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NEUROLOGY ALERT®

A monthly survey of developments in neurologic medicine

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ApoE-4 is Associated With Traumatic Encephalopathy and Alzheimer's Disease

ABSTRACTS & COMMENTARY

Sources: Luukinen H, et al. Head injuries and cognitive decline among older adults: A population-based study. *Neurology* 1999;52:557-562; Teasdale GM, et al. Association of apolipoprotein E polymorphism with outcome after head injury. *Lancet* 1997;350:1069-1071; Roberts GW, et al. Amyloid protein deposition in the brain after severe head injury: Implications for the pathogenesis of Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 1994;57:419-425; Friedman G, et al. Apolipoprotein E-4 genotype predicts a poor outcome in survivors of traumatic injury. *Neurology* 1999;52:244-248; Nicoll JAR, et al. Apolipoprotein E-4 allele is associated with deposition of amyloid beta-protein following head injury. *Nature Med* 1995;1:135-137.

For several years, investigators have conjectured that early head injury may contribute to late incidence of Alzheimer's disease (AD). Mayeux and colleagues substantiated the earlier suggestions by identifying AD as having a significantly higher incidence in patients older than age 65 who had suffered severe head injuries during early life compared to nontraumatized controls.[1] In fact, Roberts and colleagues already had identified large numbers of beta amyloid protein plaques in the brains of middle-aged and older boxers who died following months to years after developing dementia pugilistica.[2] The plaques were characterized as indistinguishable from those found in AD.

Subsequent studies by Roberts et al confirmed at postmortem the relationship of beta amyloid plaques in approximately 30% of 152 persons following severe head trauma.[3] Patients showing post-traumatic beta amyloid plaques at death ranged in age from 8 weeks to 81 years. Post-traumatic survival time ranged from four hours to 2.5 years. Increased age correlated roughly to increasing beta AP deposits in the brain. Roberts et al proposed that beta amyloid precursor protein identified in the perikaryon of neurons adjacent to beta amyloid plaques may possibly reflect an acute phase response to neuronal injury.

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INSIDE

Against the above background, three relatively recent reports emphasize the influence of apolipoprotein E (apoE) polymorphism on both immediate and long-term outcomes from brain trauma. Cementing the relationship of the apoE-4 to brain vulnerability, Nicoll and associates pointed out that approximately one-third of persons dying from acute head injury not only contain excess amounts of amyloid beta protein in the brain, but with a frequency (0.52) that is measurably higher than the apoE-4 allele appears in the general population. The figures imply that the apoE-4 allele presents a specific genetic vulnerability to the effects of brain injury. Two large clinical series support this opinion.

Teasdale and associates reported the results of a prospective clinical study to test the above conclusion. Among 89 patients, Teasdale et al found that 30 possessed the apoE-4 allele: at six months, post-trauma 17 (57%) of these died or remained either vegetative or severely disabled. Of 59 similarly injured patients without the apoE-4 allele, only 16 (27%) had similarly poor outcomes (P = 0.006). Immediate severity of the degree of initial trauma did not influence the significant difference in outcome. As noted above, the significantly worse outcomes of persons with the apoE-4 allele exceeded that found in the general population. Teasdale et al conclude that the possession of the apoE-4 allele specifically contributes to the severity of acquired brain trauma.

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Friedman and associates buttress the generic accuracy of the above findings. Their report exclusively describes patients who reached the Israel Rehabilitation Hospital following acute hospital care. Accordingly, the selection necessarily omits earlier post-traumatic deaths and patients who made prompt improvement following acute brain injury. Friedman et al evaluated 69 surviving patients and divided them into two outcomes: good outcome designated those who recovered independence from nursing-physical care and expressed functional cognition and behavior; unfavorable late outcomes identified patients who remained fully dependent on caregivers or suffered severe cognitive impairments. Patients harboring the apoE-4 had an odds ratio of 5.69 of remaining unconscious for more than seven days compared to those who lacked the allele. Furthermore, only one of 27 persons with the 4-allele had a good outcome compared to 13 of 42 comparably injured persons who reached a good functional recovery.

COMMENTARY

Most neurologists, psychiatrists, and general physicians are now aware that possession of the apoE-4 allele has a high probability of predicting late-life AD. These important reports, however, indicate two additional major risks associated with the poisonous allele. First is that possession of the apoE-4 allele materially worsens the potential neurological outcome of traumatic brain injury. The second is that the incidence of severe brain injury in persons with the apoE-4 greatly exceeds the rate of the allele in the general population. These two adverse qualities have important implications for preventive medicine. *Neurology Alert* asks, "Should amateur and professional boxers be screened for the apoE-4 allele and advised of its implications? Should skiers and other athletes be made aware of this risk factor?" Given the knowledge we neurologists now possess, should we begin to discuss it publicly in this coming Century of the Brain? **—fp**

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Possession of the apoE-4 allele carries important risks for the development of all but which of the following statements?

a. an increased risk for Alzheimer's disease in age older than 70 years.
b. an association with poor outcome for persons experiencing severe brain trauma.
c. a high association with dementia occurring in former professional prize-fighters.
d. no specific relation to the incidence of severe brain damage following severe trauma.

Alcohol and Ischemic Stroke: More on the French Paradox

ABSTRACTS & COMMENTARY

Sources: Truelsen T, et al. Intake of beer, wine and spirits and risk of stroke. The Copenhagen City Heart Study. *Stroke* 1998;29:2467-2472; Sacco RL, et al. The protective effect of moderate alcohol consumption on ischemic stroke. *JAMA* 1999;281:53-60.

Several studies have shown that moderate alcohol consumption has a protective effect on the risk of myocardial infarction; some investigators have suggested that certain types of alcoholic beverages, particularly wine, are more protective than others.[1] A beneficial effect of wine consumption has been offered as a possible explanation for the "French Paradox," namely, a low incidence of cardiovascular disease in the French population despite an unfavorable exposure to cardiovascular risk factors. The association between alcohol and ischemic stroke is less well established. Some studies suggest that moderate alcohol consumption confers a protective effect in some populations, especially women[2] and blacks,[3] but not in others, such as Asians.[4]

Truelsen and colleagues examined the influence of alcohol intake and the different types of alcohol on the risk of first-ever stroke in a large Danish prospective cohort study. More than 13,000 men and women aged 45-84 years gave information on alcohol habits and other socioeconomic and health-related factors at baseline. During 16 years of follow-up, 833 strokes occurred: 37% were ischemic, 10% were cerebral or subarachnoid hemorrhages, and 53% were not specified.

Subjects who drank wine had a statistically significant decreased risk of stroke compared with subjects who never or hardly ever drank wine. Subjects who drank wine weekly had a lower relative risk (RR) of stroke (RR 0.66; 95% CI 0.50-0.88) than those who drank wine daily (RR 0.68; 95% CI 0.70-1.02) or monthly (RR 0.84; 95% CI 0.70-1.02). In contrast, no significant effect of drinking either beer or liquor was found in either of the frequency groups.

Sacco and colleagues studied alcohol consumption among 677 patients with a first ischemic stroke and 1139 community controls matched by age, sex, and race/ethnicity. Stroke patients had a mean age of 70 years; 56% were women, 51% Hispanic, 29% black and 20% white. After adjustment for heart disease, hypertension, diabetes, current smoking, body mass index, and education, moderate alcohol consumption of up to two drinks per day was significantly protective for ischemic stroke (odds ratio [OR] 0.51; 95% CI 0.39-0.67). A protective effect of alcohol consumption was detected both in younger and older patients, in men and women, and in all racial/ethnic groups. The results demonstrated a J-shaped relationship between alcohol consumption and stroke risk: those drinking up to two drinks daily had a reduced risk compared to those who were not current drinkers, but among those drinking seven or more drinks per day, there was a significantly increased risk of stroke (OR 2.96; 95% CI 1.05-82.9).

Sacco et al found no differential protective effect among the types of alcoholic beverages. Among moderate drinkers in this study, 17% drank wine predominantly, 17% beer, 30% liquor, and 35% were combination drinkers. On average, those who were predominantly wine drinkers consumed less alcohol than those in the other groups.

COMMENTARY

These studies, in accord with others, suggest that moderate alcohol intake has a protective effect on the risk of ischemic stroke. Truelsen et al found that this benefit was strongest among wine drinkers and not among those who drank beer and liquor alone. Sacco et al found no difference in protective effect among the types of alcoholic beverages. It may be therefore that the benefits of wine drinking found in the Copenhagen study were not due to components in wine other than ethanol but, rather, due to lifestyle factors or to intake of alcohol only with meals. Support for this conclusion comes from the fact that Sacco et al found that those who drank wine predominantly drank less on average than those who drank mostly beer or liquor.

The study of Sacco et al confirms that heavy drinkers are at increased risk of stroke and should be advised to decrease or discontinue alcohol intake. On the other hand, these studies do not indicate that those who do not drink should be advised to do so. Physicians should follow the National Stroke Association's Stroke Prevention Guidelines in this matter:[5] Moderate drinkers can be advised to continue consumption of alcoholic beverages, but those who do not drink should not be advised to do so. **—jjc**

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5. Stroke Prevention Advisory Board. National Stroke Association Stroke Prevention Guidelines. *J Stroke Cerebrovasc Dis* 1998;7:162-164.

Moderate intake of alcohol lowers stroke risk in those who:

a. drink wine daily.
b. drink wine only.
c. drink beer only.
d. drink liquor only.
e. All of the above

VNS Enhances Memory

ABSTRACT & COMMENTARY

Source: Clark KB, et al. Enhanced recognition memory following vagus nerve stimulation in human subjects. *Nature Neuroscience* 1999;2(1):94-98.

Stimulation of the vagus nerve by use of a surgically implanted electrical device has gained acceptance as a treatment for medication-refractory epilepsy. Clark and associates from Southern Illinois University tested recognition memory in 10 subjects involved in a double-blind clinical trial of vagus nerve stimulation (VNS) for seizure suppression. In a carefully controlled set of experiments, they found that VNS delivered during the memory consolidation period can enhance the delayed recognition of words, but only if the stimulation is at a lower intensity than is commonly used for seizure suppression.

The 10 subjects were patients with epilepsy who had more than four seizures per month and were receiving no more than two anti-epileptic medications. Other subjects were excluded because their regimen included benzodiazepines or beta blockers. The subjects underwent baseline testing prior to stimulator implantation and were retested four times over the subsequent 24 weeks. The memory task consisted of reading several emotionally neutral paragraphs that contained highlighted nouns. Subjects were asked factual questions about the paragraphs to assess their reading comprehension. Approximately two minutes after completing the paragraphs, actual or sham VNS lasting 30 seconds was delivered. Subjects were then asked if they could recognize the previously viewed nouns from among a long list of distractor words. The stimulation parameters were varied over time, with subjects receiving either 0.5, 0.75, or 1.5 mA of stimulation or sham stimulation in combination with the noun recall task. Clark et al were blinded to the intensity of stimulation and as to whether sham stimulation was being carried out.

VNS of an intensity comparable to that used to suppress seizures (0.75-1.5 mA) actually impaired recognition memory performance slightly, reducing the mean word recognition score by 10% relative to the control state. In contrast, VNS at 0.5 mA facilitated word recognition by more than 35% (which was a statistically significant effect at the $P < 0.025$ level). There was no correlation between the performance on memory testing and self-reported seizure frequency or duration, leading Clark et al to conclude that the effect of VNS on recognition memory was not likely to be a secondary consequence of seizure suppression by the VNS device.

COMMENTARY

The vagus is a major conduit for visceral sensation, and moderate levels of stimulation of this nerve have been shown to increase levels of arousal and orientation to incoming stimuli. By delivering VNS after exposure to the target words, Clark et al provide intriguing evidence that VNS can alter and potentially enhance the memory consolidation process. The double-blind design and the use of more than one intensity of stimulation across subjects adds to the credibility of the study's findings. Confidence in the results would have been enhanced if a larger number of subjects had been studied and if additional cognitive tests had been used to distinguish between effects on concentration, learning, recall, and recognition memory. In light of the provocative nature of these findings, we expect additional investigations along these lines will eventually be carried out.

Facilitation of memory by VNS had been previously demonstrated in rodents by the same investigators. As proved to be the case in humans in the present study, only a moderate intensity of VNS (0.5 mA) delivered during the memory consolidation period enhanced memory in rats, with higher intensities abolishing the effect. In animal studies, the memory-enhancing effects of VNS were attenuated by beta blockers, an effect thought to be mediated by antagonism of peripheral catecholamine receptors. Neurologists have long been aware of the potential for peripherally acting catecholaminergic agents to cause

confusional states. This investigation provides a plausible explanation of how drugs, surgical interventions or disease states that alter vagal function may affect memory and other aspects of CNS function without necessarily acting directly on the brain.

It is of some concern that higher intensities (0.75-1.5 mA) of VNS had a mildly adverse effect on recognition memory in these subjects, especially since this level of stimulation is comparable to that now being used for seizure suppression in epilepsy patients. Although the magnitude of memory impairment associated with higher intensity stimulation was small, its occurrence creates some concern that there may be other, as yet, undiscovered cognitive side effects related to the use of VNS, which is a relatively new and promising alternative therapy for patients with medication refractory epilepsy. This issue is currently under study. These caveats aside, this innovative investigation provides justification for future studies to address the potential applicability of VNS to the treatment of disorders of memory and other areas of cognition. **—nrr**

Vagal nerve stimulation:

a. enhances memory at high stimulation intensities (0.75-1.5 mA).
b. impairs memory at moderate levels (0.5mA) of stimulation.
c. impairs memory if delivered during the memory consolidation period.
d. enhances recognition memory at moderate (0.5 mA) intensities.

Anoxic Damage to the Human Brain

ABSTRACTS & COMMENTARY

Sources: Zandbergen EGJ, et al. Systematic review of early prediction of poor outcome in anoxic-ischaemic coma. *Lancet* 1998;352:1808-1812; Krieger DW. Evoked potentials not just to confirm hopelessness in anoxic brain injury. Commentary. *Lancet* 1998;352:1796-1797.

Zandbergen and colleagues provide the results of a literature search concerning reliable indicators of death or a vegetative state in patients comatose following severe acute anoxia or anoxemia. To fulfill their goals, they selected 33 previous reports on the subject. Within these reports, they identified 14 individual clinical or neurophysiological tests used to determine factors that reliably predicted poor outcome by the end of the first week. As readers might expect, they found that by the third day after anoxic coma, absence of either the pupillary light reflex or any muscular response to noxious stimuli predicted that the patient's one-month outcome would consist of either brain death or the vegetative state. Zandbergen et al also claim that during the latter part of the week, either the absence of N-20 somatosensory evoked potentials (SSEP) or the appearance of burst-suppression or isoelectric patterns in the EEG also provided an almost certain (100%) prediction of brain death. Depending on the absence of SSEPs earlier in the first week, however, appears to be unwise of rare reports of an early, transient loss of N-20 potentials in persons who nevertheless recovered consciousness.

Krieger, in his *Lancet* commentary of Zandbergen et al's report, emphasizes the low sensitivity of SSPP in that its pattern may reappear in fairly normal form even though the patient remains severely neurologically injured. Krieger makes the sensible statement in his commentary that given the reliability of pupillary reflexes and lost motor responses makes "the futility of continuing with life support obvious without (any) measurement of the evoked potential." *Neurology Alert* agrees.

COMMENTARY

This paper, to quote Yogi Berra, provides us with "deja vu all over again." Many studies published in the medical literature indicate that skilled neurologists or cardiologists can predict brain death or poor outcome in most anoxic patients within as few as six hours following cardiac arrest or severe anoxemia. Unless such patients are restless and moving bodily members (signs that death is not an immediate outcome), therapeutic paralysis or anesthesia rarely complicate the problem by obliterating neurological responses. Levy and associates described the ultimate outcomes of 210 patients who failed to recover consciousness within six hours following a bout of severe anoxia.[1] Edgren and associates reported findings similar to Levy et al's in 262 patients following cardiac arrest.[2] Both studies noted that at the initial post-arrest evaluation, performed during the first few hours of post-anoxic coma, patients with absent pupillary and/or absent motor responses to pain had about an 80% risk of death or permanent unconsciousness. At three days, 100% of patients showing either of those findings faced only death or vegetative outcomes. It stands that in the setting of critical care medicine these sturdy clinical indicants provide imperative information that must be promptly shared with families and friends. Only rarely in your editor's experience, except when seizures occur, has electrophysiologic testing been needed for either the patient's management or the family's understanding. **—fp**

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Which of the following statements is true in managing anoxic encephalopathy?

a. EEG recording or somatosensory evoked potentials (SSEP) provide important information during the early post-anoxic hours.
b. Clinical interpretations of patients with poor outcomes always should be delayed for at least three days.
c. Clinical indications of severe anoxic brain damage can be identified within a matter of minutes to an hour or so after the event.
d. Early clinical evaluations of severe anoxic encephalopathy cannot be identified sooner than 24 hours following the event.

Neuromuscular Manifestations of HIV in the Antiretroviral Era

ABSTRACT & COMMENTARY

Source: Simpson DM, et al. Neuromuscular function in HIV infection: Analysis of a placebo-controlled combination antiretroviral trial. *AIDS* 1998;12:2425-2432.

Among 2467 largely asymptomatic hiv patients followed for more than three years in a multi-center randomized, double-blind, placebo-controlled trial studying the effects of single vs. combination antiretroviral agents (including zidovudine [ZDV], didanosine [ddI], and zalcitabine [ddC]) for HIV, 9% (225) developed peripheral neuropathy. Of these, 22% (n = 49) were felt to result from protocol treatment or a combination of protocol treatment and HIV, and in the majority were distal symmetrical polyneuropathy (DSP) in type (73%; n = 36), characterized by symptoms of burning, lancinating pain, pins and needles paresthesiae, and aching in the calves and feet. Among 34 polyneuropathy cases felt to be due to HIV or neither HIV or protocol treatment, only 15% (n = 5) were DSP. Risk factors for DSP development included older age and lower Karnofsky score (a disability scale reflecting patient's ability to perform life's activities), whereas gender, race, previous antiretroviral treatment, CD4 cell count, and body weight were not predictive.

Among 1067 antiretroviral-naïve HIV patients taken from the same cohort, only six developed myopathy while on the study drug, four with ddI and one each on combined ZDV-ddI and ZDV-ddC. Myalgia and muscle weakness were seen equally in all four treatment arms comprising ZDV alone, ddI alone, ZDV plus ddI, or ZDV plus ddC, and did not correlate with creatine kinase (CK) levels, although the latter were significantly higher in the ZDV-ddC group than in the other treatment groups. DSP and myopathy may occur with combination antiretroviral treatment and may require dose modification.

COMMENTARY

Polymyositis, necrotizing myopathy, and nemaline myopathy are well characterized forms of HIV-associated myopathy.[1-3] AZT (ZDV) myopathy, defined by the presence of ragged red fibers on muscle biopsy, is seen particularly among HIV-treated patients who have a total lifetime intake of more than 200 g of ZDV, and has been reported in 66% of this group.[4] Apoptosis of CD4- and CD8-positive T cells, though present to a significant degree in lymph nodes of HIV patients,[5] is not involved in clearing T-cell inflammation in HIV associated polymyositis and inflammatory neuropathy,[6] nor has it been demonstrated in idiopathic polymyositis, dermatomyositis, or inclusion body myositis.[7]

Highly active antiretroviral therapy (HAART) connotes a drug cocktail in which a new generation of anti-HIV drugs, protease inhibitors, including ritonavir (Norvir), saquinavir (Invirase), indinavir (Crixivan), or nelfinavir (Viracept), are added. Protease, essential for the final stage of the HIV life cycle, cleaves large polypeptide chains into functional proteins, allowing the HIV virion to mature. When protease is inhibited, structurally disorganized, noninfectious, and harmless viral particles are released from the cell. More powerful than previous antiretroviral agents in battling HIV, the effect of protease inhibitors on the central nervous system is unknown. Although ZDV penetrates the brain and improves cognition in HIV,[8] the brain may remain unprotected from HIV dementia with other drug regimens. Total elimination of HIV from the host, the end goal of HIV therapy, may, thus, prove impossible if the brain remains a relatively protected sanctuary for HIV and a source of continued virus replication and dissemination.

Protease inhibitors, metabolized by the hepatic microsomal P450 system including cytochrome P450, 2D6, 3A4, and 2C9, share this pathway with the new generation of selective serotonin reuptake inhibitor antidepressants (SSRIs). Depression, common in the HIV population, engenders the potential for metabolic competition between these agents, with resultant toxicity of both groups of medication, a situation complicated by the 5-8% incidence of 2D6 deficiency in the caucasian population. The ability of some SSRIs and protease inhibitors to inhibit the P450 system befuddles the situation even further. Fundamental knowledge of the

neuropharmacology and psychiatric potential of HAART agents will be critical in the neurologic management of HIV. **—mr**

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Risk factors for distal sensory polyneuropathy development in HIV includes:

a. race.
b. older age and lower Karnofsky score.
c. gender.
d. CD4 cell count.
e. body weight.

Is Lamotrigine the New Valproate? The Role of Lamotrigine in the Management of Generalized Epilepsy

ABSTRACTS & COMMENTARY

Sources: Eriksson AS, et al. The efficacy of lamotrigine in children and adolescents with refractory generalized epilepsy: A randomized, double-blind, crossover study. *Epilepsia* 1998;39(5):495-501; Beran RG, et al. Double-blind, placebo-controlled, crossover study of lamotrigine in treatment-resistant generalised epilepsy. *Epilepsia* 1998;39(12):1329-1333; Guerrini R, et al. Lamotrigine and seizure aggravation in severe myoclonic epilepsy. *Epilepsia* 1998;39(5):508-512.

Clinical experience with lamotrigine increasingly supports its use in primary generalized epilepsies. Retrospective and open label studies in children with generalized epilepsies provided the first data that lamotrigine could be effective as add-on therapy for generalized epilepsies.[1] The results of double-blind, placebo-controlled trials of lamotrigine as an add-on treatment for generalized epilepsy are now becoming available. The first of these trials was a double-blind, placebo-controlled study of add-on lamotrigine in the treatment of patients with Lennox-Gastaut syndrome (LGS).[2] LGS, a severe childhood generalized epilepsy characterized by multiple seizure types, including atypical absence, tonic and atonic seizures, diffuse slow-spike and wave on EEG, and permanent cognitive and psychomotor disturbances is often refractory to pharmacotherapy. In the study by Motte and colleagues, 33% of patients in the lamotrigine treatment group had a more than 50% reduction in seizure frequency. Underscoring the importance of using a placebo-control group, 16% of the patients receiving placebo in this study experienced a more than 50% reduction in seizure frequency. The treatment group showed a 32% reduction in mean seizure frequency, compared to a 9% reduction in the placebo-treated group.

Eriksson and colleagues have examined the efficacy of lamotrigine as add-on therapy in generalized epilepsy in a population of 30 children and adolescents. Twenty of the patients were diagnosed with LGS; the remaining 10 patients had a mix of generalized seizure types including tonic-clonic, tonic-atonic, myoclonic seizures, and atypical absence seizures. Eriksson et al designed the study to include an open-label segment to determine a response to lamotrigine and to titrate dose. The open-label phase lasted an average of five months, with a range of 2-12 months. A reduction in seizure frequency of more than 50% or an improvement in behavior or motor skills, or both, was taken as evidence of treatment response. Overall, approximately two-thirds of patients showed a response to lamotrigine. Lamotrigine responders were then randomized to a treatment period when they would receive lamotrigine or placebo. Following a washout period, the same population of responders then received the alternate treatment for an equal period of time. Thus, each individual served as his or her own control. Half of the responders—that is one-third of the initial cohort—experienced a more than 50% reduction in seizure frequency and showed improvement in behavior or motor skills, or both. The other half of the responders had a smaller improvement in seizure frequency but, nevertheless, showed improved behavior and/or motor skills. Responders had half as many seizures on lamotrigine as they did on placebo.

Most recently, Beran and colleagues provide evidence that lamotrigine is also effective in an adult population of 26 patients with generalized epilepsy. These patients ranged in age from 15-50 years, with a mean age of 29 years, and suffered from a range of seizure types including absence, tonic-clonic, and myoclonic, as well as combinations of these types. The study used a crossover design in which there were two treatment periods (lamotrigine or placebo) of eight weeks separated by a four-week washout period. During the lamotrigine treatment phase, doses were increased to a therapeutic range over three weeks. Beran et al found that lamotrigine treatment resulted in a more than 50% reduction of seizures in one-third of patients with absence seizures and in one-half of patients with tonic-clonic seizures. The study population included two individuals with myoclonic seizures in addition to other seizure types. Although one must be cautious interpreting results from two patients, it is interesting to note that neither patient with myoclonic seizures improved on treatment, and one experienced more frequent seizures. The evidence that lamotrigine aggravates myoclonic seizures is stronger in a study by Guerrini and colleagues. Guerrini et al found that lamotrigine worsened seizure frequency in 80% of patients—ranging in age from 2-18 years—with severe myoclonic epilepsy of infancy. Forty percent of the patients experienced a more than 50% increase in tonic-clonic seizures and 33% suffered a more than 50% worsening of myoclonic seizures.

Serious adverse effects attributable to lamotrigine were only seen in the study by Beran et al, who reported rash as a frequent side effect and as a reason for discontinuing treatment. In this study, five of 26 patients developed a mild rash that resolved without discontinuation of lamotrigine treatment. Two patients developed a more serious rash that required discontinuation of lamotrigine. All patients who developed rash were also taking valproate.

COMMENTARY

Considerable clinical evidence has accumulated supporting the use of lamotrigine as an add-on treatment for generalized epilepsy. The availability of results from double-blinded, placebo-controlled trials adds weight to the conclusion that lamotrigine appears effective. A notable exception to this, however, is the result that lamotrigine may increase seizure frequency of some patients with myoclonic epilepsy.

The mechanism of action of lamotrigine in generalized epilepsy remains unresolved. Lamotrigine has been observed to improve behavior and mood in patients and can improve memory in the normal population.[3] The mechanism for these effects is also unknown. The early data on lamotrigine identified the use-dependent blockade of voltage-dependent sodium channels as a mechanism of antiepileptic action. This mechanism is often associated with efficacy in the treatment of partial epilepsy. There is also increasing evidence that lamotrigine inhibits the voltage-gated calcium channels and limits the entry of calcium into neurons.[4] More work is necessary to determine which mechanisms confer the antiepileptic and behavioral effects of lamotrigine.

The incidence of rash varied considerably in the cited studies and bears further examination. The risk of rash that may progress to Stevens-Johnson syndrome is a considerable concern of clinicians and is greatest with concomitant use of valproate. In the study by Eriksson et al, the open-label phase of dose escalation lasted several months, and none of the 30 patients in the trial developed a rash. In contrast, the study by Beran et al achieved a therapeutic dose of lamotrigine in three weeks, and 26% of the study group, seven of 26 patients, developed a rash. These results emphasize the importance of increasing the dose of lamotrigine gradually, especially when given with valproate, which inhibits the metabolism of lamotrigine and may result in a greater blood level. In conclusion, when introduced gradually into a patient's regimen, lamotrigine is an effective add-on drug against generalized epilepsy and may also produce beneficial effects in behavior and mood. **—fred a. lado & solomon l. moshé** *(Dr. Lado is EEG Fellow, Department of Neurology, Montefiore Medical Center-Albert Einstein College of Medicine, Bronx, NY. Dr. Moshé is Professor and Director, Pediatric Neurology and Clinical Neurophysiology, Department of Neurology, Montefiore Medical Center-Albert Einstein College of Medicine, Bronx, NY.)*

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Lamotrigine is usually effective as add-on therapy in each of the following seizure syndromes or types *except*:

a. severe myoclonic epilepsy of infancy.
b. LGS.
c. tonic-clonic seizures.
d. atypical absence seizures.
e. tonic-atonic seizures.