

# The cognitive impact of antiepileptic drugs

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**Abstract:** Effective treatment of epilepsy depends on medication compliance across a lifetime, and studies indicate that drug tolerability is a significant limiting factor in medication maintenance. Available antiepileptic drugs (AEDs) have the potential to exert detrimental effects on cognitive function and therefore compromise patient wellbeing. On the other hand, some agents may serve to enhance cognitive function. In this review paper, we highlight the range of effects on cognition linked to a variety of newer and older AEDs, encompassing key alterations in both specific executive abilities and broader neuropsychological functions. Importantly, the data reviewed suggest that the effects exerted by an AED could vary depending on both patient characteristics and drug-related variables. However, there are considerable difficulties in evaluating the available evidence. Many studies have failed to investigate the influence of patient and treatment variables on cognitive functioning. Other difficulties include variation across studies in relation to design, treatment group and assessment tools, poor reporting of methodology and poor specification of the cognitive abilities assessed. Focused and rigorous experimental designs including a range of cognitive measures assessing more precisely defined abilities are needed to fill the gaps in our knowledge and follow up reported patterns in the literature. Longitudinal studies are needed to improve our understanding of the influence of factors such as age, tolerance and the stability of cognitive effects. Future trials comparing the effects of commonly prescribed agents across patient subgroups will offer critical insight into the role of patient characteristics in determining the cognitive impact of particular AEDs.

**Keywords:** antiepileptic drugs, cognition, epilepsy, medication, neuropsychology, seizure

## Introduction

The incidence of adverse effects is an important issue when prescribing antiepileptic drugs (AEDs), as some of the most effective medications for seizures are associated with a considerable degree of toxicity. Studies indicate that drug tolerability is a significant limiting factor in treatment maintenance, and drug retention rates are often determined by side-effect profiles [Bootsma *et al.* 2009; Chung *et al.* 2007]. Older AEDs may still be prescribed, owing to advantages such as lower cost, wide availability and long-term experience, but often exhibit greater toxicity than newer drugs. Recently developed agents tend to differ in terms of mechanism of action and pharmacokinetic properties, and are often better tolerated than older drugs. However, all AEDs have the potential to exert detrimental effects on cognitive function. A thorough appreciation of the negative cognitive effects linked to a variety of

AEDs makes a crucial contribution to therapeutic success.

There are currently more than 20 different agents which are licensed for use in treating seizures in the UK. These include phenobarbital and phenytoin, which were popular until the 1950s. Over the next couple of decades, sodium valproate and carbamazepine were developed. These drugs, in addition to primidone and ethosuximide, were the six agents of choice until the 1990s, when a newer generation of drugs became available. These include tiagabine, pregabalin, gabapentin, topiramate, clobazam, oxcarbazepine, lamotrigine and levetiracetam.

In terms of adverse cognitive effects the vulnerabilities of the individuals treated need to be carefully considered. Differing metabolic profiles in children, the elderly or the acutely unwell may

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lead to an increased chance of toxicity, and a further consideration is interactions with other medications the patient may be taking. Patients with existing cognitive problems may comprise one population at greater risk of the influence of agents with adverse cognitive effects.

Epilepsy can impair an individual's functioning within work and educational domains [Bishop and Allen, 2003]. As well as adverse cognitive effects, some AEDs may have the advantage of improving cognitive performance. Such beneficial influences may simply occur as a result of seizure control, or in association with positive effects on mood or psychiatric profile. However, a number of agents may demonstrate efficacy in enhancing cognitive function in a more direct way, by improving alertness or cognitive capacity.

In this review of current literature, we highlight the range of effects on cognition linked to a variety of newer and older agents used to control seizures. These include key alterations in both executive and broader neuropsychological functions, which can exert a critical influence on patients' quality of life and wellbeing. Because drug side-effect profiles are often related to patient characteristics, this review is followed by a critical discussion, which will offer recommendations for prescribing both in general and in relation to more specific clinical cases. Finally, we evaluate reviewed studies in terms of methodological limitations, providing essential guidance for insightful further research.

Relevant studies were identified through searches of PubMed and ISI Web of Knowledge (1980–2011). PubMed was searched for articles containing 'epilepsy' and 'cogniti\*' in the abstract/title, and 'drug name' (phenobarbital, primidone, phenytoin, carbamazepine, valpro\*, ethosuximide, tiagabine, vigabatrin, clobazam, zonisamide, gabapentin, pregabalin, topiramate, lamotrigine, oxcarbazepine, levetiracetam) in the title. For the ISI search, we used 'epilepsy' and 'cogniti\*' as topic, and the drug name as title. Only original studies on patients with epilepsy that were written in English were included. We excluded case studies, letters and editorials from our search. We also searched the reference lists of articles identified using this search strategy to increase the number of relevant randomized, blinded, controlled studies. Studies which failed to report findings related to cognitive effects were excluded.

## Antiepileptic drugs and cognition

### *Phenobarbital and primidone*

Some studies report few cognitive adverse effects (CAEs) with the use of phenobarbital [Wang *et al.* 2006]. However, studies involving children with epilepsy have linked this agent to lower IQ [Farwell *et al.* 1990; Camfield *et al.* 1979], and discontinuation of the drug can improve total IQ (mainly affecting nonverbal items) in children [Tonekaboni *et al.* 2006]. Phenobarbital is considered to have worse cognitive effects than valproate or carbamazepine [Calandre *et al.* 1990; Vining *et al.* 1987]. When compared with carbamazepine, primidone has been found to cause more adverse effects on motor performance and attention/concentration tests [Smith *et al.* 1987; Rodin *et al.* 1976]. One study reported attentional and memory difficulties in children [Riva and Devoti, 1996], but these effects were reversible after discontinuation. Another study [Manni *et al.* 1993] showed that when compared with controls, patients taking phenobarbital showed longer movement times, impaired attention and reduced processing speed, but no relationship was found with drug concentration.

### *Phenytoin*

Phenytoin has been implicated in declines in concentration, memory, visuomotor functions and mental speed [Pulliainen and Jokelainen, 1995; Gillham *et al.* 1990; Andrewes *et al.* 1986]. These effects may be dose related [Gillham *et al.* 1990], although one study reported no such relationship for cognitive-motor performance [Aman *et al.* 1994]. Another study reported slowed performance on information processing tasks with phenytoin in comparison with carbamazepine, but no differences for memory or selective attention [Aldenkamp *et al.* 1994]. Some studies report more detrimental effects on memory than carbamazepine [Pulliainen and Jokelainen, 1995; Andrewes *et al.* 1986], although the opposite pattern has been seen in children [Forsythe *et al.* 1991]. A double-blind placebo-controlled study indicated attention and motor performance may improve after withdrawal [Duncan *et al.* 1990], and similar improvements in concentration and psychomotor performance were noted in another controlled study [May *et al.* 1992].

Despite reported CAEs, Pulliainen and Jokelainen concluded that the long-term effects of phenytoin on cognition are relatively few and

restricted mainly to some visually guided motor functions [Pulliainen and Jokelainen, 1995]. More favourable findings include minimal cognitive effects in children [Forsythe *et al.* 1991] and elderly patients [Craig and Tallis, 1994], improvements in Stroop performance in partial epilepsy [Bittencourt *et al.* 1993], no differences on tasks assessing verbal and performance intelligence, memory and visuomotor function, before and after treatment in drug-naïve adult patients [Sudhir *et al.* 1995] and a similar cognitive profile to oxcarbazepine [Aikiä *et al.* 1992].

### Carbamazepine

A number of cognitive and psychomotor effects have been linked to carbamazepine [Gillham *et al.* 1988]. A double-blind trial reported deterioration in measures of information processing speed and attention [Wesnes *et al.* 2009]. Other studies report poorer verbal fluency in adults with partial seizures than in control subjects [Aikiä *et al.* 2006], detrimental effects on memory [Shehata *et al.* 2009; Forsythe *et al.* 1991], worse arithmetic performance [Kang *et al.* 2007] and faster motor skills after discontinuation [Duncan *et al.* 1990]. Impaired movement time, reaction time, finger tapping rate and number cancellation were seen in one study, but these effects remitted by 1 month after treatment commencement [Larkin *et al.* 1992].

A randomized, double-blind, placebo-controlled study [Hessen *et al.* 2006] involving 150 epilepsy patients on AED monotherapy (mainly carbamazepine or valproate) found that drug discontinuation significantly improved performance in tests that required complex cognitive processing under time pressure, but not in more simple tasks of attention and reaction time. A later study reported similar findings, whereby performance improved in a verbal fluency task, a Stroop task, a language task and a reaction time task after discontinuation of carbamazepine [Hessen *et al.* 2009].

In relation to other AEDs, it has been suggested that carbamazepine has a cognitive profile that is worse than levetiracetam [Lee *et al.* 2011] and lamotrigine [Gillham *et al.* 2000] but better than phenytoin [Pulliainen and Jokelainen, 1994; Andrewes *et al.* 1986]. Forsythe and colleagues reported that carbamazepine-treated children performed worse than valproate-treated children on memory tasks [Forsythe *et al.* 1991]. However, another study [Coenen *et al.* 1995]

reported that the cognitive profiles of valproate and carbamazepine were similar except for some aspects of attention and memory, in which individuals taking valproate scored better, and for some motor tests, in which individuals taking carbamazepine performed faster. These effects appear mild when compared with those of phenytoin and phenobarbital.

Detrimental effects on cognition are unlikely to be widespread. One study reported significantly worse performance on the Digit Symbol Substitution Test (DSST), but no difference for tracking tasks and visual analogue scales [Pieters *et al.* 2003]. Another study of patients with partial epilepsy showed no impairments in selective attention, memory or executive functions compared with controls, although slower information processing speed was seen with monotherapy [Engelberts *et al.* 2002]. Despite no decline in coordination, memory, concentration or mental flexibility, a lack of practice effects on tasks appeared to suggest subtle changes in cognitive function in one study [Prevey *et al.* 1996]. Similar findings were reported by Pulliainen and Jokelainen [Pulliainen and Jokelainen, 1994]. Another report indicated that for children with partial epilepsy, carbamazepine did not have significant negative effects on memory and attention tasks, although performance improved slightly after withdrawal [Riva and Devoti, 1999]. Other studies report little evidence of CAEs [Donati *et al.* 2007; Sudhir *et al.* 1995].

Some positive effects on cognition have been reported, consisting mainly of improvements in memory. For example, one study showed that story recall improved in children with benign rolandic epilepsy when treated with carbamazepine [Seidel and Mitchell, 1999]. Other beneficial effects on memory include improved immediate memory and late recall [Bittencourt *et al.* 1993] and better retrieval from episodic and semantic memory in adults and adolescents [Kälviäinen *et al.* 1995]. There may be a mild beneficial effect on hand-eye coordination in children with complex partial epilepsy in addition to improvements in memory [O'Dougherty *et al.* 1987]. Memory and visual information processing may benefit most from the use of controlled-release medication [Aldenkamp *et al.* 1987]. Despite these encouraging findings, some studies suggest carbamazepine is more likely to lead to cognitive deterioration than improvement [Helmstaedter and Witt, 2010]. Factors that

may be related to a greater incidence of cognitive effects include higher dose [Gillham *et al.* 1988; O'Dougherty *et al.* 1987], longer duration of intake [Shehata *et al.* 2009] and polytherapy [Gillham *et al.* 1988].

#### *Sodium valproate and ethosuximide*

Studies are listed in Table 1. A number of studies have indicated that valproate exerts little detrimental impact on cognitive function [Sun *et al.* 2008; Donati *et al.* 2007; McKee *et al.* 1992; Gillham *et al.* 1991]. However, a small minority of patients (5 of 364 adults in one study) can

develop parkinsonism with associated memory problems and psychomotor slowing [Ristic *et al.* 2006]. One study reported no decline in tasks assessing coordination, memory, concentration or mental flexibility, although no practice effects were seen that were evident in controls, perhaps indicating very subtle changes in cognitive function [Prevey *et al.* 1996]. Minor changes in cognitive function have been reported in elderly patients [Craig and Tallis, 1994], adults [Spitz and Deasy, 1991] and children [Stores *et al.* 1992]. However, in the latter study, modest

**Table 1.** Studies on the cognitive effects of valproate in patients with epilepsy.

Study	Design	Sample	Key findings
Gillham <i>et al.</i> [1991]	OL	76 adult patients, 26 untreated epilepsy controls and 24 HCs	Polytherapy group worse than monotherapy and controls for decision and choice reaction time, finger tapping, threshold detection and visual span. No differences for monotherapy. CAEs not related to dose. Drug levels, but not seizure frequency, correlated with impaired threshold detection.
McKee <i>et al.</i> [1992]	OL	24 adolescent/adult patients	No significant effects of VPA on decision and movement time, finger tapping, digit span, verbal learning or threshold detection.
Sun <i>et al.</i> [2008]	OL, rand	38 adult patients + 15 HCs	No increase in reaction times, little evidence of attentional impairment with use.
Ristic <i>et al.</i> [2006]	Open, 1-year follow-up	364 adult patients	1.3% of patients developed parkinsonism 2.5–10 months after treatment commencement. Of these three patients five exhibited psychomotor slowing and memory problems. AEs not related to dose, age or epilepsy duration.
Donati <i>et al.</i> [2007]	OL, rand, comparing VPA, CBZ and OXZ	112 children/adolescents with partial seizures	No evidence of cognitive impairment, improved information processing speed. No difference between AEDs for psychomotor speed, learning, memory or attention measures.
Prevey <i>et al.</i> [1996]	Rand, DB	480 treatment-naïve adult patients with partial epilepsy	No cognitive differences between CBZ and VPA, and no effects on performance on motor speed and coordination, memory, concentration and mental flexibility. Evidence of lack of practice effects on tasks may indicate subtle impairment.
Craig-Tallis <i>et al.</i> [1994]	SB, rand, comparing VPA and PHT	38 older adults with late-onset epilepsy	Minor decrements in cognitive function. Immediate and delayed verbal memory improved and choice reaction time deteriorated. No significant difference between AEDs. No relationship between AED blood levels and cognitive performance.
Spitz <i>et al.</i> [1991] Stores <i>et al.</i> [1992]	OL OL, comparing VPA and CBZ	71 adult patients 63 child patients, 47 HCs	No CAEs reported. Little difference between AEDs. Patients always worse on attention tasks <i>versus</i> controls, but this could have been

(continued)

Table 1. Continued

Study	Design	Sample	Key findings
Brouwer <i>et al.</i> [1992]	OL, crossover – VPA to VPA controlled release	12 child patients, 12 HCs	result of uncontrolled seizure discharge. Minimal cognitive impairments with VPA. Slower cognitive processing speed was evident, although this effect only reached significance in the context of greater task demands.
Duncan <i>et al.</i> [1990]	DB, PC, (stepwise), comparing VPA, PHT and CBZ	97 adult patients, 25 usual treatment patient controls	Reduction in AEDs did not lead to significant differences for Digit Symbol Substitution Test, digit span or serial subtractions, but tapping rate improved similarly for all three AEDs.
Galassi <i>et al.</i> [1990]	OL	20 adults with generalized epilepsy, 20 HCs	AED reduction indicated treatment was associated with slight deficits: worse performance than controls in relation to attention, and visuomotor performance. Cognitive performance was not related to drug level, duration of epilepsy or treatment.
Forsythe <i>et al.</i> [1991]	OL, rand, comparing VPA, PHT and CBZ	64 new child patients	After 6 months, memory was better for VPA than CBZ. Little evidence of significant cognitive effects with VPA, but memory performance was related to drug serum levels – higher pretreatment memory scores were related to later high serum levels.
Vining <i>et al.</i> [1987]	DB, comparing VPA and PHB	21 child patients	Little evidence of CAEs with VPA; favourable in comparison with phenobarbital.
De Araujo Filhou <i>et al.</i> [2006]	Open, comparing VPA and TPM	42 adolescent and adult patients	VPA better than TPM for attention, verbal fluency, short-term memory and speed-processing measures.
Meador <i>et al.</i> [2003]	DB, PC, rand, comparing VPA and TPM	76 adult patients	Cognitive problems for VPA: memory (17%), speech (7%), attention (10%), psychomotor slowing (3%), confusion (3%), language (7%) or other (3%). Testing indicated little difference in cognitive functioning for VPA versus placebo.
Glaser <i>et al.</i> [2010]	DB, rand, comparing VPA, LTG and ETX	451 child patients	More attentional problems with VPA than ETX or LTG.
Capovilla <i>et al.</i> [2010]	OL	9 children with partial epilepsy and epileptic negative myoclonus	Improved level of concentration and attention likely to be related to improved seizure control. No CAEs reported.

AEDs, antiepileptic drugs; CAEs, cognitive adverse effects; CBZ, carbamazepine; cont, controlled; DB, double-blind; ETX, ethosuximide; GBP, gabapentin; HCs, healthy controls; LTG, lamotrigine; OL, open-label; OXC, oxcarbazepine; PC, placebo-controlled; PHB, phenobarbital; PHT, phenytoin; rand, randomized; retro, retrospective; SB, single-blind; TPM, topiramate; VGB, vigabatrin; VPA, sodium valproate.

adverse cognitive effects were seen early in treatment, which could have been the result of seizure discharge. Another study showed no relationship between plasma concentration and cognitive performance in children [Brouwer *et al.* 1992]. One double-blind, placebo-controlled study reported more convincing evidence of improved motor skills after discontinuation [Duncan *et al.* 1990]. Fortunately, the CAEs associated with

valproate are likely to be reversible [Galassi *et al.* 1990].

In relation to the effects of other AEDs on cognitive function, valproate has been suggested to be preferable to carbamazepine [Forsythe *et al.* 1991], phenobarbital [Vining *et al.* 1987] and topiramate [Sun *et al.* 2008; De Araujo Filhou 2006; Meador *et al.* 2003]. However, a recent

study by Glauser and colleagues reported that attentional dysfunction was more common with valproic acid than ethosuximide (in 49% of the children compared with 33%) [Glauser *et al.* 2010]. In another study [Capovilla *et al.* 1999] ethosuximide led to no side effects in nine patients with partial epilepsy, and improvements in cognitive performance with the use of ethosuximide have been reported for individuals both with and without epilepsy [Browne *et al.* 1975]. Ethosuximide may therefore prove a more favourable option than valproate.

#### *Tiagabine*

A few CAEs have been reported with the use of tiagabine, such as deterioration in verbal memory from 3 months after baseline tests [Fritz *et al.* 2005]. However, some studies, including double-blind, placebo-controlled trials, have reported no negative impact on cognition [Aikiä *et al.* 2006; Dodrill *et al.* 1997; Kälviäinen *et al.* 1996; Sveinbjornsdottir *et al.* 1994]. It appears that most reports indicate potential for positive influences, such as improved motor speed, concentration, and verbal fluency after use [Dodrill *et al.* 1998]. An add-on study in adults with partial seizures documented similar effects on verbal fluency in addition to faster perceptual/motor speed for tiagabine in comparison with carbamazepine [Dodrill *et al.* 2000]. Patient-perceived cognition has also been shown to improve soon after treatment commencement [Cramer *et al.* 2001].

#### *Vigabatrin*

Vigabatrin has demonstrated few CAEs when compared with placebo in double-blind studies [Dean *et al.* 1999; Dodrill *et al.* 1993; Gillham *et al.* 1993] and fewer adverse effects than carbamazepine in a small, open-label, randomized, parallel-group study [Kälviäinen *et al.* 1995]. Vigabatrin had no detrimental effects on cognitive functions at 12 months, and memory retrieval and mental flexibility improved significantly. One double-blind, placebo-controlled, randomized study reported impaired performance relating to motor speed and design learning in adolescents and adults with partial epilepsy [Grunewald *et al.* 1994]. However, such negative effects were only reported in nonresponders who poorly tolerated the drug. There was also evidence of the development of tolerance in relation to CAEs. Overall, vigabatrin monotherapy seems well tolerated in relation to cognition [Monaco *et al.* 1997; Provinciali *et al.* 1996; Ylinen *et al.*

1995], including in patients with intellectual disability [Ylinen, 1998].

In a double-blind study involving 100 adult epilepsy patients, 52 taking vigabatrin and the rest placebo [Guberman and Bruni, 2000], there was a tendency for improvement on most tests of cognitive function: 15 showed improvement, one showed no change, and scores worsened for five tests. Other studies report improved cognition in children [Camposano *et al.* 2008] and in 66% of patients with epilepsy and psychosis [Veggiotti *et al.* 1999]. Improvements include better episodic memory, semantic memory and flexibility of mental processing in adolescents and adults [Kälviäinen *et al.* 1995] and decreased arithmetic response time [McGuire *et al.* 1992].

The main limitation with the use of vigabatrin is visual field constriction, which may affect 30–50% of patients [Gonzalez *et al.* 2006]. The prevalence of such difficulties may be lower in children than in adults, and the cumulative dose of vigabatrin or length of treatment may add to the personal predisposition for developing visual field constriction [Vanhatalo *et al.* 2002]. Caution in prescribing is merited, given reports of slowed response time linked to visual processing during use and possible difficulties detecting peripheral moving objects, which have implications for driving [Naili *et al.* 2009].

#### *Clobazam*

One study reported no difference between the performance of patients taking clobazam or carbamazepine on tests assessing intelligence, memory, attention, psychomotor speed, and impulsivity [Bawden *et al.* 1999]. There was little evidence of CAEs in an open study involving children [Jan and Shaabat, 2000]. In another study involving children, attention and alertness improved with clobazam [Munn and Farrell, 1993]. Although 72% reported improvements in cognition, 26% reported deterioration in at least one aspect of cognition. An open study of adolescents and adults [Montenegro *et al.* 2001] identified CAEs in just two of 97 patients.

#### *Zonisamide*

Although CAEs are often the most common reason for discontinuation of zonisamide, perhaps only 5.8% will withdraw from treatment for this reason [White *et al.* 2010]. There are conflicting findings as to the prevalence of CAEs. One retrospective analysis showed

memory loss in 35% and attentional problems in 27% of 60 patients [Park *et al.* 2007], while other reports indicate cognitive problems in 4–12% of children [Kothare *et al.* 2006; Kim *et al.* 2005]. Berent and colleagues reported difficulties with learning in association with zonisamide in a small, add-on study [Berent *et al.* 1987]. Cognitive difficulties were also reported by an open-label investigation [Park *et al.* 1999]. After 1 year of treatment, 16 patients (47%) complained of cognitive deficits. Worse performance was apparent in tasks involving attention, memory and verbal fluency, and was related to dose. These authors concluded that zonisamide has adverse effects on cognition, even after 1 year of treatment.

### *Gabapentin*

Most studies tend to report little or no cognitive impairment in association with gabapentin, including double-blind studies [Dodrill *et al.* 1999; Meador *et al.* 1999; Leach *et al.* 1997], and there may be potential for improved performance in cognitive measures [Mortimore *et al.* 1998].

### *Pregabalin*

In one study, only 4% of patients taking pregabalin reported cognitive problems [Valentin *et al.* 2009]. When present, possible CAEs include deterioration in verbal and visual episodic memory [Ciesielski *et al.* 2006]. One double-blind, randomized, placebo-controlled study involving a large sample of adolescents and adults with partial epilepsy [French *et al.* 2003] reported abnormal thinking in 2% of the placebo group, compared with 3.4% of patients taking 50 mg pregabalin, 7% taking 150 mg, 7.8% taking 300 mg and 4.5% taking 600 mg. An open study of add-on pregabalin noted few reported CAEs [Jan *et al.* 2009]. Other reports indicate that abnormal thinking may be rare [Arroyo *et al.* 2004], although one report indicated this CAE could be 9–12 times more likely with pregabalin than with placebo [Beydoun *et al.* 2005].

### *Topiramate*

Studies are listed in Table 2. Reports indicate that CAEs are not uncommon with topiramate [Bootsma *et al.* 2006], and may constitute a large proportion of the AEs in children [Mohamed *et al.* 2000]. One study found 44% of patients reported experiencing CAEs after 1 year of treatment [Lee *et al.* 2006]. However, a double-blind, randomized trial in older adults

reported CAEs including memory worsening and language difficulties in only 1–5% of patients using topiramate [Ramsay *et al.* 2008]. Whatever the frequency of CAEs, they are the most likely reason for treatment withdrawal [Tatum *et al.* 2001].

Cognitive side effects can include impaired concentration [Froscher *et al.* 2005], cognitive dulling [Coppola *et al.* 2002], psychomotor slowing [Tatum *et al.* 2001], language and comprehension problems [Fritz *et al.* 2005], detrimental effects on short-term memory [Gomer *et al.* 2007; Aldenkamp *et al.* 2000] and working memory [Jung *et al.* 2010; Lee *et al.* 2006; Fritz *et al.* 2005], poor verbal fluency [Jung *et al.* 2010; Gomer *et al.* 2007; Lee *et al.* 2006, 2003; Fritz *et al.* 2005; Thompson *et al.* 2000] and word-finding deficits [Mula *et al.* 2003b], reduced IQ score [Sun *et al.* 2008; Lee *et al.* 2003; Thompson *et al.* 2000] and cognitive speed [Bootsma *et al.* 2008a; Gomer *et al.* 2007], and abnormal thinking [Froscher *et al.* 2005]. Other studies report improvements in cognitive measures after topiramate withdrawal [Kockelmann *et al.* 2003]. For example, in one study, verbal fluency, verbal and spatial span and attention improved after treatment withdrawal, and patients then performed similarly to untreated patient controls [Kockelmann *et al.* 2003]. EEG changes may be seen in frontal regions, along with deterioration in cognitive performance [Jung *et al.* 2010].

Topiramate has been shown to exert more negative effects on cognition than a range of other AEDs. Poorer verbal fluency, attention and inhibitory performance have been reported than with lamotrigine [Blum *et al.* 2006; Kockelmann *et al.* 2004], and verbal fluency and working memory are also worse than with oxcarbazepine [Kim *et al.* 2006]. Memory and attention effects may be worse than with valproate [De Araujo Filhou *et al.* 2006], and verbal fluency, cognitive speed and short-term memory were worse than with levetiracetam in one study [Gomer *et al.* 2007].

Although some studies argue that topiramate may be more commonly linked to CAEs, there are some reports indicating these effects are rather infrequent [Brandl *et al.* 2010; Majkowski *et al.* 2005; Reith *et al.* 2003; Baker *et al.* 2002]. The rate of discontinuation due to CAEs may also be low, especially with low doses [Arroyo *et al.* 2005]. In one study, more than half

**Table 2.** Studies on the cognitive effects of topiramate in patients with epilepsy.

Study	Design	Sample	Key findings
Bootsma <i>et al.</i> [2006]	Retro, comparing TPM and LEV	402 child and adult patients	Significantly more patients reported CAEs for TPM 6 months after treatment commencement (15% versus 4%). More patients taking TPM discontinued due to CAEs.
Mohamed <i>et al.</i> [2000] Lee <i>et al.</i> [2006]	Retro OL	51 children 47 adolescent and adult patients	did not report CAEs. Significantly fewer CAEs with lower doses (50 mg versus 75/100 mg). Poorer working memory and verbal fluency with higher doses. These effects tended to remit by 1 month after withdrawal.
Ramsay <i>et al.</i> [2008]	DB, rand	77 older patients with partial-onset seizures	13% reported CAEs but only 3% discontinued as a result. Most common were memory and language problems.
Tatum <i>et al.</i> [2001]	OL, follow-up survey	701 children and adults	41.4% reported CNS dysfunction such as psychomotor slowing, but only 2.4% were on monotherapy. CAEs were predictive of discontinuation, and titration rate of >25 mg/week more likely to discontinue due to CAEs.
Froscher <i>et al.</i> [2005]	DB, PC	42 young adults and adults	The difference in TPM serum concentrations and dosages (mg/kg) for patients without AEs and patients with AEs was significant for the CAEs abnormal thinking, impaired concentration and speech problems.
Coppola <i>et al.</i> [2008]	OL, add-on	34 children and adolescent patients with intellectual disability	Concentration reduced in 38% and alertness reduced in 24%. However, these factors had improved significantly by 12 months.
Aldenkamp <i>et al.</i> [2000]	SB, rand, comparing TPM and VPA	53 adult patients	Short-term memory measure indicated more impairment for TPM, and performance deteriorated for auditory learning compared with improvement with VPA. Gradual titration led to fewer CAEs.
Gomer <i>et al.</i> [2007]	OL, comparing TPM and LEV	52 patients with partial epilepsy	TPM impaired cognitive speed, verbal fluency and short-term memory, whereas LEV showed no CAEs.
Jung <i>et al.</i> [2010]	OL	24 drug-naïve patients with partial epilepsy	Poorer working memory and verbal fluency, but no differences for attention, inhibitory and set-shifting measures. ERP changes seen in bilateral parieto-occipital, temporolimbic and dorsolateral right prefrontal regions.
Lee <i>et al.</i> [2003]	OL	Study 1 = 22 Study 2 = 16 Adolescent and adult patients	Withdrawal associated with better cognitive performance, e.g. verbal fluency, attention, language. However, verbal learning and memory did not improve. Also evidence of impaired concentration and visual motor speed.
Thompson <i>et al.</i> [2000]	Retro	18 young adult and adult patients	Poor verbal fluency, verbal IQ and verbal learning. Reducing or withdrawing TPM improved verbal fluency and learning. Design learning and figure recall were unimpaired.
Bootsma <i>et al.</i> [2008a]	Retro, comparing TPM and LEV	314 child and adult patients	One of most frequent AEs reported was mental slowing, reported by 13.8%. Of those who discontinued, 27.8% reported this CAE.

(continued)



Table 2. Continued

Study	Design	Sample	Key findings
Kockelmann <i>et al.</i> [2003]	OL, cont	20 adult patients with partial-onset epilepsy. 20 patient controls on other AEDs	Cognitive performance was not related to drug dose or serum levels. Attention, verbal fluency and working memory improved with withdrawal.
Blum <i>et al.</i> [2006]	DB, rand, comparing TPM and LTG	192 adults with partial seizures	Better inhibition and verbal fluency with LEV than TPM. The most common CAEs reported with TPM were memory (7%) and attention (6%) problems.
Kockelman <i>et al.</i> [2004]	Retro, comparing TPM (polytherapy) and LTG	84 adult patients	TPM was linked to worse verbal fluency and working memory, but memory and attention were relatively unaffected. TPM led to worse cognitive performance than LTG on 20 of 23 cognitive measures. There was little evidence dose was linked to cognitive performance.
Kim <i>et al.</i> [2006]	OL, comparing TPM and OXC	60 adolescent and adult patients	Worse verbal fluency and digit span for TPM. More CAEs with TPM than OXC (50% versus 20%). Few CAEs with 50 mg/day TPM (dose related).
De Araujo Filhou <i>et al.</i> [2006]	OL, comparing TPM and VPA	42 adolescent and adult patients	Worse attention, verbal fluency, processing speed and short-term memory with TPM than VPA.
Majkowska <i>et al.</i> [2005]	DB, PC	264 treatment-resistant patients with partial-onset seizures	9% reported CAEs with TPM versus 5% for PC. However, CAEs were the effects most likely to lead to discontinuation.
Baker <i>et al.</i> [2002]	OL	209 adult patients with refractory epilepsy	Low incidence of CAEs. Only 4.4% withdrew because of CAEs, which included memory difficulties (6.1%), concentration difficulties (4.5%), cognitive problems (3.0%), confusion (3.0%), and amnesia (1.5%).
Brandl <i>et al.</i> [2000]	OL, add-on (monotherapy)	53 child patients	No difference for verbal memory or Digit Symbol Substitution Test. Better cognitive profile with monotherapy than add-on.
Reith <i>et al.</i> [2003]	Retro	159 child and adolescent patients	Cognitive impairment was reported rarely (6 patients).
Arroyo <i>et al.</i> [2005]	DB, rand	470 child and adult patients	The most common neurobehavioural adverse events included concentration/attention problems (50 mg, 7%; 400 mg, 8%) and memory difficulty (4%; 8%).
Moreland <i>et al.</i> [1999]	Retro	49 child and adolescent patients	22% reported CAEs, but 16% demonstrated increased alertness.
Lee <i>et al.</i> [2006]	OL	47 adolescents and adults	After 1 year, 44% reported CAEs such as memory deficits (42%), speech problems such as tip of the tongue phenomena (25%), attention/concentration deficits (11%), and psychomotor slowing (6%).
Rosenfeld <i>et al.</i> [1997]	OL, comparing TPM and VPA	12 adult patients	Only 1 patient reported cognitive dysfunction.
Coppola <i>et al.</i> [2002]	OL, add-on	45 child and adult patients	Cognitive dulling reported in 4/45 patients.
Gerber <i>et al.</i> [2000]	Retro	75 child and adolescent patients	CAEs such as memory problems and confusion were not related to dose increase, but could be linked to existing

(continued)

Table 2. Continued

Study	Design	Sample	Key findings
Kanner <i>et al.</i> [2003]	OL	596 young adult and adult patients	behavioural problems and concurrent LTG. CAEs were reported by 41.5%. They were associated with PAEs. A past psychiatric history was a predictor of CAEs.
Mula <i>et al.</i> [2003b]	OL	431 adult patients	7.2% developed word-finding difficulties, which were related to the presence of simple partial seizures and a left temporal EEG epileptic focus. This CAE was not linked to titration rate.
Mula <i>et al.</i> [2003a]	OL, cont	70 patients with temporal lobe epilepsy and 128 with cryptogenic epilepsy	CAEs were more likely in patients with hippocampal sclerosis. The most common CAEs in this group were impaired memory (17%) and slowed thinking (13%).
Huang <i>et al.</i> [2008]	SB, comparing TPM and LEV	79 adults with partial epilepsy	No difference between AEDs using cognitive abilities screening instrument. There were slightly more cognitive complaints with TPM. For TPM, orientation scores deteriorated, but for those with existing cognitive difficulties, recent memory improved.

AEDs, antiepileptic drugs; CAEs, cognitive adverse effects; CBZ, carbamazepine; cont, controlled; DB, double-blind; ERP, event Related Potential; ETX, ethosuximide; GBP, gabapentin; HCs, healthy controls; LTG, lamotrigine; OL, open-label; OXC, oxcarbazepine; PAE, psychiatric adverse effects; PC, placebo-controlled; PHB, phenobarbital; PHT, phenytoin; rand, randomized; retro, retrospective; SB, single-blind; TPM, topiramate; VGB, vigabatrin; VPA, sodium valproate.

the children taking topiramate experienced adverse effects that could interfere with learning at school, but 20% demonstrated increased alertness or improved behaviour [Moreland *et al.* 1999]. Reassuringly, CAEs tend to reverse with discontinuation [Lee *et al.* 2006; Rosenfeld *et al.* 1997]. Studies have also indicated that certain individuals may be more vulnerable to CAEs with topiramate, including those with temporal lobe epilepsy [Mula *et al.* 2003b], existing cognitive difficulties [Coppola *et al.* 2008] or a past psychiatric history [Kanner *et al.* 2003].

#### Lamotrigine

Studies are listed in Table 3. One double-blind, placebo-controlled crossover study of 81 patients with refractory partial seizures demonstrated no adverse effect on cognition in association with lamotrigine [Smith *et al.* 1993], and other studies have reported similar findings [Bootsma *et al.* 2008b; Gillham *et al.* 2000; Aldenkamp *et al.* 1997]. For example, in a double-blind, placebo-controlled study involving children, there were no differences in the results of cognitive tasks assessing reaction time, recognition memory, attention, visual search and working memory [Pressler *et al.* 2006]. Positive effects on cognitive function in

epilepsy have also been reported [Placidi *et al.* 2000; Banks and Beran, 1991]. Attention processes, short-term memory, and motor and mental speed were investigated in 25 epilepsy patients taking carbamazepine plus lamotrigine as add-on therapy [Aldenkamp *et al.* 1997]. There were no significant score decreases after adding lamotrigine, and most changes were in a positive direction. It has been suggested that positive effects on cognition are related to EEG changes [Marciani *et al.* 1998]. Lamotrigine has also been shown to have a favourable cognitive profile in comparison with other AEDs. Verbal fluency and attentional/inhibitory performance is better than with carbamazepine [Lee *et al.* 2011], list learning may be better than with oxcarbazepine [Seo *et al.* 2007], and a double-blind, randomized study of adults with partial seizures showed performance was better with lamotrigine than topiramate for verbal fluency, the Stroop test and the DSST [Blum *et al.* 2006].

#### Oxcarbazepine

Studies have indicated no deterioration in learning, memory or attention in patients treated with oxcarbazepine [Donati *et al.* 2006; McKee *et al.* 1994], and little evidence of cognitive problems

**Table 3.** Studies on the cognitive effects of lamotrigine in patients with epilepsy.

Study	Design	Sample	Key findings
Smith <i>et al.</i> [1993]	DB, PC, rand, crossover	81 adolescents and adults with refractory partial seizures	No detrimental effect on attention, concentration or psychomotor speed.
Aldenkamp <i>et al.</i> [1997]	OL, comparing LTG + CBZ with CBZ only	25 adults with partial epilepsy	There were no significant differences for measures of motor and mental speed, and short-term memory with add-on LTG. Small changes were in the direction of improvement.
Bootsma <i>et al.</i> [2008b]	Retro	314 child and adult patients	Little evidence of CAEs. Some patients reported feeling more active and 'clear'.
Gillham <i>et al.</i> [2000]	DB, rand, comparing LTG and CBZ	260 adult patients	Evidence of improvement in cognition with LTG but deterioration with CBZ, according to a health-related quality-of-life measure.
Pressler <i>et al.</i> [2006]	DB, PC, crossover	61 children with mild or well-controlled epilepsy	There were no CAEs according to performance on measures assessing attention, reaction time, verbal and nonverbal short-term memory and working memory.
Banks <i>et al.</i> [1991]	DB, PC, crossover	25 adults with refractory partial epilepsy	LTG did not specifically impair cognitive or mnemonic function.
Placidi <i>et al.</i> [2000]	OL	13 adults with partial seizures	No negative effect on attention, reaction time, concentration or memory.
Marciani <i>et al.</i> [1998]	OL	11 adults with partial epilepsy	No evidence of CAEs.
Lee <i>et al.</i> [2001]	OL, rand, comparing LTG and CBZ	116 adults with partial epilepsy	Better performance with LTG versus CBZ for verbal fluency and inhibition/attention measures.
Seo <i>et al.</i> [1997]	Retro, comparing LTG and OXC	60 adolescent and adult patients	No differences in reported CAEs. Learning and attention measures improved for both groups, but list learning showed a greater improvement with LTG.
Blum <i>et al.</i> [2006]	DB, rand, comparing TPM and LTG	192 adults with partial seizures	Better inhibition/attention and verbal fluency with LEV than TPM. CAEs were more common with TPM. However, a few patients reported CAEs with LTG, such as memory difficulties (4/96).

AEDs, antiepileptic drugs; CAEs, cognitive adverse effects; CBZ, carbamazepine; cont, controlled; DB, double-blind; ETX, ethosuximide; GBP, gabapentin; HCs, healthy controls; LTG, lamotrigine; OL, open-label; OXC, oxcarbazepine; PC, placebo-controlled; PHB, phenobarbital; PHT, phenytoin; rand, randomized; retro, retrospective; SB, single-blind; TPM, topiramate; VGB, vigabatrin; VPA, sodium valproate.

after 4–12 months of treatment [Aikiä *et al.* 1992]. A multicentre, randomized, open-label study in children and adolescents reported little evidence of CAEs [Donati *et al.* 2007], while another study involving children with benign epilepsy with centrotemporal spikes showed no deterioration in cognitive tasks, and evidence of mild improvement in some cases [Tzitiridou *et al.* 2005]. One study documented improvement in an information processing speed task in patients with partial epilepsy [Donati *et al.* 2006].

#### Levetiracetam

Studies are listed in Table 4. In one study of patients with intractable epilepsy, levetiracetam was compared with topiramate [Huang *et al.* 2008]. There were no significant differences in cognition for these AEDs, and no significant negative effects were reported with the use of levetiracetam in this study. Many other studies have reported no detrimental effects on cognition [Levisohn *et al.* 2009; Huang *et al.* 2008; Gomer *et al.* 2007; Piazzini *et al.* 2006]. No

**Table 4.** Studies on the cognitive effects of levetiracetam in patients with epilepsy.

Study	Design	Sample	Key findings
Huang <i>et al.</i> [2008]	SB, comparing LEV and TPM	79 adults with partial epilepsy	No difference between AEDs using cognitive abilities screening instrument. There were slightly more cognitive complaints with TPM.
Gomer <i>et al.</i> [2007]	OL, comparing LEV and TPM	52 adults with partial epilepsy	No CAEs on tests of cognitive speed, verbal fluency and short-term memory with LEV, but differences for TPM. Cognitive performance not related to dose.
Levisohn <i>et al.</i> [2009]	DB, PC, rand	120 child and adolescent patients	CAEs were reported more frequently for LEV versus placebo (9.4% vs. 2.9). These included memory and attentional problems.
Piazzini <i>et al.</i> [2006]	OL, cont, add-on	35 adults with treatment-resistant partial epilepsy, 35 similar controls on usual treatment	Significant improvements in attention and verbal fluency were seen with the addition of LEV.
Neyens <i>et al.</i> [1995]	SB, add-on	10 adult patients taking CBZ or PHT	No cognitive differences with LEV on tasks involving attention, memory and information processing.
Wheless and Ng [2002]	OL, add-on	39 child patients	Improvements in cognition/concentration (13%) and alertness (13%) were reported by some patients. In some patients these effects seemed unrelated to seizure control.
Von Stülpnagel <i>et al.</i> [2010]	OL	32 children with benign idiopathic partial epilepsies of childhood	According to parent interview, cognition improved in 10/32 patients and worsened in none. Improved cognition was reported in cases showing reduced seizures.
Helmstaedter and Witt [2010]	OL, comparing LEV and CBZ	498 adult patients	Patients taking LEV rated their cognitive status as improved and showed improvements on verbal learning and memory tasks.
Cramer <i>et al.</i> [2000]	DB, PC, rand, add-on	246 adults with partial-onset seizures	Cognitive functioning was reported as improved on a quality-of-life measure in comparison with placebo.
Wu <i>et al.</i> [2009]	OL	94 adults with generalized tonic-clonic or partial-onset seizures	Mini-Mental State Examination scores improved by 1 year, including most significant improvement for short-term memory recall and language.

(continued)

**Table 4.** Continued

Study	Design	Sample	Key findings
Ciesielski <i>et al.</i> [2006]	OL, add-on, comparing LEV and PGB	20 adults with treatment-resistant partial epilepsy	Trend for improvement in visual short-term memory with LEV, but no significant differences for attention, working memory or executive function tasks. No significant differences between AEDs for cognition.
López-Góngora <i>et al.</i> [2008]	OL, add-on	32 adult patients	Evidence of improvements in working memory, verbal fluency, motor functioning, attention and prospective memory.
Rosche <i>et al.</i> [2004]	Retro, comparing LEV and TPM	39 adult patients	Minor improvements in cognition for LEV but not TPM. Improved digit span and fluid intelligence scores.
Helmstaedter <i>et al.</i> [2008]	OL, cont	288 adult patients, 43 patients on usual medication	Reports of improved psychomotor speed, concentration, and remote memory. Such effects were not related to type of epilepsy, cotherapy, dose, drug load or psychiatric history.
Zhou <i>et al.</i> [2008]	DB, PC, rand, then OL	28 adults with partial-onset seizures	Better set-shifting and delayed logic memory soon after treatment. Improved verbal fluency, attention and other aspects of memory. Improved cognition according to quality-of-life measure.
Lippa <i>et al.</i> [2010]	OL	24 elderly patients with cognitive impairment	Improved Mini-Mental State Examination score and cognitive functioning according to Alzheimer's Disease Assessment Scale.

AEDs, antiepileptic drugs; CAEs, cognitive adverse effects; CBZ, carbamazepine; cont, controlled; DB, double-blind; ETX, ethosuximide; GBP, gabapentin; HCs, healthy controls; LTG, lamotrigine; OL, open-label; OXC, oxcarbazepine; PC, placebo-controlled; PHB, phenobarbital; PHT, phenytoin; rand, randomized; retro, retrospective; SB, single-blind; TPM, topiramate; VGB, vigabatrin; VPA, sodium valproate.

significant changes in psychomotor function, memory or information processing were found in a study of 10 patients when levetiracetam was added to carbamazepine or phenytoin [Neyens *et al.* 1995]. In fact, levetiracetam seemed to improve reaction time, tapping rate and memory.

Other studies have reported improved cognitive functioning with levetiracetam. An open study

reported improvements in cognition/behaviour in 10 of 39 children [Wheless and Ng, 2002], while another study involving children with atypical benign childhood epilepsy found that 10 of 32 patients reported improvements in cognition, while the remainder stated no differences [Von Stülpnagel *et al.* 2010]. One controlled study provided more conservative estimates of improvement [Helmstaedter and Witt, 2010], reporting that executive functions improved in 15% but

deteriorated in 5% of patients. Some studies report improved cognition according to quality-of-life scores [Wu *et al.* 2009; Cramer *et al.* 2000].

Levetiracetam may have the potential to improve a range of cognitive abilities. These include visual short-term memory [Ciesielski *et al.* 2006], working memory [López-Góngora *et al.* 2008; Rosche *et al.* 2004], motor functions [López-Góngora *et al.* 2008], psychomotor speed and concentration [Helmstaedter *et al.* 2008], and fluid intelligence [Rosche *et al.* 2004]. A randomized, double-blind, placebo-controlled study reported improved performance in set-shifting, attention and delayed logic memory tasks in patients with partial seizures in comparison with controls [Zhou *et al.* 2008]. One study reported that improvements in prospective memory, working memory and motor functions were related to seizure reduction [López-Góngora *et al.* 2008]. However, improvements in psychomotor speed, concentration and remote memory were not related to type of epilepsy, medication parameters or psychiatric history in another study [Helmstaedter *et al.* 2008].

Individuals with existing cognitive weaknesses may benefit most from levetiracetam. A blinded study showed recent memory improved most in patients with poor baseline scores [Huang *et al.* 2008]. In addition, at least two studies have reported improvements on the Mini-Mental State Examination with use [Lippa *et al.* 2010; Wu *et al.* 2009], one of these in elderly patients with cognitive impairment [Lippa *et al.* 2010].

## Discussion

### *Summary of study findings*

The older agents likely to have the greatest cognitive toxic potential are phenobarbital and perhaps primidone. Carbamazepine has the potential to lead to mild but sometimes significant difficulties relating to motor speed and performance on more attention-demanding tasks. The cognitive effects associated with phenytoin may be more obvious but are generally restricted to visually guided motor functions. Minimal difficulties are also likely with sodium valproate taken at low doses. Further investigation is needed, but ethosuximide may be the older drug that shows the best cognitive profile.

With regards to newer drugs, topiramate is associated with more consistent evidence of detrimental influences on cognition. Little data are available at present for zonisamide, but findings so far indicate that adverse long-term effects are possible. Study findings for tiagabine are relatively promising, with the potential for positive effects on verbal fluency and visuomotor performance, although it is unclear whether these may be the result of seizure control. There is currently limited evidence of CAEs with the use of clobazam, and reported 'abnormal thinking' in association with pregabalin requires further specification. There is only limited evidence that vigabatrin interferes with cognition and this agent may exert a range of cognition-enhancing effects, including improvements in memory and mental flexibility. However, its use is restricted owing to reported visual field defects. More favourable options may include gabapentin and oxcarbazepine, which have been associated with only minor cognitive difficulties. Based on the evidence reviewed, the agents least likely to interfere with cognitive processes are levetiracetam and lamotrigine. The current review indicates the most consistent evidence of widespread positive effects on cognition is for levetiracetam, which may be particularly beneficial in cases with existing cognitive limitations.

### *Implications for clinical practice*

Importantly, the data reviewed suggest that the effects exerted by an AED could vary depending on factors linked to patient characteristics and individual susceptibility. Although reported findings are mixed, many of these potentially influential treatment and patient variables clearly compel further investigation in more focused and rigorous experimental designs.

The amount of an AED administered, or AED combinations, may be linked to the incidence of cognitive effects. CAEs may be dose related for phenytoin [Gillham *et al.* 1990], zonisamide [Park *et al.* 1999] and carbamazepine [Gillham *et al.* 1988], with the strongest evidence available for topiramate [Kim *et al.* 2006; Lee *et al.* 2006; Froscher *et al.* 2005; Thompson *et al.* 2000]. However, other studies report no relationship between CAEs and dose for valproate [Ristic *et al.* 2006; Gillham *et al.* 1991], topiramate [Kockelmann *et al.* 2004; Kockelmann *et al.* 2003; Gerber *et al.* 2000] and levetiracetam [Helmstaedter *et al.* 2008; Gomer *et al.* 2007]. Drug concentration has been linked to CAEs

for valproate [Forsythe *et al.* 1991; Galassi *et al.* 1990], carbamazepine [Gillham *et al.* 1988; O'Dougherty *et al.* 1987] and topiramate [Froscher *et al.* 2005]. Other studies have reported no such association for valproate [Brouwer *et al.* 1992], topiramate [Kockelmann *et al.* 2003] and phenobarbital [Manni *et al.* 1993]. Titration rate is also potentially influential, and there is mixed evidence regarding whether this factor may lead to increased risk of CAEs with topiramate [Mula *et al.* 2003b; Tatum *et al.* 2001; Aldenkamp *et al.* 2000].

The use of concurrent medications appears to increase the likelihood of CAEs with many AEDs such as valproate [Gillham *et al.* 1991], carbamazepine [Gillham *et al.* 1988] and topiramate [Brandl *et al.* 2010; Mula *et al.* 2003b], but is perhaps less relevant in relation to levetiracetam [Helmstaedter *et al.* 2008]. Combining topiramate with lamotrigine led to an increased likelihood of cognitive problems in one study [Gerber *et al.* 2000].

Certain individuals may be more vulnerable to the CAEs associated with particular AEDs. These include refractory cases, patients with different kinds of epilepsy and younger or older patients. One study of vigabatrin reported CAEs in a relatively limited set of individuals classified as nonresponders [Grunewald *et al.* 1994], although the characteristics of these individuals were poorly specified. Improvements in seizure control are particularly important in relation to attributing the cause of positive effects on cognition. In relation to levetiracetam, some studies report associations between enhanced cognition and seizure reduction [Von Stülpnagel *et al.* 2010], while others argue improvements may be independent of seizure reduction [Wheless and Ng, 2002]. Although AEDs such as topiramate and carbamazepine could have the potential to affect cognitive function in a wide variety of cases, some studies have reported that temporal lobe epilepsy may be a risk factor for the development of CAEs [Mula *et al.* 2003a, 2003b; Gigli *et al.* 1996]. Word-finding difficulties in particular have been linked to the presence of simple partial seizures and left temporal EEG focus [Mula *et al.* 2003b]. There is little evidence that patients with a longer history of epilepsy are more likely to be susceptible to CAEs with sodium valproate [Ristic *et al.* 2006; Galassi *et al.* 1990], although duration of drug intake has been shown to be a related factor for CAEs

with carbamazepine [Shehata *et al.* 2009]. Age has sometimes been shown to be unrelated to the presence of CAEs [Ristic *et al.* 2006], but is likely to play a role in the expression of cognitive difficulties, and one complicating factor in the examination of age effects is the use of differing instruments with individuals of different age groups.

Current or previous cognitive or psychiatric problems may also be linked to the cognitive effects of an AED. With topiramate, CAEs may be most likely in individuals with intellectual disability [Coppola *et al.* 2008] or previous cognitive difficulties [Gerber *et al.* 2000]. Other risk factors associated with the use of topiramate in adults include the occurrence of psychiatric adverse events and having a past psychiatric history [Kanner *et al.* 2003], and depression and hippocampal sclerosis in temporal lobe epilepsy [Mula *et al.* 2003a]. In relation to levetiracetam, one study reported that psychiatric history was not associated with cognitive effects [Helmstaedter *et al.* 2008], although another report indicated this agent could be more likely to lead to cognitive improvements in cases with existing cognitive difficulties [Huang *et al.* 2008].

#### *Limitations and recommendations for future research*

Particular AEDs may have greater potential for negative or beneficial impacts on cognition in epilepsy, and these effects may be mediated by both treatment and patient characteristics. However, it is difficult to compare findings across studies owing to variation in study design, treatment group and assessment tools. Analysis is also limited by the availability of studies for particular agents. Many investigations have been conducted into agents including topiramate, whereas there are limited data available for AEDs such as ethosuximide and pregabalin.

There are significant difficulties relating to the consistency of available information pertaining to study methodology. Many studies fail to assess cognitive effects using a wide variety of tasks. Some reports fail to clearly indicate patient characteristics such as epilepsy type, seizure type or focus (left/right/frontal/temporal). Other useful information such as effect size is rarely available. Furthermore, many reports have failed to investigate predictive factors for the development of CAEs. Future studies should seek to determine whether reported changes in

cognition are linked to drug efficacy in treating seizures rather than direct effects on cognition *per se*.

It can be particularly difficult to differentiate between AEDs on the basis of cognitive findings. In some cases there could be age-difference effects, which could partly reflect the assessment of children through behavioural observation and parent report, by comparison with older patients' self report. The inclusion of different kinds of patient groups (e.g. treatment-naïve patients, refractory patients, patients with epilepsy after brain injury) and control measures (healthy individuals or nonmedicated patients; no treatment, placebo or alternative medication etc.) further complicate comparisons across studies. The CAEs reported by these studies will at least partly reflect the differing clinical characteristics and specific vulnerabilities of the groups compared.

Another problem relates to poor definitions of cognitive functions, and lack of consensus in the terms used to refer to cognitive abilities. Some studies refer to 'mental processing speed', others refer to 'psychomotor speed', and yet others use terms such as 'information processing rate'. It is often unclear as to whether such descriptions refer to the same ability. Vague terms are also used, such as 'cognitive dulling' and 'abnormal thinking'. These need to be better specified in order to be informative. In addition, particular tasks are sometimes reported as measuring slightly different cognitive abilities that are often closely linked, such as memory, learning and attention. For example, tasks such as the Stroop test may be considered to make demands in terms of attention, concentration, response inhibition and maybe even memory. Future studies need to use consistent, more precisely defined terms and consider the individual contributions of different cognitive abilities or processing stages involved in tasks and assessments.

A number of randomized, double-blind trials have been conducted. These studies appear favourable as they control for bias, although this approach could lack ecological validity. Add-on trials may be problematic because of a possible increase in the incidence of side effects due to the potentiation of toxicity. However, these studies do have value in relation to current prescribing practices, as many patients are only successfully

treated with a combination of different AEDs. What may constitute a more rigorous investigation may provide data that are not so readily applicable in everyday clinical practice. Consistent evidence across studies using rigorous and more naturalistic methods will provide a good indication of the reliability of study findings.

More specific, systematic studies are needed to fill the gaps in our knowledge and follow up reported patterns in the literature about the cognitive effects linked to AEDs. Longer-term investigations would also offer critical insight, because individuals may gradually develop tolerance to an AED's side effects. It is also informative for studies to investigate whether performance alters on discontinuation, in order to determine if effects are reversible. Systematic trials are needed that compare the effects of commonly prescribed agents across subgroups of patients with epilepsy (e.g. in partial *versus* generalized epilepsy). Comparing age-defined subgroups could also be useful, as drug effects are likely to differ between younger and older children.

A wide range of assessments clearly need to be included in future research. Studies investigating cognition should include tests of a range of executive functions including working memory; verbal fluency; response inhibition; set-shifting and measures assessing transient, sustained and divided attention; short and long-term aspects of verbal and visual memory; and motor functioning including dexterity and reaction time tests. One useful outcome of future research would be the identification or development of tailored instruments that are sensitive to the specific cognitive changes associated with particular AEDs.

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