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A senior clinical editor for Advanced Studies in Medicine (ASiM) interviewed Dr Meador to discuss cognitive impairment in patients with epilepsy.

ASiM: What is the prevalence of cognitive impairment or memory problems in people with epilepsy? Has this been studied?

Dr Meador: The International Bureau for Epilepsy conducted a survey last year of 425 patients on cognitive function. That study showed that 44% [of patients with epilepsy] complained of difficulty in learning, 45% thought they were slow thinkers, 59% felt sleepy or tired or had trouble with sedation, and approximately 63% thought that the drugs may be affecting their ability to do activities or to achieve goals.1 Therefore, it’s very prevalent. Drugs are one factor. If you look at studies in patients with epilepsy before they ever receive drugs, as a group, their cognitive performance is impaired. However, it is broader than that.

Epilepsy is not one disease, and there is a tremendous amount of variation [within each type], from patients who are highly intelligent with cognitive performance completely intact to patients who are severely mentally retarded. And, in fact, patients who have brain damage are over-represented in the epilepsy population. Epilepsy can be caused by brain damage or can be a result of genetics, or a whole variety of other factors can cause epilepsy. Therefore, all of these factors can contribute to cognitive impairment. There are seizure-related variables that also contribute. There is brain substrate damage before the seizures begin and damage caused by the seizures. There are also transient alterations caused by the seizures when the seizure happens.

Of course, if a patient is having a complex partial seizure or a generalized convulsion, their cognition is impaired. There are also postictal effects when patients have trouble thinking clearly from minutes to days after a seizure. The issue of interictal discharges is not as clear, although there is some evidence to suggest that interictal discharges do play a role, but no clear evidence as to the extent.2–6

Long-term damage can occur, such as hippocampal and thalamic atrophy, hypometabolism, and neuronal loss.7 The data on the long-term effects are controversial, but patients who have many generalized seizures will develop some brain damage over time. And, even if patients have several complex partial seizures, there is some evidence of progressive effects over an extended period of time (eg, 20–30 years). For patients who have repeated or frequent generalized seizures or status [epilepticus], the damage can occur quickly.

In addition, there are treatment-related variables, such as the antiepileptic drugs (AEDs), and there are variable effects of the drugs on cognition. There are risks in surgery. The most common surgery is temporal lobectomy, for which the major risk is memory loss.
or word-finding difficulties, especially if the surgery is performed on the left side of the brain. The risk of temporal lobectomy can be largely predicted based on whether the surgery is performed on the language-dominant side of the brain, if there is no lesion (e.g., hippocampal sclerosis), if there is no focal dysfunction (as evidenced by positron emission tomography images, Wada, or other functional tests), or if neuropsychological function (e.g., verbal memory) is not present before surgery. Also, there can be risks from surgeries in other sites of the brain, which are location-dependent (e.g., aphasia for left perisylvian surgery).

Vagal nerve stimulation doesn’t seem to pose any cognitive risk, but the down side is that it rarely makes patients seizure-free. Being seizure-free can impact cognition, and it certainly can impact a patient’s quality of life rather dramatically.

There are non–seizure-related variables that can affect cognition, such as psychosocial issues; all of these variables may contribute to cognition or behavioral problems.

Patients with epilepsy have a higher incidence of mood disorders than patients with other serious medical conditions. The most commonly diagnosed forms of epilepsy come from the limbic areas, such as the temporal lobes, which are the same regions that have the lowest seizure thresholds (e.g., focal epilepsy). The limbic areas also are important in mood processing. Damage or dysfunction in this area can lead to seizures, or it can lead to mood alterations. The AEDs may also impact mood—positively or negatively.

**A/SiM:** When a patient complains of cognitive impairment or memory problems, how do you treat this patient?

**Dr Meador:** If this patient has had a long history of epilepsy and has memory problems, I first ask about their seizure control because that could be contributing to memory problems. Memory problems in patients with epilepsy are common and are caused by a variety of factors. With focal epilepsy, many of those [types of seizures] involve the temporal lobes, which are important for producing memories. The same structures that have the lowest seizure threshold are also important in memory production. The physiology that causes the medial temporal lobe to be suited for making memories probably adds to its ability to produce seizures. Therefore, damage to that area can cause memory problems.

The AEDs can cause some memory problems; some drugs more than others. Other types of cerebral damage or ongoing damage from seizures can also contribute. In addition, other processes can potentially contribute to memory problems, such as vitamin B₁₂ deficiency.

However, what is interesting is that several studies show—but not well—the patient’s complaint of memory problems or cognitive impairment is correlated with their performance. In a University of Alabama study, patients who had undergone surgery and complained of memory problems were more likely to be depressed than to have had an actual decline in their memory. The actual correlations for patients’ perceptions of memory or cognitive performance to actual performance, although significant, show that the R-values are low—approximately 0.1 or 0.2. The R-values for the relationship between complaints of memory or cognitive problems and the correlation with mood scales is high (approximately ≥0.7). Therefore, a clinician must determine early in the evaluation of memory complaints whether the patient has a mood disorder.

**A/SiM:** Therefore, assuming that a patient’s seizures are well controlled, what do you consider?

**Dr Meador:** Mood and other factors that can impact memory and cognition. I may order cognitive testing at that time, depending on the severity of the patient’s problem, whether the patient has already been tested, and whether the possibility of testing has been discussed. Formal testing may not be done if the patient has a mild problem that is common with epilepsy. If there’s a significant mood problem, I may first prescribe treatment and also check blood tests for results that can contribute to memory impairment, but the yield on that is usually low. Mood actually impairs vigilance more than simple attention and, secondarily, affects memory.

Antiepileptic drugs can produce significant memory impairment. In our studies involving healthy volunteers, we compared the amount of recall for a memory test that is heavily loaded for attention, such as a paragraph memory. The patients using the older standard drugs, such as phenytoin, carbamazepine, and valproate, showed approximately 20% loss of the information they would have recalled if they were not using AEDs. The study also showed that some of the newer drugs, such as gabapentin and lamotrigine, don’t reduce recall for paragraph memory.
It's possible that several of the other newer drugs don't significantly affect memory, but there is no formal data to date. I suspect that some AEDs, such as levetiracetam, are well tolerated. In terms of cognitive effect, topiramate is similar or a little bit worse than some of the other standard drugs, especially at the higher doses and especially in polytherapy. Polytherapy and higher dosages are more likely to produce a greater number of cognitive adverse effects than any of the drugs. If the initial dosing of topiramate is slower and is used as monotherapy in lower dosages, there are clearly less cognitive effects. I can't tell you specific numbers because good neuropsychological data at the low dosages are not available.

Patients should be told that every medicine has its advantages and disadvantages. With my patients, I discuss the various pros and cons of AEDs I'm considering for their treatment. Some of the drugs cause cognitive issues. If cognitive issues alone are considered, then drugs such as lamotrigine, gabapentin, and levetiracetam are treatment possibilities. Use of phenobarbital and topiramate, certainly at higher dosages, should be avoided; however, individual variability is a factor. Some patients will have problems, especially behavioral disorders, even with the drugs that are generally well tolerated. For example, although gabapentin is well tolerated in older adults, it can cause behavioral problems in young children, especially children with mental disabilities.

Gabapentin and levetiracetam don't have pharmacokinetic interactions, but most of the other drugs do—the AEDs affect other drugs or other drugs affect them. These effects can be substantial; enzyme induction from phenytoin, carbamazepine, and phenobarbital can affect other drugs such as immune suppressors for patients who have undergone transplantation or have used chemotherapeutic agents or birth control pills. Some drugs can cause weight gain. Valproate causes higher weight gain; gabapentin and carbamazepine can produce some weight gain. Some drugs, such as topiramate and zonisamide, can cause weight loss. Some drugs are better for certain types of pain than are other drugs. Therefore, all of these factors should be considered for each patient.

Mood issues also must be considered. Several of the drugs are used routinely in patients with psychiatric disorders. Drugs that have positive psychotropic effects can be helpful in patients with epilepsy. Valproate, carbamazepine, and lamotrigine have demonstrated effectiveness in patients with psychotic episodes; gabapentin and topiramate also are being used, but there are no substantiated results as yet. Psychotropic profiles are not well defined for some of the newer drugs. Lamotrigine is probably best defined in that regard, but valproate and carbamazepine have a long history of use for their psychotropic effects.

With women patients, the clinician should discuss whether the drug interferes with birth control pills and whether there are teratogenic effects of the drug that may affect future pregnancies. There is recent evidence that valproate appears to produce an increased risk, as compared to the other drugs, to the unborn child. Therefore, it's not simply choosing a drug that doesn't cause cognitive problems. If that were the case, then I could choose no drug treatment for my patients, but the goal is to control the seizures without creating new problems.

Treatment of patients with epilepsy is complex. If a patient complains of memory problems, changing medicines is a consideration to control the seizure or to reduce cognitive adverse effects. Neuropsychological testing also may be considered as well as other tests because of additional risk factors for memory problems.

**ASiM:** How do you counsel patients regarding memory problems? When they are first diagnosed, do you even discuss this issue with them? If the patients find that they are having these problems, how do you talk to them about it?

**Dr Meador:** Usually with a new patient we will go through a review of systems. Even if they don't complain of a specific problem, we may ask them, “Are you having memory problems?” It's best to give incremental information to a new patient. If they are particularly concerned about memory problems, address that issue at the first office visit. If that's not an immediate issue, wait a visit or 2 before discussing memory problems or other issues. It's important to have a new patient undergo diagnostic radiology testing (eg, for patients with new-onset epilepsy, memory problems may be caused by a brain tumor, stroke, or some other problem). The physician must know about those factors.

Although a patient with new-onset epilepsy is undergoing blood workup, other blood tests can be ordered for complaints such as memory loss. A mood scale to assess the possible contribution of mood to the patient’s memory, cognition, and quality of life also can be performed. During the first office visits, the
physician may elect not to talk in detail to the patient about cognition as it relates to the epilepsy. Another contributing factor to the patient's cognitive problems may be a recent seizure. When I initiate drug treatment with my patients, I always discuss the risks and the relative risks of that drug, along with other factors such as a rash, weight gain, weight loss, interactions with other drugs, thinning of the bones, or birth defects. If patients are not complaining of memory or cognitive problems, discuss those issues at a later time because, at some point, cognition is a major concern for most patients.

AS/M: What are the longer-term effects of cognitive problems in children, the elderly, and other adults?

Dr Meador: Again, it depends on the patient because in the groups you described, the patients are not homogenous—broad spectrum of patients. Within the adult group there are variable factors, such as IQ, background, education, training, and history. For example, a patient who has a fifth-grade education and does manual labor may not be bothered by the cognitive adverse effects as much as a patient who has a high-level cognitive job and whose performance would be affected by even mild cognitive symptoms. A physician may have difficulty determining cognitive or memory problems in patients who are mentally disabled. Cognitive problems in these patients are easier to diagnose during gross sedation. More commonly, behavioral problems are seen in patients with mental disabilities.

Physicians must be aware that elderly patients are more sensitive to the effects of any kind of centrally acting drug for pharmacokinetic and pharmacodynamic reasons. Brodie et al did a head-to-head comparator study of lamotrigine and carbamazepine use in elderly patients with new-onset epilepsy. In this group, lamotrigine was better tolerated, but the study didn't include cognitive testing. The new Veterans Administration co-op study, to date published only in abstract form, compared lamotrigine, gabapentin, and carbamazepine. Results showed that lamotrigine and gabapentin were better tolerated by patients than was carbamazepine. Because these drugs are less likely to cause adverse effects, I always consider these drugs for my elderly patients. Some evidence is starting to emerge about relative tolerance in elderly patients with some of these drugs. Elderly patients usually respond to the drugs better, thus they often can be treated with lower dosages, which produce fewer cognitive adverse effects.

In children, the literature is still uncertain. The potential for long-term effects [from cognitive problems] has never been proven completely. Farwell et al did a study involving children who had febrile convulsions and were treated with phenobarbital. Years ago, the general practice was to prescribe phenobarbital for children with febrile convulsions to prevent them from progressing to lifelong epilepsy. Febrile convulsions are common, and patients with febrile convulsions have an increased risk for epilepsy. In the study by Farwell et al, phenobarbital treatment didn't prevent the children from developing epilepsy; instead, it impaired the patient's cognition for some time, although the children seemed to recover after the phenobarbital was discontinued. The concern is that if a child has cognitive problems while they are on medication throughout their entire childhood, throughout their development, and when they are going to school and learning, then they don't learn as well. What is the lifelong impact on their ability to achieve and earn a living? Lowering intelligence levels by just a few points during childhood could have a major impact on a patient's lifelong earnings.

AS/M: How do children typically present if they have cognitive impairment? Is it lower grades or the child having trouble remembering, or do the parents notice some change?

Dr Meador: It could be any or all of those scenarios, but I'm not necessarily talking about effects of the drugs. Children with epilepsy comprise a heterogeneous population. Some children have a standard range or above standard range of intelligence, but others have severe mental disabilities or degeneration because of the epilepsy or the underlying disease. Separating the effects of underlying disease from seizures on cognition can be difficult. If the underlying disease is severe, as in infantile spasms, a large percentage of those children become impaired. It's probably a function of the underlying disease and not of the epilepsy itself, but the seizures do play some role. Irrespective of the underlying disease, if patients have many generalized convulsions, then clearly the seizures can impair their cognition and even brain structure. It's somewhat controversial, but if a patient has multiple complex partial seizures over a long period of time, the result may be impaired memory and shrinkage of the hippocampus over approximately 3 decades.

Some seizures seem to be less damaging, such as classic absence seizures in children. Children can have
many classic absence seizures and may never have any neural damage and no long-term cognitive sequelae. A patient with typical childhood-onset partial epilepsy may have a standard cognitive range or have problems in school performance or display hyperactivity. Other children who present with infantile spasms have gross mental disabilities. There's a real variety of how epilepsy may affect the child, depending on the seizure type, the underlying etiology, the age of onset, and the number of seizures. In general, the earlier the age of the onset, the more cognition is adversely affected.

REFERENCES