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Neuropsychological and Behavioral Effects of Antiepilepsy Drugs

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Abstract Antiepilepsy drugs work by decreasing neuronal irritability, which may also result in the non-desired side effect of decreased neuropsychological function. In addition to cognitive side effects, antiepilepsy drugs (AEDs) may be associated with behavioral effects which may range from irritability and hyperactivity to positive psychotropic effects on mood. There have been many new medications released since the 1990s, and although they tend to have more favorable side effect profiles compared to their older counterparts, there continues to be a risk of decreased cognitive function with the majority of these agents. The effects of in utero antiepilepsy drug exposure are increasingly being investigated, and differential drug risk is beginning to be described for both anatomic and cognitive outcomes. Patients with epilepsy undergoing neuropsychological evaluations are commonly on AEDs, and it is important for the clinician to recognize the potential contribution of AED therapy to neuropsychological profiles. The present article serves to provide an overview of our current understanding regarding the risks of antiepilepsy drug use for both cognitive and behavioral side effects.

Keywords Antiepilepsy drugs · Neuropsychological · Cognitive and behavioral side effects

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Patients with epilepsy often have cognitive or behavioral difficulties, which may include mild attention and concentration problems, difficulty in recent memory and learning, executive dysfunction, and social intelligence, as well as non-cognitive features of hyperactivity, irritability, and mood disturbance. Many factors potentially contribute to neuropsychological and cognitive performance in epilepsy patients including etiology and underlying brain substrate giving rise to a patient's epilepsy, seizure type and seizure syndrome, the age of seizure onset, and age at the time of the precipitating injury, as well as seizure-specific influences including seizure frequency, intensity, and duration (Lennox 1942; Meador 2005).

Although neuropsychological function is multifactorial and will reflect multiple contributions, understanding the effects of antiepilepsy drugs (AEDs) on cognitive and behavior has special significance since the selection of AEDs can often be modified not only according to traditional measures of treatment effectiveness such as efficacy and tolerability, but also with respect to negative neuropsychological side effects. Because many AEDs have positive psychotropic benefits, these effects may affect initial treatment choice, or subsequently modify AED treatment selection. After choosing the medication based upon seizure type or epilepsy syndrome in order to maximize treatment efficacy, the cognitive and behavioral risk/benefit ratio is a primary factor to consider when formulating treatment plans. The presence of cognitive side

effects associated with AEDs is an important concern described by epilepsy patients taking medications (Carpay et al. 2005). Consequently, it is important for the neuropsychologist to be able to determine the potential contributions of AEDs to cognitive performance, as well as the patient's subjective perception of performance which may be mediated by mood and affective state.

Antiepilepsy drugs are developed to decrease neuronal irritability, which reduces the likelihood of seizure development and propagation. Although all AEDs do not necessarily have the same relationship between electrophysiological slowing and decreased cognition (Salinsky et al. 2005a), reduced neuronal excitability is thought to be a primary factor contributing to decreased neuropsychological function. Different AEDs may be associated with greater risks of neuropsychological impairment, and when neuropsychological deficits emerge, all neuropsychological domains are not affected equally. Confounding the application of these principles on the individual patient level, therapeutic doses for individual patients also vary considerably. Since many cognitive deficits emerge in a dose-dependent fashion, successful epilepsy management at low doses for a given agent may not be associated with meaningful drug-related side effects, although if higher doses are necessary to achieve seizure freedom, cognitive side effects might then emerge. In addition, there is a poor correlation between subjective reports of cognitive difficulty and objective neuropsychological performance. Patients are understandably more likely to attribute cognitive difficulty to external causes such as medications rather than their disease, and beneficial effects on mood may decrease the likelihood of subjective cognitive complaint.

Individual variability exists with respect to developing cognitive side effects; doses that are generally associated with a high risk of cognitive impairment at the group level may produce little or no cognitive difficultly in selected individual patients. Conversely, relatively low doses that would not usually be considered to impair cognition may, in selected cases, result in notable cognitive difficulty. This individual response variability in one of the great contemporary clinical research challenges, namely, being able to develop techniques to identify individual patient characteristics that can be used prospectively to match patients with AEDs with a high likelihood of treatment combined with a small chance of adverse somatic or behavioral side effects (e.g., pharmacogenomics).

The magnitude of AED-related cognitive impairment is generally modest in monotherapy, and also when serum AED concentrations are within standard therapeutic ranges. Nevertheless, diminished quality of life (Gilliam 2002) and mild memory effects may be observed with therapeutic blood levels. Thus, important cognitive or behavioral side effects may still be present even when AEDs are used appropriately and there is no manifest drug toxicity on the clinical examination.

Even with relatively mild cognitive side effects, there are circumstances or contexts in which decreased cognitive function assumes greater importance such as with learning and school performance in children (Aldenkamp et al. 1995; Loring and Meador 2004), when driving or operating machinery, or when cognitive skills may be vulnerable such as with the elderly (Aldenkamp et al. 1995). The risks of cognitive side effects increases with polypharmacy and with increasing AED dosages/blood levels that are sometimes necessary to treat difficult to control epilepsy (Meador 2005). Decreasing the number of AEDs frequently improves cognition and may even reduce the number of seizures (Vermeulen and Aldenkamp 1995). Nevertheless, the goal of epilepsy treatment is complete elimination of seizures, not simply seizure frequency reduction, and for some patients this requires polypharmacy. In these cases, the trade-off between the benefits of reduced seizure frequency are balanced against negative effects of AEDs related to cognitive, quality of life, and general health issues. This cost-benefit ratio needs to be determined on an individual patient level on the basis of specific individual preferences and clinical condition. These considerations will change based upon such factors of seizure type and syndrome, patient age, family and social support, or monotherapy versus polytherapy, and co-morbid disease.

Individuals over 65 years of age have the highest incidence of epilepsy among all adult age groups: approximately twice that associated with younger adults. Older AEDs are often used in this population, although the elderly have increased susceptibility to the cognitive effects of these agents (Garrard et al. 2003, 2007; Lackner et al. 1998) for both pharmacodynamic and pharmacokinetic reasons. For example, cognitive side effects of benzodiazepines appear to increase the risk of hip fracture in the elderly (Cumming and Le Couteur 2003). Nevertheless, there are few studies that have specifically examined the cognitive effects of AEDs in persons over the age of 65 years.

Our understanding of the comparative neuropsychological effects of AEDs has been limited due the absence of direct head-to-head comparative AED studies with appropriate experimental designs. Although it is beyond the scope of this paper to review the methodological concerns associated with establishing the relative cognitive and behavioral risk of AEDs, there are three primary issues making this a difficult area to perform studies in a largely clinical setting. The first results from failure to randomize to clinical treatment, since patients with more difficult to control epilepsy are more likely to try newer drugs, and hence, have cognitive skills prior to treatment that are not

representative of the population. The second factor reflects difficulty in establishing comparable drug levels since patients are treated clinically across a wide range effective dosing, but which may have varying effects on cognitive function. Third, the absence of blinding is also a concern in many studies. Finally, variance in seizure control may alter results. For example, patients who are not controlled by a specific AED are likely to have the AED change, and consequently, are lost to follow up neuropsychological assessment.

There are several additional methodological issues. The choice of specific neuropsychological measures and differing test-rest schedules also contributes to our difficulty of making direct AED comparisons. Neuropsychological test selection is not trivial since even similar appearing measures such as the California Verbal Learning Test and Rey Auditory Verbal Learning test have differing sensitivity to the effects of lateralized epilepsy. Further, the duration of treatment used in some of the crossover studies may be inadequate to determine the effects of long term therapy on neuropsychological status, a concern that holds special significance for pediatric AED studies since the cognitive effects occur against the backdrop of normal cognitive development.

Similar limitations exist when trying to characterize psychiatric side effects of AEDs. Because behavioral and psychiatric side-effects are not formally assessed in most clinical trials, they are usually reported by combining events into a single overall psychiatric variable. In addition to psychiatric adverse events being poorly defined using common reporting systems (e.g., WHO, CO-START), the absence of standardized or structured approaches to characterized behavioral AED-induced changes makes replication by independent investigators and comparisons across agents difficult.

Antiepilepsy drugs are often conceptualized as either "older" (in widespread use before the 1990s) or "newer" (introduced in the 1990s or later) agents. Among the older agents, a greater risk of cognitive impairment is associated with barbiturates and benzodiazepines. Across the other older medications, which we discuss below, carbamazepine (Tegretol, Carbatrol), phenytoin (Dilantin), and valproate (Depakote), few consistent differences in neuropsychological side effects exist, and there are generally modest cognitive effects when these medications are used in monotherapy and when doses are in therapeutic ranges.

After many years of relatively few AED treatment options from which to choose, many new AEDs were introduced beginning in the 1990s. Although these treatments did not provide the hoped-for significant overall improvement in treatment efficacy, these agents are generally associated with more favorable neuropsychological profiles. In addition, since patient responses differ for individual treatments, additional AEDs increase the probability of finding a safe and effective medication on the individual level, although the likelihood of become seizure free after failing any two AEDs is low (Kwan and Brodie 2001a). Many studies of the newer AEDs have used older AEDs as comparators rather than direct comparisons across newer AEDs simultaneously. Consequently, additional comparative studies are needed in order to make a full determination across all AEDs. Behavioral and cognitive side effects are important components in evaluating overall treatment effectiveness (Kwan and Brodie 2001b).

Older AEDS

Phenytoin (Dilantin) and carbamazepine (Tegretol, Carbatrol) remain two of the most commonly prescribed medications; in fact, carbamazepine is the most widely prescribed medication worldwide. The reason for the continuing popularity of these drugs includes a variety of factors, such as an established efficacy with a known safety and side effect profile, as well as cost, which is considerably less than for newer agents. Carbamazepine and phenytoin do not have distinct neuropsychological profiles from each other as demonstrated in several blinded, randomized, crossover, monotherapy study in patients with newly treated partial epilepsy (Dodrill and Troupin 1991; Meador et al. 1990). The cognitive effects of carbamazepine and phenytoin are slightly better than phenobarbital (Meador et al. 1990). However, across all three drugs, similar neuropsychological performance was seen across the majority of neuropsychological tests. Because a placebo condition cannot be easily conducted in a monotherapy patient population due to ethical concerns involved with failure to provide established efficacious treatment, it is difficult to determine whether the absence of a more robust phenobarbital effect was due to the treating physician, who was unblinded to specific treatment condition, minimizing phenobarbital dose to the lower end of the expected therapeutic blood levels because of observed complaints of sedation.

In addition to the difficulty in obtaining baseline or non-drug condition against which various drug conditions can be compared, one of the limitations of performing AED studies in patient populations is the potential confounding effects that seizures as well as the effects of the underlying brain substrate have on cognition. The potential interaction of brain impairment on cognitive risk, in which a small cognitive effect may create no additional burden in an already compromised system, may have the potential for greater disruption when used in populations without the

same baseline impairments. This is particularly important for AEDs since they are often prescribed for non-epilepsy indications such as pain or various psychiatric disorders. Because of these issues, as well as the aforementioned concern regarding the difficulty of obtaining non-drug/baseline performance levels in most monotherapy epilepsy population, cognitive, and behavioral effects of AEDs have also been studied in healthy volunteers thereby allowing some estimate of the overall cognitive burden. In these studies, no consistent neuropsychological differences have been found between carbamazepine, phenytoin, and valproate (Meador et al. 1991, 1993), although as with the patient study, phenobarbital is associated with the greatest neuropsychological risk (Meador et al. 1995). Combining drugs to estimate drug effects relative to non-drug conditions, approximately half of the neuropsychological variables, which consisted of tests of motor and psychomotor speed, attention, memory, and learning, were negatively affected by AEDs in comparison to the non-drug condition.

Although now over 20 years old, the Veterans Administration (VA) Cooperative study comparing the cognitive effects of carbamazepine, phenobarbital, phenytoin, and primidone in patients with new-onset epilepsy remains one of the best patient studies examining the cognitive effects of AEDs using the older agent (Mattson et al. 1985). Little consistent pre- to post-AED treatment change in neuropsychological outcomes were observed, but results were confounded by design issues (Meador 2005). A second VA Cooperative study also found no consistent cognitive differences between carbamazepine and valproate when used in the initial treatment of partial epilepsy, although both drugs apparently diminished the expected practice effect from repeated testing, suggesting modest cognitive AED effects (Prevey et al. 1996). Several other patient studies report modest negative effects of carbamazepine and phenytoin on cognition, with little meaningful differences between them (Pulliainen and Jokelainen 1994; K. R. Smith Jr. et al. 1994). Thus, among the older AEDs, there appears to be little difference in neuropsychological function among carbamazepine, phenytoin, and valproate. Because carbamazepine has become the most widely prescribed AED worldwide, and because it has established tolerability and known risks of adverse events, it is a common AED comparator against which the cognitive profiles of newer AEDs can be established.

The behavioral effects of phenobarbital are well established, with a high rate of drug discontinuation due to hyperactivity in multiple clinical reports (Glauser 2004; Herranz et al. 1988; Wolf and Forsythe 1978). Children prescribed phenobarbital for seizure prophylaxis after a febrile seizure tend to have lower IQs or display IQ declines compared with controls (Anonymous 1992; Farwell et al. 1990), although this difference does not always reach significance (Wolf et al. 1981). IQ improves following PB discontinuation (Anonymous 1992; Farwell et al. 1990; Sulzbacher et al. 1999), as does its negative effect on P300 latency (Chen et al. 2001). However, the effects of phenobarbital may still be detected on measures of academic achievement when tested as many as three to 5 years later (Sulzbacher et al. 1999). Based upon the persistence of cognitive side effects following drug discontinuation, it appears that many children do not fully catch up and compensate for "lost time" associated with decreased cognitive processing during drug therapy, which illustrates the importance of conducting pediatric AED studies to determine the effects of these treatments on cognition in the developing brain.

Newer AEDs

Since the early 1990s, many AEDs were introduced including felbamate (Felbatol) gabapentin (Neurontin), lamotrigine (Lamictal), pregabalin (Lyrica), topiramate (Topamax), tiagabine (Gabatril), vigabatrin (Sabril), levetiracetam (Keppra), and zonisamide (Zonegran). Despite the large number of new agents, the majority of neuropsychological studies have compared newer drugs to older AEDs with a higher risk of cognitive impairment, or against newer drugs at doses that do not reflect current prescribing patterns, making the comparative effects of newer agents incompletely established. Direct head-to-head comparative studies of newer drugs likely will require federal support such as with the VA cooperative studies rather than relying only on industry funded research. Because there are no significant differences in efficacy, the primary benefit of many newer agents is better tolerability, which includes neuropsychological factors and psychiatric side effects.

Felbamate (Felbatol)

Felbamate (Felbatol) is a broad-spectrum AED that was approved in the United States in 1993 for both partial and generalized seizures. Because it was the first of the "new generation" AEDs to become available in the 1990s, its release was enthusiastically anticipated. Soon after it was available, unfortunately, felbamate was found to cause idiosyncratic adverse events including aplastic anemia and liver failure. Although never removed from the market, felbamate use has been limited by its serious side effect profile. Anecdotally, felbamate is described as "alerting," which may be a beneficial feature for some patients, but can be problematic for others. Although a decade's worth of experience in which approximately 35,000 new exposures occurred with only a single case of aplastic anemic reported (Pellock et al. 2006), no neuropsychological or behavioral

studies have been conducted and it is unlikely that any formal studies will be conducted.

Gabapentin (Neurontin)

Gabapentin (Neurontin) has a novel mode of action, which is thought to involved potentiation of GABA-mediated inhibition and possibly inactivation of sodium channels. It was approved by the FDA in 1993 for adjunctive therapy in the treatment of partial epilepsy. Gabapentin enjoys a favorable CNS-related side effect profile, with few CNS effects reported, even at relatively high doses or with rapid dose escalation (Chadwick et al. 1998).

The cognitive and neuropsychological effects of gabapentin also appear to be relative few. In healthy volunteers, single low gabapentin doses were associated with EEG slowing but with subtle improvement in concentration (Saletu et al. 1986). Of course, the generalizability of any single dose findings to chronic therapy is extremely limited.

In a longer term healthy volunteer term study contrasting gabapentin with carbamazepine in a randomized double blind crossover design, better performance associated with gabapentin compared to carbamazepine on 8 of 31 neuropsychological measures (Meador et al. 1999). Compared to non-drugs, carbamazepine was associated with decreased performance on 13 measures, whereas gabapentin performance was poorer than non-drug on four variables. One measure (verbal memory) was better on gabapentin than non-drug. In a different report, no carbamazepine versus gabapentin differences were reported on a brief neuropsychological test battery or in quantitative EEG in a double-blind, parallel-group study in healthy volunteers (Salinsky et al. 2002). Both studies suggest that gabapentin, although well-tolerated cognitively, is not without some small risk to neuropsychological function.

Because of its favorable safety profile and absence of drug–drug interactions, gabapentin is frequently used to treat seizures in the elderly, and its cognitive effects in this population appear similar to those observed in younger subjects, with fewer cognitive side effects compared to carbamazepine in a randomized, double-blind crossover study of healthy elderly volunteers (Martin et al. 2001).

In an add-on study with patients on established AED treatments, gabapentin was associated with improved performance on 1/10 cognitive measures (Stroop Word Reading) (Mortimore et al. 1998). Several dose-ranging studies, one adjunctive and one with monotherapy conversion to gabapentin, have failed to demonstrate a significant dose effect over the ranges of 600–2,400 mg/day (Dodrill et al. 1999; Leach et al. 1997). Thus, across multiple reports including patients and healthy volunteers, and across multiple dose ranges, the cognitive effects of gabapentin appear modest, and generally less than those associated with carbamazepine.

Although gabapentin is well tolerated, it has been reported to produce behavioral side effects in children, including irritability, hyperactivity, and agitation (D. O. Lee et al. 1996; Wolf et al. 1995). According to the package insert, the most significant behavioral effects in pediatric epilepsy patients these can be classified into the following categories: 1) emotional lability (primarily behavioral problems); 2) hostility, including aggressive behaviors; 3) thought disorder, including concentration problems and change in school performance; and 4) hyperkinesia (primarily restlessness and hyperactivity). In adult patients with epilepsy, a chart review revealed that gabapentin was associated with less than 1% incidence of behavioral side effects (Weintraub et al. 2007), suggesting an age-dependent risk for behavioral side effects.

Lamotrigine (Lamictal)

Lamotrigine is thought to act by stabilizing sodium channels and reducing glutamate (Leach et al. 1986). It was approved in 1994 as adjunctive treatment for partial and generalized epilepsy, and for conversion to monotherapy in partial epilepsy patients being treated with other AEDs. Although lamotrigine is generally well tolerated, risk of serious rash including Stevens-Johnson syndrome has resulted in a “black box” warning in its FDA package insert. With proper titration, the risk of serious rash with lamotrigine appears no greater than with carbamazepine (Brodie et al. 1995; Mackay et al. 1997; Wong et al. 2001).

Lamotrigine is associated with fewer CNS adverse effects on measures such as eye movements and body sway than diazepam, carbamazepine, and phenytoin (Cohen et al. 1985; Hamilton et al. 1993), and is associated with better neuropsychological outcome compared to carbamazepine in more than half of neuropsychological measures employed (e.g., cognitive speed, memory, mood factors, sedation, perception of cognitive performance, and quality of life) in healthy volunteers (Meador et al. 2001). The superiority of lamotrigine over older AEDs has been demonstrated in multiple healthy volunteer studies (A. P. Aldenkamp et al. 2002; Cohen et al. 1985; Hamilton et al. 1993).

Similar neuropsychological findings have been demonstrated in patient studies, with no incremental impairment noted in add-on studies compared to placebo (Placidi et al. 2000; Smith et al. 1993). In children, no significant differences were present for lamotrigine compared to placebo on a computerized battery of cognitive tests (Pressler et al. 2006). In the recent VA Cooperative study of elderly patients with new onset epilepsy, lamotrigine was the best tolerated, followed by gabapentin and then carbamazepine, although no formal neuropsychological data was reported (Rowan et al. 2005). Based upon available data, it appears that lamotrigine is associated with a favorable neuropsy-

chological profile in both young and older adults, as well as children with epilepsy.

Lamotrigine has beneficial effects on mood, and although AEDs are often used in off-label application in psychiatry, lamotrigine received an FDA indication in 2003 for use in the treatment of bipolar disorder. Multiple epilepsy patient studies have demonstrated beneficial effects of lamotrigine on quality of life compared to either carbamazepine or placebo (Brodie et al. 1995; Gillham et al. 1996; D. Smith et al. 1993). The positive psychotropic properties of lamotrigine have been reported in epilepsy patients with severe cognitive impairment as well as in patients diagnosed with bipolar disorder (Buchanan 1995; Meador and Baker 1997; Uvebrant and Bauzienè 1994). These effects are not simply the result of decreased seizure frequency or severity, and one could certainly argue that if better seizure control were the cause of improved mood, other AEDs which reduce seizures should have a similar effect.

Levetiracetam (Keppra)

Levetiracetam's mechanism of action, though incompletely established, putatively involves the modulation of the protein functions of the synaptic vesicle protein SV2A, which is its binding site and was approved by the FDA in 1999 for adjunctive use in treating partial epilepsy. Levetiracetam has a favorable side effect profile based upon standard tolerability metrics such as somatic adverse events (including CNS), although few published studies of formal neuropsychological data exist. One small study found no changes in cognitive performance in patients with chronic epilepsy who were treated with levetiracetam (Neyens et al. 1995). When comparing levetiracetam to carbamazepine or oxcarbazepine in healthy volunteers, carbamazepine had the greatest effect on neuropsychological tests and on quantitative EEG, while levetiracetam had the least (Mecarelli et al. 2004). In a separate healthy volunteer study, we also found fewer cognitive deficits using levetiracetam compared to carbamazepine (Meador et al. 2007b). Across all measures, significant differences were present for 42% (23 of 55) of the variables, all favored levetiracetam and none favored carbamazepine. Compared to the non-drug average, carbamazepine was worse for 65% (36 of 55) and levetiracetam was worse for 12% (4 of 33). Differential effects were seen for attention/vigilance, memory, language, psychomotor speed, graphomotor coding, reading/naming speed, subjective perceptions, and electrophysiological measures. Carbamazepine was associated with an increase in low frequency (<10 Hz) EEG power and changes in ERP measures. One observational patient study reported no change in cognitive functioning in patients being treated with levetiracetam as either monotherapy or as adjunctive therapy (Gomer et al. 2007). Thus, data from both healthy volunteers and patients suggest little cognitive effects associated with levetiracetam monotherapy.

Although levetiracetam is associated with a favorable cognitive side effect profile, there does appear to be increased risk of irritability in selected patients, although others patients may experience positive behavioral effects (Bootsma et al. 2007). According to the package insert, 13.3% of LEV patients experience behavioral side-effects compared to 6.2% of placebo patients. One recent chart review found the highest rate of reported psychiatric side effects in patients taking levetiracetam (15.7% incidence) compared to other newer generation AEDs (Weintraub et al. 2007), although other reviews suggest that the psychiatric side effects of levetiracetam are not significantly higher than other AEDs in either adult populations (Cramer et al. 2003).

There are, however, few data about levetiracetam behavioral effects in children. In one recent adjunctive trial in children with refractory partial epilepsy, hostility was reported in 11% of children taking levetiracetam (Glauser et al. 2004). In September 2005, the FDA made changes to the safety labeling for levetiracetam to warn of the risks of somnolence, fatigue, and behavioral abnormalities associated with levetiracetam use in pediatric patients. Compared to placebo, children on levetiracetam had increased rates of depression (3 vs. 1%), hostility (11.9 vs. 6.2%), nervousness (9.9 vs. 2.1%), and personality change (37.6 vs 18.6%). Slightly less than 11% of the sample reported in the new package insert had behavioral symptoms that required drug discontinuation or dose reduction. Frank psychosis in children has also been reported (Kossoff et al. 2001), and there appears be a biologic risk for developing psychiatric adverse events independent of titration schedule (Mula et al. 2003). Behavioral effects with monotherapy levetiracetam in children with less severe epilepsy have not been described.

Oxcarbazepine (Trileptal)

Approved for use in 1990, oxcarbazepine (Trileptal) is chemically similar to carbamazepine but has different metabolites and is associated with a smaller risk of skin rash is much less (3 vs. 7%) (Schmidt and Elger 2004). The overall tolerability of oxcarbazepine appears slightly better than carbamazepine, phenytoin, and valproate, although there are very few formal studies examining oxcarbazepine's cognitive impairment.

Despite the apparent tolerability profile compared to older therapies, oxcarbazepine's cognitive benefit appears modest. One small study observed no difference from phenytoin in a small randomized monotherapy study of new onset epilepsy patients (M. Aikia et al. 1992), and one healthy volunteer study with two doses of oxcarbazepine

found increased reaction time, but surprisingly, improvement on a cancellation task combined with increased subjective alertness (Curran and Java 1993).

Oxcarbazepine's slight neuropsychological impairment is accompanied by slight EEG slowing in healthy volunteers, although the magnitude of oxcarbazepine's effect was smaller than that observed with carbamazepine (Salinsky et al. 2004). In a different report, oxcarbazepine's neuropsychological profile was similar to that of phenytoin (Salinsky et al. 2004), and phenytoin is generally considered to have mild-to-moderate negative neuropsychological effects (Meador et al. 1991, 1995).

In children with newly diagnosed partial epilepsy followed for 6 months, no difference between oxcarbazepine compared to either carbamazepine, valproate, or combined carbamazepine/valproate polytherapy on a variety of standard neuropsychological measures and specialized computerized tasks (Filippo Donati et al. 2006, 2007) was found. Thus, as suggested by the few adult studies, oxcarbazepine does not appear to afford significant cognitive benefit in children compared to traditional AEDs.

Pregabalin (Lyrica)

Approved for use in treatment of partial onset seizures in 2005, pregabalin's effect on cognition has not been fully explored. A randomized double-blind three-period crossover of 450 mg/day of pregabalin in healthy volunteers showed no significant effect on objective measures of reaction time, vigilance and short term memory, although it was associated with subjective sedation, critical flicker fusion, and divided attention (Hindmarch et al. 2005).

Tiagabine (Gabatril)

Tiagabine is a GABA reuptake inhibitor, is used to treat partial epilepsy, and was introduced in 1995. Tiagabine was not associated with either cognitive EEG changes in an adjunctive double blind patient study (Sveinbjornsdottir et al. 1994). No effects were also reported in a randomized, open-label extension study (Kalviainen et al. 1996). A parallel-group, add-on, randomized, double-blind dose response study in epilepsy patients also failed to reveal any significant cognitive or behavioral effects (Dodrill et al. 1997). When compared to carbamazepine and phenytoin as adjunctive therapy for epilepsy patients, no significant difference was found with phenytoin, although tiagabine was associated with increased verbal fluency and faster psychomotor speed than carbamazepine (Dodrill et al. 2000). In a monotherapy study in newly treated epilepsy patients treated for 52 weeks, the effect of tiagabine was comparable to that of carbamazepine, with a greater negative effect of carbamazepine on verbal fluency (Marja Aikia et al. 2006a). No significant effects on mood have been suggested (Marja Aikia et al. 2006b).

Topiramate (Topamax)

Introduced in 1996, Topiramate has multiple mechanisms of action, including blockade of voltage-dependent sodium channels, potentiation of GABA-mediated effects, carbonic anhydrase inhibition, and glutamate antagonism, and consequently has a broad spectrum of application. Of the newer AEDs, topiramate generates the greatest concern over its potential negative neuropsychological effects, which includes decreased function that some suggest is specific to language and other suggest is related to decreased frontal lobe function (Gross-Tsur and Shalev 2004; Kockelmann et al. 2003; S. Lee et al. 2003; Martin et al. 1999).

Topiramate has greater neuropsychological side effects than carbamazepine, lamotrigine, valproate, gabapentin, and tiagabine (Fritz et al. 2005; Meador et al. 2003, 2005; Salinsky et al. 2005a, b). Importantly, there are individuals who display a disproportionate sensitivity to the medication (Meador et al. 2003), although the ability to predict these individuals at increased cognitive risk does not presently exist.

Topiramate produced somnolence, slowing, memory problems, and language difficulties in clinical trials. When compared to lamotrigine and gabapentin in a single-blind, randomized, parallel group study in 17 healthy volunteers (Martin et al. 1999), topiramate was associated with significantly greater effects on cognition than the other two agents tested; however, the titration rate for topiramate was faster than recommended. Similarly, considerable cognitive deficits were demonstrated in a non-randomized sample of epilepsy patients when formally evaluated using a neuropsychological battery (Thompson et al. 2000) though, once again, the results may not reflect the typical risk for the majority of patients because the magnitude of the effect may have been exaggerated by the retrospective, non-randomized study design.

Two multicenter, randomized, double-blind, parallel group, adjunctive therapy studies in patients with partial epilepsy examined the cognitive effects of topiramate compared to valproate (Aldenkamp et al. 2000; Meador et al. 2003). In both studies, topiramate or valproate were added slowly to patients on stable doses of monotherapy carbamazepine monotherapy. In the first study (Aldenkamp et al. 2000), the mean topiramate dose was 251 mg/day and valproate dose was 1,384 mg/day. At the end of three month maintenance dosing, topiramate impaired performance on only one of 17 variables in comparison to valproate, and that was on a verbal memory task. Comparable results were found in the second study (Meador et al. 2003), where the target dose for topiramate was 400 mg/day and

for valproate, 2,250 mg/day. Following 8 weeks of dose escalation and an additional 12-week maintenance period, only symbol-digit modalities and controlled oral word association were significantly poorer for topiramate compared to valproate out of a total of 24 tests. Importantly, there appeared to be patients at greater individual risk for developing cognitive decline, suggesting individual differences in susceptibility to neuropsychological side effects.

In a double-blind healthy volunteer, placebo-controlled, parallel study, subjects given topiramate (300 mg/day) performed significantly worse on half of the neuropsychological variables compared to subjects taking gabapentin (3,600 mg/day) (Salinsky et al. 2005a, b). Significant topiramate vs. gabapentin and topiramate versus placebo differences in test–retest scores were present in four of six target measures (Digit Symbol, Story Recall, Selective Reminding, Controlled Oral Word Association), suggesting the absence of an expected practice effect associated with topiramate.

Topiramate is associated with greater cognitive impairment compared to lamotrigine. In a healthy volunteer study, direct comparison of performance on both drugs revealed significantly better performance on 33 (80%) variables for lamotrigine and none for topiramate. Differences spanned both objective cognitive and subjective behavioral measures. Comparison of TPM to the non-drug average revealed significantly better performance for non-drug average on 36 (88%) variables, but none for topiramate. Comparison of LTG to non-drug average revealed better performance on seven (17%) variables for non-drug average and four (10%) variables for LTG. Similar differences between lamotrigine (mean dose = 500 mg/day) and topiramate (mean dose = 300 mg/day) were seen in a multi-center, double-blind, randomized, prospective study of adults with partial seizures who were treated with lamotrigine or topiramate as adjunctive therapy to carbamazepine or phenytoin (Blum et al. 2006).

An important point involving topiramate is that greater cognitive risk is associated with higher topiramate doses. Across a variety of neuropsychological measures, there appears to be a strong relationship between the risk of cognitive difficulty and total daily dose (Lee et al. 2006; Loring et al. 2007). At low doses, comparable to what many patients may be taking for migraine prophylaxis, there is very low risk of cognitive impairment, with a much higher risk of cognitive difficulty at higher doses. Dosing, therefore, is a very important variable to consider in evaluating the findings on neuropsychological function since many of them were conducted using doses that are higher than those that are typically used in current clinical use.

In summary, although most patients will tolerate topiramate, there is a subset of individuals at risk for clinically significant cognitive side effects. Factor affecting these adverse effects include titration rate, maintenance time, dose, polytherapy, and individual susceptibility.

Vigabatrin (Sabril)

Vigabatrin is a structural analogue of GABA, which irreversibly inhibits the degradative enzyme GABA-transaminase resulting in an increase in brain GABA levels. Vigabatrin was never approved for use in the United States due to evidence of visual field constriction associated with its use (Miller et al. 1999), although it is generally available in most other countries. Compared to placebo, vigabatrin has produced few adverse effects on either cognitive or quality of life measures in patients with epilepsy in four double-blind, randomized, add-on studies (Dodrill et al. 1993, 1995; Gillham et al. 1993; Grunewald et al. 1994). Single-dose vigabatrin was associated with less impairment than single dose lorazepam (Saletu et al. 1986). Vigabatrin produced fewer adverse effects than carbamazepine in a small, open-label, randomized, parallel-group patient study (Kalviainen et al. 1995). Although abnormal behaviors such as depression and psychosis have been reported in 3.4% of adults in controlled clinical trials, vigabatrin does not appear to be associated with greater risk than other AEDs (Ferrie et al. 1996).

Zonisamide (Zonegran)

Zonisamide was introduced into the US market in 2000, although it was widely used in Japan and Europe for approximately 10 years prior to its United States debut. It is approved for adjunctive therapy in treating partial epilepsy, and works by blocking presynaptic voltage-sensitive sodium and calcium channels in neurons, and also has mild inhibitor of carbonic anhydrase. Despite a wide therapeutic index, zonisamide may cause sedation. In a small add-on study in patients (Berent et al. 1987), zonisamide was reported to impair cognition (e.g., learning), but habituation appears across the 24 weeks of study. However, other formal studies involving zonisamide do not exist, which probably reflects its relatively late introduction into the U.S. market after being established in other parts of the world for a decade.

Risk for Cognitive Effects of AEDs from In Utero Exposure

Although the majority of children born to mothers with epilepsy are normal, the greatest developmental risk to children should theoretically occur as a result of in utero AED exposure, and in fact, these children are at increased risk for poor anatomical and behavioral outcomes (Pennell 2004). In animal studies, adverse effects on behavioral

neurodevelopment from *in utero* AED exposure have been demonstrated at doses associated with clinically relevant blood levels and at doses that are lower than those associated with major developmental physical malformations (Adams et al. 1990; Finnell and Dansky 1991; Fisher and Vorhees 1992).

The role of AEDs in contributing to the developmental delays in children born to mothers with epilepsy is beginning to receive increasing attention. In a retrospective study of two cohorts of men exposed to phenobarbital prenatally, valproate exposure was associated with a reduced verbal IQ of appropriately seven IQ points (Reinisch et al. 1995). In two retrospective cohorts (N. Adab et al. 2001, 2004; Vinten et al. 2005), *in utero* valproate exposure was associated with adverse cognitive effects and with developmental delays in children younger than six years of age (N Adab et al. 2004). The second cohort, which had children older than 6 years of age, those exposed to valproate were found to have a higher rate of special education in school as well as a verbal IQ that was 10.7 points lower than comparable children who were exposed in utero to carbamazepine (Adab et al. 2001, 2004; Vinten et al. 2005).

Two prospective studies of in utero AED exposure exist. One report described a 12.7 point reduction in Verbal IQ score was associated with exposure to valproate (Gaily et al. 2004). More recently, a large multi-center study has reported lower Bayley Developmental Quotients for children exposed to valproate (DQ=86) when tested at 2 years compared to carbamazepine (DQ=91), lamotrigine (DQ=95), or phenytoin (DQ=91) (Meador et al. 2007a). These data are consistent with multiple studies that suggest an increased risk of valproate exposure for congenital malformations (Artama et al. 2005; Cunnington et al. 2005; Marson et al. 2007; Meador et al. 2006; Vajda and Eadie 2005; Wide et al. 2004; Wyszynski et al. 2005).

The mechanisms of anatomical and behavioral teratogenesis likely differ given that their peak risk occurs at different times during the pregnancy (anatomical risk during the first trimester, behavioral risk during the final trimester). However, drug effects on cell survival are potentially relevant for ultimately determining differential drug risk on developmental outcome. Clonazepam, diazepam, phenobarbital, phenytoin, or valproate produce widespread neuronal apoptosis when administered to neonatal rats (Bittigau et al. 2003a, b). Similar apoptotic effects were not observed with levetiracetam or topiramate in the same animal model when given in monotherapy at clinically relevant doses (Glier et al. 2004; Manthey et al. 2005), and preliminary results with either carbamazepine or lamotrigine monotherapy did not reveal drug-induced apoptosis (Katz et al. 2006; Kim et al. 2004, 2006). When combined with other pro-apoptotic AEDs; however, carbamazepine, lamotrigine, or topiramate enhanced cell death, whereas levetiracetam did not. Thus, these animal studies suggest possible adverse effects of AEDs on neonatal and fetal brain development, though further studies are clearly needed.

Conclusions

Patients with epilepsy face an increase risk of cognitive impairment relative to the general population due to a variety of factors, including the effects of repeated seizures in addition to the disease states that underlie the epilepsy. Epilepsy treatment may also affect cognition and behavior, either positively or negatively. Antiepilepsy drugs effect on cognition are often times smaller than that associated with the disease, although their effects may create additional cognitive burdens that can potentially be avoided or minimized with monitoring and change in therapy when appropriate. When used in monotherapy with anticonvulsant blood levels within the standard therapeutic ranges, the cognitive effects of AEDs are generally relatively modest, although significant effects sometimes occur as seen in decreased quality of life measures, or at times, significant neuropsychological or behavioral impairment.

Polypharmacy increases the risk of neuropsychological side effects in older agents, although whether polytherapy involving the newer agents presents the same cognitive risks has not been addressed. Nevertheless, the goal in the treatment of epilepsy is to find the AED that will provide maximum seizure control while producing minimal side effects. For some patients, the best risk-to-benefit ratio may require the judicious use of polypharmacy or anticonvulsant blood level above "standard therapeutic range" in monotherapy, though cognitive side effects may be more severe in under these conditions.

Several newer AEDs, (e.g., gabapentin, lamotrigine, levetiracetam) appear to have fewer adverse cognitive effects than the older agents, though additional comparisons between new AEDs are required to fully assess the cognitive side effect profile of these newer anticonvulsant agents. Of the newer agents, topiramate is associated with the greatest risk of cognitive impairment, although this risk is decreased with slow titration and low target doses.

The effects of in utero AED exposure have only recently been the subject of formal investigations. A growing body of evidence suggests that in utero valproate exposure is more likely than other commonly used AEDs to cause anatomical teratogenesis and impair cognitive development. The effects of AED on the developing nervous system, whether it be prenatal exposure, treatment of infantile epilepsy, or pediatric epilepsy treatment during the school years, is an important area for future research since the public health consequences of using treatment options asso-

ciated with poorer outcomes when other similarly effective treatment options with fewer developmental risks exist, is great.

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