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### Summary

Antiepileptic drugs (AED) alter neuronal excitation levels and may result in neurocognitive changes. In recent years several new AEDs have been introduced which additionally are used to treat mood disorders, neuropathic pain, and migraine. Generally, very few controlled trials have systematically examined the neurocognitive side effects of AEDs. In particular, polytherapy with the newer AEDs is underinvestigated. In this paper we review the most relevant data on neurocognitive side effects of AEDs in current use in Switzerland for the long term treatment of epilepsies.

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**Key words:** Cognition, side effects, antiepileptic drugs

### Neurokognitive Wirkungen von in Langzeittherapie häufig verwendeten Antiepileptika: eine Übersicht

Antiepileptika modulieren die neuronale Aktivität und können neurokognitive Prozesse beeinflussen. Zahlreiche neue Antiepileptika wurden in den letzten Jahren eingeführt. Einige dieser neuen, aber auch ältere Präparate werden zur Behandlung von affektiven Störungen, neuropathischem Schmerz und neuerdings zur Migräneprophylaxe eingesetzt. Vor dem Hintergrund der hohen Prävalenz von Epilepsie und auch nicht-epileptologischen Indikationen von Antiepileptika muss man konstatieren, dass nur wenige Studien zu möglichen neurokognitiven Effekten den Standards evidenzbasierter Medizin genügen. Insbesondere fehlen Studien zur Polytherapie mit neuen Antiepileptika. Dieser Artikel gibt eine aktuelle Übersicht zu neurokognitiven Effekten von Antiepileptika, die zur Langzeittherapie der Epilepsie in der Schweiz eingesetzt werden.

**Schlüsselwörter:** Kognition, Nebenwirkungen, Antiepileptika

### Aperçu des effets neurocognitifs d'antiépileptiques fréquemment utilisés dans les traitements épileptiques au long cours

Les antiépileptiques modulent l'activité neuronale et peuvent influencer des processus neurocognitifs. De-

puis quelques années, les introductions de nouveaux antiépileptiques se succèdent à intervalles rapprochés. Certains de ces nouveaux produits, ainsi que d'autres déjà plus anciens, sont utilisés pour le traitement de troubles affectifs, de douleurs neuropathiques, et plus récemment aussi dans la prophylaxie de la migraine. Compte tenu de la forte prévalence d'indications des antiépileptiques dans le traitement de l'épilepsie ainsi que non-épileptologiques, force est de constater que très peu d'études seulement sur les effets neurocognitifs potentiels suffisent aux normes d'une médecine basée sur l'évidence. Il manque en particulier des études sur la polythérapie au moyen des nouveaux antiépileptiques. Le présent article fait un tour d'horizon des effets neurocognitifs d'antiépileptiques utilisés en Suisse pour le traitement au long cours de l'épilepsie.

**Mots clés :** cognition, effets secondaires, anti-épileptiques

### 1. Introduction

Cognitive impairment as a secondary consequence of epilepsy is a common occurrence [1]. In general, cognitive impairment in epilepsy results from a variety of interacting factors, namely aetiology, age of onset, type of epilepsy, type of seizures, seizure frequency, seizure duration, seizure severity, duration of epilepsy, and cognitive side effects of antiepileptic drugs (AED) [2]. Although the usefulness of AED therapy for seizure control is undisputed, there is evidence that several AEDs may contribute to or aggravate cognitive problems in some patients. Deficits in both global mental functions, such as consciousness, energy, and drive, and specific cognitive functions, such as attention, memory, and language may be more debilitating than the seizures themselves in certain patients and circumstances.

Because of the growing number of competing AEDs consideration of not only their efficacy and tolerability but of their cognitive side effects has become increasingly essential when selecting AEDs and in optimising compliance in long term treatment. To reduce adverse effects and to prescribe the most favourable AED to a patient, the prescriber requires a profound knowledge about the side effects of an increasing number of available AEDs. In addition, since AEDs are also used in the treatment of various other disorders such as neuropathic pain, mood disorders, and recently, migraine, the issues of neurocognitive AED effects have to be recog-

## Abbreviations

AED	= Antiepileptic drug
CalCAP	= California Computerized Assessment Package
CBZ	= Carbamazepine
CLZ	= Clozapine
COWAT	= Controlled Oral Word Association Test
CRT	= Choice Reaction Time
FL	= Fluency
GABA	= Gamma-aminobutyric acid
GBP	= Gabapentin
IQ	= General intelligence
HLS	= High-level Speed
IR	= Interference Resistance
LEV	= Levetiracetam
LLS	= Low-level Speed
LPS	= Leistungsprüfungssystem
LTG	= Lamotrigine
LTM	= Long-term Memory
OXC	= Oxcarbazepine
PB	= Phenobarbital
PGB	= Pregabalin
PHT	= Phenytoin
PIQ	= Performance Intelligence Quotient
PRM	= Primidone
QOLIE	= Quality of life in epilepsy
RT	= Reaction time
TMT	= Trail Making Test
TPM	= Topiramate
VIQ	= Verbal Intelligence Quotient
VPA	= Valproate
WCST	= Wisconsin Card Sorting Test
WISC-R	= Wechsler Intelligence Scale for Children-Revised
WM	= Working Memory
ZNS	= Zonisamide

nised beyond the boundaries of epileptology. The aim of this review is to provide the reader an update of recent research about the cognitive side effects found in the most frequently used AEDs in long term treatment.

## 2. Methods

Potentially relevant studies were identified via a Medline database search and epilepsy journals. The inclusion criteria were available full text articles in English published after 1985. Furthermore, we followed an evidence-based approach meaning that only randomised clinical trials or placebo-controlled studies with psychometrically assessed cognitive functions were selected.

Recent statistics from the retail market provided by IMS Health GmbH show that lamotrigine (LTG), valpro-

ate (VPA), and carbamazepine (CBZ) are the most frequently used AEDs in Switzerland for long term treatment of epilepsies followed by levetiracetam (LEV), oxcarbazepine (OXC), topiramate (TPM), and gabapentine (GBP). Pregabalin (PGB), phenytoin (PHT), phenobarbital (PB), primidone (PRM), and zonisamide (ZNS) are less frequently prescribed. Medications in this review are presented in alphabetical order, IUPAC (International Union of Pure and Applied Chemistry) nomenclature is enclosed in parentheses. For each AED trade name in Switzerland and indication as described in Documed (Documed AG, Basel 2005), mechanisms of action, absolute and relative side effects on cognition, relative effects compared with other AEDs, and dose effects on cognition are listed. If existent, placebo-controlled, randomised, double-blind studies investigating absolute side effects of an AED are presented in more detail in a table whereas clinical trials are described in the text. In the case of several clinical trials investigating the same drug, current representative studies have been selected for citation.

The main challenge for anyone wishing to systematise data from different studies on neurocognitive AED effects is the use of a plethora of neuropsychological tests. To integrate and systematise results from different studies, we assigned the various psychometric measures used by the different investigations to five cognitive domains, two frequently used tasks, and general intelligence which lead to the following seven categories:

1. *Low Level Speed (LLS)*: speed tasks that do not require cognitive decisions (e.g. finger tapping)
2. *High Level Speed (HLS)*: speed tasks that require cognitive decisions (e.g. choice reaction time, digit cancellation etc.)
3. *Working Memory (WM)*: classical working memory tasks (e.g. digit span backwards) and short-term memory (e.g. immediate recall)
4. *Long-term Memory (LTM)*: verbal and nonverbal memory tasks with delayed recall
5. *Verbal Fluency (FL)*: generative tasks that require divergent thinking and are considered to be measures of executive functions (e.g. letter fluency, Controlled Oral Word Association Test (COWAT))
6. *Interference Resistance (IR)*: a measure of attentional resistance against interfering stimuli (Stroop Test)
7. *General Intelligence (IQ)*: tests providing a measure of intelligence (e.g. Raven's Matrices, Wechsler Intelligence Scale).

### 3. Side Effects of Antiepileptic Drugs

#### 3.1 Carbamazepine [(Z)-5H-dibenzo[b,f]azepine-5-carboxamide]

*Indication:* CBZ is available as Carsol<sup>®</sup>, Neurotop<sup>®</sup> retard, Tegretol<sup>®</sup>, and Timonil<sup>®</sup>/- retard. It is indicated for use as an anticonvulsant drug, in the treatment of pain associated with true trigeminal neuralgia, and in the treatment of mania, bipolar disorders, and in alcohol withdrawal syndrome. In epilepsy, CBZ can be prescribed to children and adults and may be used alone or with other anticonvulsants.

*Mechanism of action:* The main action of CBZ is inhibition of voltage-activated sodium channels and, consequently, inhibition of action potentials and excitatory neurotransmission. Therefore, high-frequency, repeti-

tive neuronal firing is limited [3].

*Absolute effects:* A randomised, double-blind, placebo-controlled withdrawal study with 93 adults with epilepsy found a significant improvement after 7 months in different speed-related measures in the discontinuation group but not in the non-discontinuation group (table 1) [4]. Notably, in two withdrawal studies with children (N=25) and adults with epilepsy (N=18) respectively, no main effect of CBZ on cognitive functioning was found [5, 6]. However, in three clinical trials a total of 75 healthy subjects were treated over 5 to 10 weeks with CBZ. After medication, a decline in some HLS tasks and in verbal short term memory was reported. Results on LLS, LTM, and IR were contradictory [7-9]. In summary, there is some evidence that CBZ influences processing speed for low and high level tasks and verbal short term and working memory. For LTM and IR the results are contradictory and IQ does not seem to be in-

**Table 1:** Overview of studies. For details refer to the text. Only randomised, double-blind and placebo-controlled

AED	Study	Design	Subjects	Mean dose [mg/day]
CBZ	Hessen et al., 2007	Withdrawal	93 EA	n.a.
GPB	Salinsky et al., 2005	Parallel group	24 HA	3600
LTG	Zoccali et al., 2007	Parallel group Add-on (CLZ)	51 PA	200
	Aldenkamp et al., 2002	Parallel group	20 HA	50
	Smith et al., 1993	Crossover Add-on (various)	62 EA	400
LEV	Zhou et al., 2008	Parallel group	24 EA	3000
		Add-on (various) Not blinded		
PGB	Hindmarch et al., 2005	Crossover	23 HA	150
TPM	Salinsky et al., 2005	Parallel group	23 HA	330
VPA	Hessen et al., 2006	Withdrawal	33 EA	n.a.
	Aldenkamp et al., 2002	Parallel group	20 HA	900
	Thompson et al., 1981	Crossover	10 HA	1000

Subjects: number of participants; E=epilepsy, P=psychiatric; O=other, H=healthy; A=adult, E=elderly; C=children

fluenced by CBZ.

*Relative effects:* In studies with healthy subjects, the CBZ group performed worse than the GBP, LEV, and OXC groups in several tasks with a speed component [7, 8, 10]. Depending on the study, the medication phase lasted 8 days to 5 weeks. Additionally, Meador et al. found worse performance in WM, LTM, and IR in the CBZ as compared to the GBP group [8]. Comparing CBZ to PHT in healthy volunteers and patients with epilepsy, respectively, treatment with PHT turned out to have a more disadvantageous impact on LLS and HLS than CBZ treatment [11, 12]. Gillham et al. found an impairment, although at a low level of significance, in HLS in patients with epilepsy taking CBZ compared to those taking VPA [13]. In other neuropsychological functions such as WM, LTM, and IQ, CBZ seemed to exhibit the same profile as GBP, PHT, PB, OXC, and VPA [6, 7, 14, 15]. Compared to LTG, the side effect profile of CBZ is unfavourable.

Meador et al. conducted a double-blind, randomised crossover study with 25 healthy volunteers. After 10 weeks of medication with either medication subjects showed worse performance after CBZ in some speed relevant tasks, in verbal short term memory, and in verbal LTM [9]. Kang et al. compared the cognitive effects of CBZ with TPM in 88 children with epilepsy and reported significantly better results for the CBZ group in two subtests (arithmetic and the maze) of the Korean version of the Wechsler Intelligence Scale for Children-Revised (WISC-R). Unfortunately, the test battery used consisted only of the WISC-R and the Bender Gestalt Test [16]. An analysis with pooled data from two randomised studies comparing cognitive effects of TGB and CBZ in adults with epilepsy revealed no significant differences between the TGB and CBZ group in LLS, HLS, WM, LTM, FL, IR, or IQ [17]. Dodrill et al. conducted a randomised, double-blind clinical trial comparing CBZ

studies are listed in this table. Studies that do not fulfil the criteria are described in the text.

Duration of treatment	Altered cognitive functions	Unchanged cognitive functions
12 months	HLS (-)	LLS, HLS
12 weeks	---	LLS, HLS, LTM, FL, IR, IQ
24 weeks	FL (semantic) (+)	FL (phonemic), IR
12 days	LLS (auditory RT) (+)	LLS (visual RT), HLS, WM
18 weeks	---	HLS, IR
16 weeks	HLS (WCST) (+), LTM (+)	HLS, WM, LTM, FL, IR, IQ
3 days	---	HLS, WM
12 weeks	HLS (digit symbol, Stroop words) (-) LTM (story recall delayed), WM (-) FL (-)	LLS, HLS (digit cancellation, divided attention task) LTM (selective reminding test) IR, IQ
12 months	HLS (CalCAP: response reversal word, form discrimination) (-)	LLS, HLS (CalCAP: CRT, sequential RT, language discrimination, degraded words distract)
12 days	LLS (visual RT) (-)	LLS (auditory RT), HLS,
2 weeks	HLS (decision making for colour or category) (-)	WM LLS, HLS (visual scanning, perceptual speed), WM, LTM, IR

and TGB as add-on therapy on PHT in 124 adults with epilepsy. After 16 weeks of treatment, the TGB group performed significantly better in a HLS task and FL than the CBZ group [18].

*Dose effects:* A randomised, placebo-controlled, double-blind cross-over study with 10 elderly patients with epilepsy failed to find dose related effects of CBZ on LLS, HLS, WM or IQ [19].

### 3.2 Gabapentin [2-[1-(aminomethyl)cyclohexyl]acetic acid]

*Indication (Neurontin):* The agent GBP is contained in Gabapentin®, Gabapentin-Mepha®, Gabapentin Sandoz® and Neurontin®. It is indicated in epilepsy as a monotherapy in patients older than 12 years with focal seizures with or without secondary generalization. GPB can be prescribed as add-on therapy to children older than 3 years with focal seizures. Additionally, GBP is used in the treatment of neuropathic pain in diabetic neuropathy or postherpetic neuralgia in adults.

*Mechanism of action:* Despite having a very similar structure to GABA (Gamma-aminobutyric acid), GBP does not bind on GABA receptors directly but rather enhances the GABA system indirectly via potentiation of GABA release and inhibition of GABA transaminase. There are also demonstrated effects on both sodium and calcium ion channels and inhibition of glutamatergic release [20].

*Absolute effects:* GBP is considered to be a drug with a mild cognitive profile. This has been found in multiple studies using both patients with epilepsy and healthy volunteers. In a large double-blind multicenter study conducted by Dodrill et al., 201 patients suffering from complex partial seizures were tested on all main neuropsychological functions before and again 26 weeks after receiving GBP as monotherapy. They found no overall changes in all main tasks of cognitive functioning (HLS, LLS, WM, LTM, FL, IR, and IQ) [21]. Salinsky and colleagues conducted two studies that included a total of 28 healthy subjects taking a relatively high dose of 3600mg GBP. Again, neuropsychological scores collected 12 weeks after initiation revealed no impairments in all 7 categories tested (**table 1**) [15, 22].

While a number of studies found no impairments in tests measuring psychomotor speed or immediate or delayed recall [15, 21, 23], Meador et al. found both slower reaction times (HLS) and impaired recall scores (LTM) in 35 healthy subjects after 5 weeks of administration of GBP [8]. This conflicting data is also seen in IR. In a study by Mortimore et al., 15 patients with epilepsy showed worse performance, but in many other studies, performance in the Stroop test was not affected by GBP [23, 24].

*Relative effects:* When compared with CBZ, studies almost uniformly report better results for GBP. In three randomised, double-blind studies including one with a

crossover design, 73 healthy subjects who received GBP scored better in the majority of neuropsychological tests, including LLS, HLS, WM, LTM, FL, and IR [7, 8, 15]. Two randomised studies used TPM as a comparison drug and both observed a favourable profile for GBP. Salinsky et al. tested 39 healthy subjects after 12 weeks of treatment and found scores of HLS, LTM, and FL to be better in the GBP group. Similar results have come from Martin et al., finding better outcomes for HLS and LTM when treated with GPB [22, 25].

Taken together, there is a wealth of reliable data suggesting a very mild cognitive profile for GPB and predominance of GPB over CBZ and TPM in LLS, HLS, WM, LTM, FL, and IR.

*Dose effect:* Two studies focussed on possible correlations of drug concentration level and performance. Mortimore et al. found that, although not significant, LTM performance positively correlated with serum levels in a delayed recall test [24]. On the other hand, Salinsky et al. found no effects of dose-dependency with a relatively high dose of 3600 mg [15], and Leach et al. used an increasing dosage interval design every 4th week and found no correlation whatsoever [23].

### 3.3 Lamotrigine [6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine]

*Indication (Lamictal):* There are five different drugs with LTG as an agent: Lamictal®, Lamotrigin Desitin®, Lamotrigin Helvepharm, Lamotrigin Sandoz, and Lamotrin-Mepha®. LTG is indicated in epilepsy as mono- or add-on therapy in patients older than 12 years for the treatment of partial epilepsy with or without secondary generalised tonic-clonic seizures. As add-on therapy LTG is indicated in children aged 2-12 years with partial epilepsy. It is not recommended as initial monotherapy in children. Moreover, LTG serves in the prevention of depressive episodes in bipolar disorders in adults.

*Mechanism of action:* LTG inhibits voltage-gated sodium channels, with pronounced preference for channels in rapidly firing neurons. LTG also inhibits voltage-operated calcium channels, resulting in reduced glutamate release, thus preventing neuronal activity. In addition, LTG shows double the potency in inhibiting glutamate release than inhibiting GABA release [26].

*Absolute effects:* There are many studies with both patients and healthy volunteers that uniformly indicate a good cognitive profile for LTG. Placebo-controlled crossover studies found little or no difference in performance under LTG as compared to the non-drug condition (**table 1**) [27, 28].

In a recent study, Zoccali et al. administered LTG to psychiatric patients as an add-on to Clozapine (CLZ) and they showed better scores in FL compared to the placebo treated group (**table 1**) [29]. In an add-on study by Placidi et al., performance of 13 patients with epilepsy

showed no difference 3 months after initiation of treatment with LTG in HLS, WM, or LTM [30]. In two crossover studies with a total of 71 healthy adults, Meador et al. found that only 26 of 40 variables favoured the non-drug group. More importantly, subjects scored better in 10% of the tests when treated with LTG. These included psychomotor speed (reading) and FL [9, 31]. Also Aldenkamp et al. found faster LLS scores in 20 healthy subjects. However, this was seen only in the auditory but not in the visual reaction time task (table 1) [32]. Smith et al. investigated 62 adults with epilepsy and found no differences in scores of HLS (choice-reaction and digit cancellation) or IR (table 1) [27]. Depending on the specific test that was conducted to measure HLS, studies show conflicting results [28, 31, 32]. The same holds true for memory-related tasks (LTM) [28, 32], or IR [29].

In summary, these discrepancies suggest that LTG has a very subtle effect on cognition which is likely to be counterbalanced by interindividual compensatory mechanisms, thus suggesting that LTG has a mild or even absent impact on cognition.

*Relative effects:* Compared to other AEDs, LTG shows a clearly favourable profile in the majority of the cognitive tasks studied. In three crossover studies with a total of 109 healthy subjects who took LTG better performance was reported in the majority of the neuropsychological tests (LLS, HLS, WM, LTM, FL, IR) when compared to TPM [31, 33] or CBZ [9]. In comparison to TPM, healthy subjects receiving LTG were faster and more precise in tests measuring high level psychomotor functions [32, 34]. In a double-blind multicenter study 124 patients with epilepsy randomly received either LTG or TPM as an add-on medication. Scores on retests 16 weeks after initiation favoured LTG over TPM in LLS, HLS, LTM and IR [35].

### 3.4 Levetiracetam [(2S)-2-(2-oxopyrrolidin-1-yl)butanamide]

*Indication:* The substance LEV is contained in the drug Keppra®. It is an anticonvulsant prescribed as mono- or add-on therapy in partial seizures with or without secondary generalisation and as add-on therapy in juvenile myoclonic epilepsy. Depending on the type of epilepsy, Keppra® can be used in children older than 4 years and adults.

*Mechanism of action:* The mechanism of action of LEV is not completely understood, but it is suggested that it is essential in the control of exocytosis and may prevent the exocytosis of glutamate. LEV may also influence GABAergic activity by increasing chloride currents [3].

*Absolute effects:* An add-on study with systematic data collection of 24 adults with epilepsy showed an improvement in the Wisconsin Card Sorting Test (WCST) and in verbal LTM functions after a 12 week period at the maximum LEV dose (1500mg/day) compared to pla-

cebo. The authors could not find any difference between the LEV group and the placebo group in HLS, WM, visual LTM, FL, or IR (table 1) [36]. Apart from this study, only a few studies have investigated the cognitive side effects of LEV and little information exists as to the effects of LEV on cognition. In three clinical trials with patients suffering from epilepsy, no difference in any cognitive function after medication with LEV was reported [37-39]. One clinical trial with 28 healthy subjects found a decline in HLS after 4 weeks of medication with LEV (2000mg/day) [40]. To summarise, improved or stable performance has been shown for LEV in a number of studies with patients suffering from epilepsy. A decline in HLS was reported by one clinical trial with healthy subjects.

*Relative effects:* Compared to other AEDs, the side effect profile of LEV is very favourable. In an unblinded study without randomisation, Gomer et al. compared LEV to TPM in 51 adults with epilepsy and found better results for LEV in HLS, FL, and verbal and spatial short term memory [38]. Mecarelli et al. reported that healthy adults on OXC and LEV showed the same performance in LLS and IR, whereas CBZ resulted in worse performance in some speed relevant tasks and failed to show, as seen with LEV and OXC, an improvement in IR [10]. In another study with healthy adults, the CBZ group showed worse performance in HLS, than the LEV group [40]. In a clinical trial, the short term impact of LEV and PGB on cognition was examined in 20 adult patients with medically refractory partial epilepsy before and shortly after add-on titration. Patients were not randomly assigned to the treatment arms. All measured functions, such as HLS, WM, LTM, FL, and IQ, revealed no significant differences between the two drugs. Tendencies in favour of LEV were found in visual short term memory and verbal LTM [37].

### 3.5 Oxcarbazepine [10,11-Dihydro-10-oxo-5 H -dibenz(b,f)azepine-5-carboxamide]

*Indication:* Trileptal®, the drug with OXC as the active pharmaceutical ingredient, is indicated in partial seizures with or without secondary generalised tonic clonic seizures and in generalised tonic clonic seizures. OXC can be prescribed to children older than 1 month and adults and can be taken as mono- or combination therapy.

*Mechanism of action:* OXC is a non-toxic derivative of CBZ. Nevertheless, its biotransformation pattern is different. OXC has demonstrable effects on neuronal ion channels [41]. The main action is inhibition of voltage-activated sodium channels and, consequently, inhibition of action potentials and excitatory neurotransmission [3].

*Absolute effects:* There is a lack of systematic research with placebo-controlled studies on the cognitive side effects of OXC. In a clinical trial with 70 chil-

dren with benign childhood epilepsy, Tziritidou et al. found a slight improvement in full-scale and performance IQ (PIQ), due to improvement in three subtests, after 18 months of medication with OXC and no difference in verbal IQ (VIQ) [42]. Consistent with these results, Donati et al. investigated the cognitive effects of OXC in 47 children with a history of at least two unprovoked partial seizures and reported a trend toward improvement in a computerised visual searching task and in the Raven's Matrices after 6 months of medication [14]. However, in a study with 14 healthy subjects after 12 weeks of medication, a decline in WM and IR was reported along with unclear results in LLS and HLS and no difference in LTM and IQ [43]. In summary, treatment with OXC seems to have a positive effect on non verbal intelligence and on some components of HLS in children with epilepsy. Treatment using OXC in healthy subjects appeared to have adverse effects on WM and IR and no effects on LTM and IQ.

*Relative effects:* Comparing the cognitive side effects of OXC to CBZ and VPA in children with epilepsy, all three drugs seem to have similar effects on LLS, HLS, WM, LTM and nonverbal IQ [14, 43]. However in healthy subjects, CBZ showed more unfavourable effects on LLS and IR than OXC, whereas LEV did not differ from OXC in these two functions [10]. Furthermore, two clinical trials found no differences in LLS, HLS, WM, LTM, and IR with PHT or OXC in healthy subjects and patients with epilepsy, respectively [43, 44].

### 3.6 Phenobarbital [5-ethyl-5-phenylpyrimidine-2,4,6(1H,3H,5H)-trione]

*Indication:* Phenobarbital is available as Aphenylbarbit, Luminal, and Phenobarbital 50 Hänseler. It is indicated in epilepsy, in states of agitation, febrile convulsions, and as an adjunct in the treatment of withdrawal symptoms. PB is administered to adults; treatment with PB is not recommended for children.

*Mechanism of action:* PB and other barbiturates exert their antiepileptic effect primarily by enhancing the activation of GABA receptors. They increase the mean channel open duration without affecting open frequency or conductance [45]. This process results in an increased chloride influx and hyperpolarises the postsynaptic neuronal cell membrane, hence impeding the transmission of epileptic activity.

*Absolute effects:* There is no current systematic research with placebo-controlled studies regarding the cognitive side effects of PB. Clinical studies show conflicting results. PIQ in children with epilepsy seems to improve after withdrawal of PB [46, 47]. In addition, some evidence exists for an improvement in HLS and mental flexibility (cancellation test, Trail Making Test (TMT)) following discontinuation of PB [5, 46]. Due to the paucity of research on the cognitive side effects of PB a final conclusion can not be reached at this point.

*Relative effects:* One study with 59 healthy subjects taking PB showed impairments in HLS compared to those taking VPA and PHT. In other cognitive functions, such as LLS, WM, LTM, and IR, there were no differences found between the 3 treatments [48]. In a randomised clinical trial and a clinical withdrawal study investigating 73 and 70 children with epilepsy treated respectively with CBZ, PB or VPA, Chen et al. found no differences in VIQ, PIQ or FSIQ between the three groups [6, 49].

*Dose effect:* In a cross-sectional retrospective study conducted by Jokeit et al., patients with epilepsy with high PB serum levels (38.4 mg/l) performed worse in verbal and non verbal LTM tasks than patients with lower serum levels (18.7 mg/l) [50].

### 3.7. Phenytoin [5,5-diphenylimidazolidine-2,4-dione]

*Indication:* Phenytoin is an agent in the following drugs: Phenhydan tablets / injection and Phenytoin-Ge-rot. It is indicated in focal, generalised and generalised tonic-clonic seizures, simple (Jackson-seizures) and complex focal seizures (temporal lobe), in psychomotor seizures, in the prophylaxis and treatment of seizures in traumatic brain injury and in Trigeminal neuralgia. PHT is not effective in absence status epilepticus or in the prophylaxis and therapy of febrile seizures.

*Mechanism of action:* PHT blocks voltage-gated sodium channels, therefore limiting repetitive neuronal firing of action potentials. A problem that is especially worthy of consideration is the nonlinear kinetics of PHT, meaning that beyond a certain point, a small increase in dosage may lead to a dramatic increase in serum level. In addition, PHT is tightly protein bound and acts as a CYP-450 inducer, which makes it a special candidate for drug interactions [51].

*Absolute effects:* There is a large body of evidence from numerous studies showing that PHT negatively affects psychomotor speed. In a study conducted by Salinsky et al., 12 healthy volunteers showed slower reaction times 12 weeks after PHT treatment in LLS and HLS (visual and auditory reaction time, and finger tapping) [43]. However, there are some studies suggesting improvement after discontinuation of PHT. Studies testing seizure-free patients with epilepsy in a follow-up design after up to two years found minimal decline in LLS and HLS which were reversible after complete drug withdrawal [52-54]. Duncan et al. observed improved scores in LLS (finger tapping) and HLS (letter cancellation task) after complete PHT withdrawal [55]. Meador et al. administered 59 healthy adults PHT and found impaired performances in HLS, LTM (verbal), IR. However, LLS, WM, and LTM (visual) remained unaffected [48]. In an add-on study with 39 patients suffering from allergies or pulmonary or rheumatologic illnesses, Brown et al. tested declarative memory one week after administration and found no significant impairments [56].

*Relative effects:* In a randomised crossover study by Meador et al., healthy subjects treated with PHT performed better than those treated with VPA in HLS and IR [48]. Regarding memory, patients taking PHT were found to perform worse compared to patients taking VPA [13]. However, these findings have not been replicated in long-term designs. In a follow-up study, Craig et al. retested elderly patients one year after initiation of treatment and found that cognitive differences in LLS, HLS, and WM between PHT and VPA were minimal [57]. Thirty patients receiving either PHT or VPA after undergoing craniotomy who were tested up to 12 months after treatment initiation showed no differences in performance in HLS, WM, LTM, and FL [58]. Aikiä et al. found no differences in HLS or memory between 29 patients that were treated for one year either with PHT or OXC [44]. The absence of any advantage between these two drugs was replicated by Salinsky et al. who retested 26 patients 12 weeks after treatment using a battery of tests including LLS, HLS, WM, LTM, and IR [43].

PHT was found to have a stronger negative impact on psychomotor speed compared to CBZ. Reduced reaction times in LLS and HLS were found in 25 patients on PHT monotherapy in contrast to CBZ monotherapy [11]. In the Multicenter Holmfrid Study, performance of children with epilepsy was slower on PHT compared to CBZ. Even after drug withdrawal, the children in the PHT group still showed reduced HLS scores in a binary choice reaction time task [59]. Newly diagnosed patients with epilepsy who were treated with PHT performed worse in HLS and LTM compared to both CBZ treated patients and a non-treated control group [60].

*Dose effect:* In the same study mentioned above, Pulliainen et al. found that visual psychomotor speed was more affected in patients with high PHT serum levels [60]. In one retrospective study with patients suffering from temporal lobe epilepsy, Jokeit et al. observed that memory-related impairments (visual and auditory WM and LTM) correlated with PHT serum level concentration. In a group of 34 patients, retention of new material was impaired only when patients showed initial high doses of AED [50].

Dodrill and colleagues reanalysed patients' scores obtained in cognitive tasks with measures of psychomotor speed serving as covariates. Initially, test results favoured the low serum concentration group over the high level group, meaning that only patients with a high initial drug concentration showed impairments on LLS, HLS, and WM. However, after motor speed (finger tapping) was factored out, all previous significant differences disappeared, leading the authors to conclude that PHT monotherapy did not have any negative impact on cognition independent of psychomotor slowing [61, 62].

### 3.8. Pregabalin [(S)-3-(aminomethyl)-5-methylhexanoic acid]

*Indication:* The trade name of Pregabalin is Lyrica®. It is indicated in the treatment of peripheral and central neuropathic pain in adults and as add-on therapy in partial seizures with or without secondary generalisation in adult patients with epilepsy.

*Mechanism of action:* PGB is structurally related to the antiepileptic drug GBP. The site of action is an auxiliary subunit of voltage-gated calcium channels. PGB subtly reduces the synaptic release of several neurotransmitters and it reduces neuronal excitability and seizures [63].

*Absolute side effects:* In a placebo-controlled study, 23 healthy subjects showed no significant differences in a series of tasks that measured HLS and WM. It is noteworthy, however, that tests were conducted three times on three consecutive days after the drug had been administered (day 1, 2, and 3), making it impossible to rule out possible practice effects. Moreover, the authors used a subtherapeutic dosage of 150 mg/d (table 1) [64].

In a clinical trial, the short-term impact of PGB on cognition was examined in 10 adult patients with medically refractory partial epilepsy before and one week after add-on titration. After medication with PGB, patients manifested impairments in LTM of verbal and visual information, but no difference was found in HLS, WM, or FL [37].

*Relative side effects:* In the same study mentioned above, cognitive side effects of LEV and PGB were compared in a total of 20 patients with epilepsy. Although patients receiving LEV reported fewer subjective adverse effects, the neuropsychological profile revealed no significant differences but only tendencies in LTM (verbal) and WM (visual), both in favour of the LEV group. However, as the authors mention, the relatively small sample size of 10 patients per group, as well as the short interval of one week, prevent the results from being very conclusive. Notably, when results were compared to the baseline within-group, the PGB group show impaired episodic LTM in delayed recall, which might explain the between-group advantage of LEV (see above) [37].

### 3.9. Primidone [5-ethyl-5-phenyl-hexahydroprymidine-4,6-dione]

*Indication:* Mysoline®, the drug with PRM as its agent, is indicated in the treatment of Grand Mal, psychomotor epilepsies, focal seizures, Petit Mal, and myoclonic and akinetic seizures. Additionally, PRM can be prescribed for essential tremor.

*Mechanism of action:* The mechanism of PRM's antiepileptic action is still not completely known. PRM per se has anticonvulsant activity due to its two metabo-

lites, phenobarbital and phenylethylmalonamide. It is believed to work via interactions with voltage-gated sodium channels which inhibit high-frequency repetitive firing of action potentials [65].

*Side effects:* There are no recent studies published about cognitive side effects of PRM. Neurocognitive side effects resemble those of phenobarbital.

### 3.10 Topiramate [2,3:4,5-Bis-O-(1-methylethylidene)-beta-D-fructopyranose sulfamate]

*Indication:* Topamax® contains the agent Topiramate. TPM is indicated as monotherapy in patients older than 7 years with newly diagnosed epilepsy, as add-on therapy in children older than 2 years with partial or tonic clonic seizures, and as add-on therapy in the treatment of seizures associated with the Lennox-Gastaut syndrome. In addition, TPM is prescribed as a prophylaxis of migraine in adults and adolescents aged 16 years and older. Its use in the treatment of acute migraine has not yet been tested.

*Mechanism of action:* Topiramate possesses the ability to modulate several neurotransmitter systems: inhibition of sodium channels and carbonic anhydrase, modulation of GABA receptors, glutamate receptors, calcium channels, and potassium channels. Collectively, modulation of each of these processes leads to a reduction of excitatory neurotransmission and enhancement of inhibitory neurotransmission [66].

*Absolute effects:* A randomised, double-blind, placebo-controlled study by Salinsky et al. with healthy subjects found impairment in graphomotor speed, WM, LTM, and FL after 12 weeks of medication with TPM compared to healthy subjects taking placebo. No difference in cognitive functions between the two groups was found in motor tasks, IR, or different measures of processing speed (**table 1**) [22]. Impairments in FL or WM (digit span, Corsi block span) were reported in several clinical studies [38, 67-70]. The results on processing speed are quite heterogeneous, with some studies finding a decline in speed [38] and others unable to find such a decline [71]. Contrary to the results reported by Salinsky et al., evidence from clinical trials indicated that LTM is not affected by the intake of TPM [70, 72]. In summary, impairments in FL and WM were reported by several different studies, results on speed are quite conflicting and LTM does not appear to be affected by TPM.

*Relative effects:* Compared to other AEDs, TPM shows more side effects in a number of cognitive functions. Kang et al. investigated in a randomised, double blind clinical trial 88 children with epilepsy who were treated with either CBZ or TPM. After 28 weeks of treatment the TPM group performed worse on the subtests arithmetic and maze of the Korean version of the WISC-R [16]. A study with 51 adults with epilepsy taking either TPM or LEV revealed a significant change in cognitive performance over time dependent on treatment.

While the LEV group demonstrated no change in cognitive performance, the TPM treated patients worsened in three cognitive domains: HLS (TMT-A), FL, and WM (verbal and spatial) [38]. Meador et al. conducted a randomised, double-blind crossover study with 47 healthy adults taking LTG and TPM. The TPM group showed a worse side effect profile in tasks measuring LLS, HLS, FL, and in immediate and delayed recall of short stories. No significant difference between the two medications was found in IR [31]. In a clinical trial with 42 patients with epilepsy receiving either LTG or TPM as add-on therapy, significantly worse performance was found in the TPM group in measures of FL and verbal and visual short term memory, whereas no difference was found in HLS and LTM [73]. Martin et al. conducted a randomised, single blind study with 17 healthy adults taking either LTG, GBP or TPM. After 4 weeks of medication the TPM group showed worse performance in one of two HLS tasks than the other two groups. The adverse effect of TPM on FL was only present 3 hours after medication administration and was no longer reported after 2 and 4 weeks of treatment [25]. In another randomised, double-blind clinical trial with 124 patients with epilepsy, LTG and TPM as add-on therapy to CBZ or PHT were compared. The authors reported worse performance for the TPM group in FL, IR, and in a task measuring HLS (symbol digit modalities) [35]. In a double-blind, randomised, placebo controlled study with 62 adults with epilepsy treated with either TPM or VPA as add-on therapy to CBZ for 12 weeks at the target dosage, the TPM group showed worse performance in a task for HLS (symbol digit modalities test) and in FL. No difference in performance was found in HLS (CRT), LTM, or short term memory [74]. Similar results on FL and HLS have been reported by other researchers, but they also found a significant difference in WM in favour of VPA [67, 68]. TPM showed more side effects on HLS, LTM, and FL than GBP [22].

*Dose effect:* Lee et al. studied the long-term cognitive side effects of low-dose TPM monotherapy in patients with epilepsy. Thirty six patients with target doses of 50, 75, and 100 mg/day completed baseline and one-year follow-up neuropsychological testing. TPM had significantly negative effects on WM (digit span) and FL. These adverse effects were dose-related and significantly improved after withdrawal from TPM [70].

### 3.11 Valproic acid [2-propylpentanoic acid]

*Indication:* A number of drugs with VPA as their agent are available: Convulex®, Depakine®, Depakine® Chrono, Orfiril®, and Valproat Sandoz®. VPA is in particular indicated in the monotherapy of generalised types of idiopathic epilepsy. As an add-on therapy it is effective in different types of seizures. VPA is also indicated in the treatment of manic episodes in patients with bipolar disorders. A favourable effect in the prevention of

manic episodes has not been proved.

*Mechanism of action:* The mechanism of action of VPA in epilepsy and bipolar disorder is still not completely understood. On the one hand it enhances GABA-mediated neurotransmission, on the other hand, VPA alters the expression of multiple genes [75].

*Absolute effects:* Studies with systematic data collection report impairments mainly in HLS tasks with VPA (**table 1**). A randomised, double blind, placebo-controlled discontinuation study with 27 patients with epilepsy found improvement in performance after withdrawal of VPA on tests that required complex cognitive processing under speed demands [4]. Evidence for impairment in fast elementary decision making after administration of VPA was found in a study of 10 healthy subjects [76]. Results of a randomised, placebo-controlled study with 20 healthy adults showed an impairment in LLS (visual RT) with VPA. Auditory LLS, HLS, and WM was not affected (**table 1**) [32]. In a study with 279 patients with traumatic brain injury, no impairment in motor functions, attention, LTM, verbal skills, or performance skills was found [77]. In line with the results mentioned above, impairment in HLS was reported in several clinical trials [5, 57, 78]. WM decline as a result of VPA was only reported in one clinical study with psychiatric patients [79]. A few clinical studies which were unable to find any negative effects of VPA [80] or even a positive effect of VPA therapy in children with childhood absence epilepsy or juvenile absence epilepsy on fine motor fluency, HLS, or visual LTM [81] have been published. In summary, studies with systematic data collection have generally found an impairment in HLS and no effects on VPA on LTM, WM, FL, and IR.

*Relative effects:* There is good evidence that VPA exhibits fewer adverse effects than TPM, especially in FL, short term memory, and in some aspects of HLS. No significant differences were reported in LTM, IR, or IQ [67, 68, 74]. The former studies were conducted with patients with epilepsy. However, two studies comparing VPA and PHT in either patients with epilepsy or healthy subjects revealed no differences in LLS, HLS, WM, LTM, FL, or IR [48, 57, 58]. Meador et al. also compared PB to VPA in healthy subjects and reported worse performance in several HLS tasks for the PB group [48]. In a study with 30 healthy volunteers treated with VPA, LTG or placebo, the VPA group performed worse in an auditory reaction time task than the LTG and placebo group. All other measurements (finger tapping, visual reaction time, choice reaction time, and LTM task) revealed no differences between the three groups [32]. In a randomised, parallel-group clinical trial with 90 children with epilepsy, the adverse side effects on LLS, HLS, WM, LTM, and IQ were the same for VPA, OXC, and CBZ [14]. Similar to the previous study, Chen et al. found no difference in IQ in children with epilepsy 7 months after withdrawal from CBZ, PB or VPA [6].

*Dose effect:* A dose effect of VPA on cognitive performance (LLS, HLS, WM, and IQ) has not been reported [19].

### 3.12 Zonisamide [1,2-benzisoxazole-3-methanesulfonamide]

*Indication (Zonegran):* Zonisamid is available as Zonegran®. It is indicated as add-on therapy in the treatment of adult patients with partial seizures with or without secondary generalisation.

*Mechanism of action:* The exact mechanism of action is not known for ZNS. However, it is speculated about a possible role in blocking receptive firing of voltage-gated sodium channels and a reduction of calcium channel currents. ZNS is also believed to work via the GABAergic system, i.e. it inhibits the release of the GABA transport protein which eventually leads to an increased concentration of GABA. It also increases the level of glutamate transport protein, thus diminishing the amount of extra cellular excitatory glutamate. The pharmacokinetics of ZNS are complex and nonlinear, with higher steady-state plasma levels [82].

*Absolute effects:* Berent et al. tested nine patients with refractory epilepsy before, 12 and 24 weeks after treatment with the drug. When they compared the results elicited 12 weeks after drug treatment, patients showed impaired scores in WM and LTM while psychomotor tasks remained unchanged. When analysed more closely, results showed that initial acquisition of verbal learning was affected, while that of visual stimuli was not. However, when testing delayed recall, patients had difficulties in both verbal and visual recall. But interestingly, all these differences disappeared when test scores from the third session were compared to the first, revealing no significant impairment on all tasks measured. Also, subjects' plasma concentrations were lower in the third session compared to the second session. Explaining this fact, the authors found a significant correlation between subjects' plasma level and scores in neuropsychological tests. The authors thus suggest a possible development of tolerance to the adverse effect of ZNS, leading to diminished or absent neuropsychological impairment after initial drug treatment [83].

*Relative effects:* Effects of ZNS and CBZ were compared in a 12 week monotherapy study by Ojemann et al. They found impaired scores on VIQ in patients receiving treatment with ZNS [84].

*Dose effect:* In the same study, patients showed worse performance on verbal as compared to nonverbal tests at high doses of ZNS [84]. Park and colleagues investigated 34 patients with epilepsy in a one-year follow-up study in which patients were divided into four different groups according to their daily dosage (100, 200, 300, and 400mg/day). Compared to performance at baseline, the authors found impaired performances in HLS, WM, LTM, and FL one year after initiation of treatment. Similar to the study mentioned above, the authors did find significant correlations between daily AED dosage and neuropsychological scores in HLS, LTM, or FL; all showing greater impairment at higher AED concentrations [85].

## 4. Discussion

The neurocognitive effects of AEDs depend on the type of drug, its dosage, serum levels, drug interactions, duration of treatment, and, probably more importantly, on the neurobiochemical characteristics of each individual patient. Generally, several of the newer AEDs apparently have a more positive neurocognitive profile (e.g. GBP, LTG, LEV) than older AEDs. These newer drugs with minimal neurocognitive effects may even lead to enhanced patient compliance over the long run. Unfortunately, the effects of polytherapy with newer AEDs have not been addressed in recent studies. Among the newer AEDs, TPM has the greatest risk of cognitive impairment despite slow titration and low target doses. And, although there are currently only very little data available on ZNS, it probably has a worse neuropsychological profile compared to GBP, LEV, and LTG. However, reversible side effects should not in principle limit a trial with TPM or ZNS to test whether a difficult to treat patient benefits from either of these drugs.

The neurocognitive effects of most AEDs considered here are generally relatively modest. Even mild cognitive side effects, however, are of considerable importance in situations with high attentional and cognitive demands such as education, training, teaching, driving, and operating complex technical systems. Moreover, it should be taken into account that the majority of studies investigated adult patients and not children or the elderly who are likely to be more prone to cognitive effects of AEDs because of their limited cognitive resources.

In patients who are difficult to treat there might be a trade-off between benefits from improved seizure control with high doses of AEDs or polytherapy and cognitive side effects. Neither seizure frequency nor cognitive side effects alone allow a valid evaluation of costs and benefits in specific individual circumstances. In such situations we suggest the use of a comprehensive quality of life assessment (e.g. QOLIE 89) that helps to more objectively evaluate the patient's gain from changes in AED treatment in the presence of cognitive side effects.

An often neglected problem in studies of neurocognitive AED effects is that most AEDs are either activating or sedating [86]. This is the reason why several AEDs are well established in the treatment of affective and, in particular, bipolar disorders. Therefore, changes in mood states should be taken into account in studies of neurocognitive AED effects in order to control for mood mediated changes in cognitive test performance.

Various studies on neurocognitive AED effects that were not considered for inclusion in this review had methodological constraints and methodological weaknesses. Ten years have passed since Cochrane et al. stated that the major problems in studying AED effects are the considerable number of different neuropsychological tests with frequently unknown test-retest-reliability,

variable patient inclusion criteria, the frequent absence of control groups, non-randomised treatment, and insufficient statistical power [87]. Recently Hessen et al. published an impressive study that could influence future studies as a methodological example [4]. These authors investigated neurocognitive side effects of AEDs prior to and after withdrawal of AEDs in seizure-free patients with epilepsy using a prospective, randomised, double-blind, placebo-controlled parallel group design with very few ethical obstacles.

A shortcoming of the study by Hessen et al., as well as the majority of studies covered in this review, is that only a small range of cognitive functions were examined. Long term memory consolidation, higher order executive functions, or ecologically valid and important functions such as reading rate are rarely considered and, therefore, the results cannot simply be generalised into wider domains of complex activities of daily life.

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