores were related to verbal and non-verbal memory. The results of the study are blurred by several methodological problems, including sample size, lack of a control group and possible drug interactions.

Akaho[11] assessed cognitive function in 48 healthy volunteers using event-related potentials and cognitive tests from the WMS. Carbamazepine 400 to 800 mg/day, phenytoin 200 to 250 mg/day, valproic acid 800 mg/day and zonisamide 200 to 400 mg/day were evaluated in a placebo-controlled, double-blind, crossover design conducted over one week. Comparing endpoint to baseline, zonisamide showed reduced scores on the Attention Index from WMS. Carbamazepine, phenytoin and valproic acid showed no significant changes on WMS.

3. Conclusion

Several studies have examined the established old AEDs but no certain conclusions have been reached as to what degree individual drugs have an effect on cognition. Data regarding the cognitive effects of the new drugs are sparse. Studies have been performed on most of the new drugs, but in many instances only in small samples, and generally with the same methodological problems as in the studies on established drugs. Only suggestions about differences between the drugs can be given. Among the new AEDs, topiramate seems to be troublesome in some of the studies, at least in the initial treatment phase, if given in high doses or by rapid titration. Whether any differences exist between topiramate and other new drugs in steady-state treatment is a point of controversy. The other new AEDs have not displayed important cognitive effects in studies using neuropsychological tests. In studies in which new AEDs are compared with old AEDs, there is a tendency in favour of the newer agents in some of the studies.[9,12,13,67] This is demonstrated in neuropsychological testing by improvement in test scores for the new drugs compared to 'no significant differences' for the old ones, although the differences are small. The 'new drug superiority' is also found in some of the studies[49,50] looking at subjective complaints of cognitive effects, but this finding may also reflect other aspects of QoL as mentioned in section 1. In general, it should be noted that the scientific evidence for differentiating between the different AEDs is modest and does not give rise to any certain conclusions.

The lack of evidence for cognitive effects may be the result of the methodological problems and limitations in the existing studies. Some of the most important questions are whether the cognitive tests actually measure cognitive phenomena of clinical significance, and whether the methodological difficulties are to big to meet the challenges in measuring small or medium cognitive effects of the AEDs.

There is no doubt that cognition holds an important place in QoL aspects of epilepsy. Cognitive function in patients treated with AEDs will, therefore, still be an important matter of concern, and a theme which should continue to be discussed and examined.

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