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A Review of the 54th Annual Meeting of the American Academy of Neurology

SPECIAL REPORT

Editor's Note: *A number of important and interesting papers in movement disorders were presented at the 54th meeting of the American Academy of Neurology held in Denver, Colo, from April 13-20, 2002. Interested readers can access the full text of these abstracts at www.aan.com.*

MEDICAL AND SURGICAL TREATMENTS OF PARKINSON'S DISease (PD) were a primary focus of the AAN meeting. Hubble and colleagues assessed the effect of a novel adenosine A2A receptor antagonist in patients with PD (*S21.001*). They demonstrated that treatment with this agent (named KW-6002) reduced the amount of time patients spent in the off state by 1.7 hours, without worsening dyskinesias. In patients with mild PD, Bianchine and colleagues assessed the tolerability of Rotigotine, a new dopamine agonist available as a transdermal patch (*S21.002*). They showed a dose-dependent improvement in motor performance with minimal adverse events. Two presentations that received significant media attention concerned possible evidence of a neuroprotective effect of 2 new dopamine agonists in PD. Marek (*S11.004*) presented data from the Parkinson Study Group consortium on the rate of nigrostriatal dopaminergic degeneration after initial treatment with pramipexole or levodopa in the CALM-PD study (recently reported in *JAMA*. 2000;284:1931-1938). Using serial SPECT imaging of the dopamine transporter, they demonstrated a slower rate of loss of striatal tracer uptake in patients treated with pramipexole (16% at 46-month follow-up) vs. those treated with levodopa (26% at the same time period). In a similar study, Whone and colleagues (*S11.006*) used fluorodopa PET scanning to measure progression of PD in early patients treated with ropinirole vs. levodopa. Patients treated with ropinirole experienced a 13% decline in fluorodopa uptake over 2 years, whereas patients treated with levodopa lost 20% over the same time. Although methodological questions remain about these 2 studies (for instance whether treatment with agonist or levodopa affects SPECT or PET scanning results), the similarity of these findings suggests the possibili-

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INSIDE

ty that treatment with agonists in early PD may be neuroprotective.

Several other papers are worthy of mention, including Merino-Andreu (*S21.005*) studied 56 moderately disabled Parkinson patients with polysomnography and multiple sleep latency testing. One third of their patients were unaware of experiencing daytime sleep episodes that lasted as long as 12 minutes, suggesting that this problem is highly prevalent in Parkinson patients. Ondo and colleagues (*P06.016*) presented a double-blind, placebo-controlled study of modafinil as a treatment for excessive daytime sleepiness in PD, showing that this agent (recently approved for use in narcolepsy) is safe and effective. Many poster presentations confirmed earlier studies of the success of bilateral subthalamic nucleus stimulation in patients with advanced PD. The expense of the procedure has led some investigators to explore subthalamotomy as an alternative. Su presented data (*P01.103*) on 8 patients treated with this procedure (both unilateral and bilateral), showing sustained benefit in bradykinesia, tremor, and gait at 18-month follow-up.

Three important papers were presented in the area of transplantation for PD. Watts (*S31.004*) presented results of 6 patients treated with unilateral stereotaxic implantation of cultured human retinal pigment epithelial cells attached to microcarrier beads, demonstrating moderate improvement in motor performance without significant adverse events. More impressive, Gill (*S31.003*) presented 5 patients who were treated with continuous infusion of glial derived neurotrophic factor directly into the dorsal putamen. A dramatic improvement in motor deficits (by rating scales and videotapes) was seen, with a reduction in dyskinesias. A placebo-controlled, double-blind study of this technique is planned. Transplant studies should be viewed with caution, as demonstrated by Pillai and colleagues' PET imaging study of Parkinson patients treated with embryonic dopamine cell transplantation (*S31.005*). Despite adequate engraftment of the transplant, motor improvements were only observed in patients younger than age 60. So-called "runaway dyskinesias" seen in the placebo-controlled, double-blind surgical trial of embryonic dopamine cell transplantation were also reported in a patient transplanted in another such trial, also occurring in the medication-free off state (*P01.116*).

Recent advances in hyperkinetic movement disorders were presented as well. Higgins (*S36.001*) used linkage disequilibrium to refine the location on chromosome 2p23 of a susceptibility locus for autosomal dominant early-onset essential tremor. Verbessem and colleagues reported a negative result of a double-blind, randomized, placebo-controlled trial of oral creatine in 41 patients with Huntington's disease (*S46.004*), showing no change in cognitive or motor status. Thomas described the clinical heterogeneity of patients with pantothenate kinase-associated neurodegeneration (*S41.001*). Patients affected with this autosomal recessive disorder may present in adulthood as well as in childhood, with adults more frequently affected with parkinsonism and children more frequently presenting with dystonia. Three papers summarized recent work on inherited myoclonus-dystonia. Asmus (*S07.005*) identified 6 novel loss-of-function mutations in the epsilon-sarcoglycan gene, and Ozelius (*P05.143*) reported further mutations in other families afflicted with this condition. Grimes (*S07.004*) presented a family with myoclonus-dystonia in which linkage to the epsilon-sarcoglycan gene was excluded: instead linkage to chromosome 18p11 was proposed. Finally, Frucht and colleagues reported their PET scanning study of patients with posthypoxic myoclonus, or Lance-Adams syndrome (*S60.001*). They demonstrated a highly significant increase in glucose metabolism in cerebellar vermis and ventrolateral thalamus, implying activation of the cerebello-thalamo-cortical loops in these patients. —**STEVEN FRUCHT**

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Hypothermia After Cardiac Arrest: A Neurological Perspective

ABSTRACTS & COMMENTARY

Sources: *N Engl J Med.* 2002;346:549-556; Bernard SA, et al. *N Engl J Med.* 2002;46:557-563.

Out-of-hospital cardiac arrest is a major cause of morbidity and mortality due to the neurological sequelae of hypoxic-ischemic injury. Hypothermia may benefit this or other neurological injuries by decreasing cerebral oxygen consumption or perhaps, more importantly, by controlling downstream effects of hypoxia such as free radical production, excitatory amino acid cascades, and osmotic swelling. Hypothermia has been successfully piloted as a neuroprotective strategy in stroke but has been less successful as a potential treatment for head trauma. In the latter case, a large proportion of patients who presented to the emergency room were already hypothermic, making it more difficult to show an additional treatment effect.

Achieving therapeutic hypothermia is not simple. Hypothermia is induced to a mild (32-34ºC), moderate (30-32ºC), or more extreme (< 30ºC) temperature. This involves surface cooling blankets and may also demand more invasive measures such as urinary bladder or peritoneal irrigation. Hypothermia also requires intubation, sedation, and paralysis to assure patient comfort and blunt shivering responses. Rewarming must be done in a controlled fashion as even passive rewarming, if too rapid, may result in rebound increases in intracranial pressure with significant brain swelling. Hypothermia may result in important medical complications including infections related to impaired immunity, primarily pneumonia, and hematological problems, such as thrombocytopenia. For these reasons, successful use of therapeutic hypothermia requires a skilled ICU team able to optimally both use this modality and effectively manage complications.

Two recently published studies, one European and the other Australian, examined patients following cardiac arrest and suggest that mild hypothermia in this population might be both feasible and beneficial. In the European group, 75 of 136 patients (55%) in the hypothermia group had favorable outcomes compared with normothermia—54 of 137 patients (39%)—a statistically significant result. Favorable outcome was defined as a "good recovery" (Category 1) or "moderate disability" (Category 2). Unfavorable outcomes occurred in patients with "severe disability" (Category 3), a vegetative state (Category 4), or death (Category 5). Mortality at 6 months was also significantly reduced with hypothermia. Patients in the normothermia group were more likely to have diabetes, a previous history of coronary artery disease, or to have received bystander CPR. None of these changed the outcome in multivariate analyses. Hypothermia was initiated in an average of 105 minutes (range, 61-192 minutes) after resumption of spontaneous circulation. The goal temperature of 32-34ºC was achieved in an average of 8 hours (range, 4-16 hours) and maintained for 24 hours as per the study protocol. There was a nonsignificant trend toward increased bleeding and sepsis in the treatment group, but overall the hypothermia was safe.

In the Australian group (Bernard and colleagues), with a smaller number of patients, 21 of 43 patients in the hypothermia group had a favorable outcome compared with 9 of 34 treated with normothermia (P = 0.046). A favorable outcome was defined as discharge to home or rehabilitation. Unfavorable outcomes occurred in patients who died or in a tiny minority (n = 2 for the whole study) who were sent to a long-term nursing facility. Mortality was not significantly different between the treatment groups. Hypothermia was maintained for 12 hours. The rapidity of hypothermia induction was not reported.

The studies differed in a few important ways. The European group required that there be an estimated interval of 5-15 minutes between the patient's collapse, with no more than 60 minutes until restoration of spontaneous circulation. This and other strict inclusion criteria resulted in a low rate of inclusion; only 275 patients were enrolled from a total of 3551 screened. The European study randomized patients 1:1 with an algorithm dictated by the coordinating center. In contrast, the Australian study split patients based on odd or even days of the month, which by chance generated 25% more patients in the active treatment group. In both studies, blinding was maintained for the physicians adjudicating outcome but not for treating physicians. As Bernard et al note, this is an unavoidable source of bias in a study such as this since cooling involves ice packs, cool air blankets, and other devices impossible to hide at the bedside. The development and approval of indwelling cooling catheters will undoubtedly facilitate therapy and might allow blinding if needed.

COMMENTARY

It is surprising that such a short duration of

hypothermia (only 12-24 hours) produced such dramatic benefits. A large degree of neuronal damage due to hypoxia probably occurred in the minutes to hours before therapy was initiated and ongoing secondary mechanisms of injury likely persisted for 48-72 hours after therapy was completed. It is furthermore encouraging that even mild hypothermia, a more safe and feasible therapy than severe cooling, was so effective in these studies. A more aggressive magnitude and duration of hypothermia in the setting certainly merits further investigation.

The use of global outcome scores in these patients, which categorized outcomes in terms of level of disability as well as discharge disposition and mortality, provided these investigators the power to show an overall benefit for this therapy. With this approach, however, subtleties may be lost. A patient sent home with severe amnesia, totally dependent on family for their activities of daily living, would still be categorized as favorable based on their methodology. Because these studies do not provide any specifics regarding the neurological exam of these patients (not even a relatively blunt instrument such as the Glasgow Coma Scale), it is difficult to glean any further neurological insight into these patients' condition.

Neurologists are often called to the bedside acutely or in the days immediately following cardiac arrest to provide prognosis. Deep sedation and paralysis for the purposes of hypothermia makes this exercise impossible. Neurologists should, nevertheless, advocate for this therapy. Given an otherwise untreatable and protean condition, cardiac arrest victims should be cooled as quickly and probably for as long as possible for optimal neuroprotection. At the very least, cardiac arrest victims who arrive already cold, should be maintained as such and any patient who develops even mild pyrexia should be aggressively defervesced at least normothermia with acetaminophen or practical cooling measures. **—ALAN Z. SEGAL**

New Treatments for Vascular Dementia?

ABSTRACTS & COMMENTARY

Sources: Erkinjuntti T, et al. *Lancet.* 2002;359:1283-1290; Pratt R, et al. Second International Congress on Vascular Dementia (ICVD), Salzburg, Austria, Jan. 24-27, 2002.

Vascular dementia (VaD) is the second most common cause of dementia after Alzheimer's disease (AD). VaD is a pathologically heterogeneous disorder encompassing dementia that is temporally associated with single large cerebral infarcts, multiple small infarcts, lacunar infarcts, or leukoariosis. Most therapies have been directed at treating risk factors associated with these processes (eg, hypertension), inhibiting platelet function with aspirin, increasing cerebral blood flow, or ameliorating behavioral sequelae of dementia such as depression or agitation. Two new studies now describe the effects of the cholinesterase inhibitors galantamine and donepezil on cognition, behavior, and function.

Erkinjuntti and colleagues randomized patients with VaD to galantamine (n = 396) or placebo (n = 196) in a multi-center, double-blind study and followed them for 6 months. All patients had dementia of mild-to-moderate severity (Mini-Mental State Exam score 10-25) had radiographic evidence of cerebrovascular disease, and met standard criteria for probable or possible VaD (essentially, dementia with memory loss and impairment in 2 other cognitive domains). Some patients with VaD also met the accepted criteria for possible AD. Data were analyzed with the last observation carried forward on an intention-to-treat basis. Patients who received galantamine (12 mg twice a day) demonstrated a 2.7-point improvement ($P < 0.0001$) in cognition at 6 months on the cognitive subscale of the AD assessment scale (ADAS-Cog) compared to the group who received placebo. The ADAS-Cog is a 70-point standardized instrument that is used in most AD clinical trials to evaluate cognitive function. Although the study was not powered to perform adequate subgroup analysis, in the group with VaD alone the mean improvement in ADAS-Cog score was 1.9 points ($P = 0.06$). In the group with mixed dementia (VaD plus AD), the effect was 2.7 points in favor of galantamine ($P = 0.0005$).

Positive effects were also seen on the clinician's interview-based impression of change plus caregiver input (CIBIC-plus), a measure of a patient's overall condition over time that encompasses cognition, behavior, and function. Compared to placebo, more patients who received galantamine demonstrated improvement or no change (74% vs 59%; $P = 0.001$). Other significant benefits with galantamine included independent measures of functional independence (the disability assessment in dementia) and behavioral symptoms (the Neuropsychiatric Inventory). The rate of withdrawal from the trial due to adverse effects, largely nausea and vomiting, was higher in the galantamine group (20%) than in the placebo group (8%). Erkinjuntti et al attributed the high rate of discontinuation with galantamine to the rapid dose-escalation

schedule. The drug has been better tolerated in trials that used a more extended titration of dosage.

Pratt and colleagues presented similar, but limited, findings from a randomized, double-blind, placebo-controlled 24-week trial of donepezil (either 5 or 10 mg/d) in 616 patients with VaD. Patients meeting criteria for probable (76%) or possible (24%) VaD plus radiographic evidence of cerebrovascular disease were studied. In contrast to the galantamine trial, patients with possible AD were excluded. Significant improvement with donepezil treatment compared to placebo was reported on the ADAS-Cog ($P < 0.001$), as well as on the CIBIC-plus ($P = 0.004$ for 5 mg donepezil/d and $P = 0.047$ for 10 mg donepezil/d). Discontinuation rates were 8.8% in the placebo group, 10.1% with 5 mg/d donepezil, and 16.3% with 10 mg/d donepezil.

COMMENTARY

The benefits of cholinesterase inhibitors to treat AD are well established. They are believed to partially compensate for the brain's deficit of acetylcholine in AD patients by inhibiting the breakdown of the neurotransmitter at central cholinergic synapses. They also might have direct effects on nicotinic receptors. Three of the 4 cholinesterase inhibitors approved by the FDA are in common use: donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Reminyl®). All 3 drugs given in randomized, placebo-controlled, double-blind clinical trials have had approximately equivalent positive effects on cognition, behavior, and function in patients with AD. Erkinjuntti et al and Pratt et al have now demonstrated therapeutic effects of galantamine and donepezil on cognition and overall condition in patients with VaD that compare in magnitude to those seen in patients with AD. Nausea and loss of appetite are the most common side effects, seen especially at the initiation of treatment. There is a relative contraindication for patients with cardiac conduction abnormalities, a theoretical risk due to potential negative effects from added cholinergic stimulation leading to heart block or bradycardia. This concern may be relevant in the VaD population, which has a higher prevalence of cardiac disease.

It is sometimes difficult to distinguish between VaD and AD. To diagnose VaD in the galantamine study, dementia must have occurred within 3 months of stroke symptoms, appeared abrupt in onset, or progressed in stepwise fashion. Many patients with VaD, either alone or mixed with AD, do not have such clear-cut temporal features. The study by Erkinjuntti et al supports the benefits of galantamine treatment regardless of the exact diagnosis. However, one should note an important distinction between VaD and AD. As might be predicted by the natural course of VaD, patients who received placebo had little change in cognition (ie, the ADAS-Cog score) over 6 months. This contrasted AD in which deterioration occurs due to degenerative progression. Thus, the positive effect of cholinesterase inhibitors on the ADAS-Cog score in patients with VaD might represent an actual improvement in cognition rather than just a stabilization of cognition as in AD.

Patients with AD suffer from a pathologically defined loss of cholinergic neurons in the basal forebrain. No such selective deficit has been documented in VaD. Thus, the mechanism of action of cholinesterase inhibitors in VaD is unclear but may reflect a generalized modulatory effect on cortical and subcortical cholinergic systems. Also, the underlying pathophysiology of VaD is diverse and represents different underlying etiologies (eg, large vessel occlusive disease vs small vessel lipohyalinosis) and lesion sites (eg, single vessel territories vs diffuse subcortical white matter disease). At present, the evidence is inadequate to recommend cholinesterase inhibitors for all patients with VaD. Finally, it may seem easy to dismiss the relatively small numerical improvements seen with cholinesterase inhibitor treatment (eg, 2.7/70 points on the ADAS-Cog). Greater emphasis should be placed on demonstrating effects on maintenance of independent functioning and improvement in quality of life. **—GREGG L. CAPORASO**

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Chemotherapy in Adult High-Grade Glioma

ABSTRACT & COMMENTARY

Source: Stewart LA. *Lancet.* 2002;359:1011-1018.

THE INFILTRATING NATURE OF HIGH-GRADE GLIOMAS makes complete resection of these tumors virtually impossible. Therefore, standard treatment generally consists of cytoreductive surgery followed by radiation therapy. Nevertheless, prognosis is poor with a median survival time of 9 months and only 5-10% of patients surviving at 2 years (Bleehen NM, Stenning SP. *Br J Cancer.* 1991;64:769-774). Randomized trials on the effect of systemic chemotherapy on survival and recur-

rence in adults with high-grade glioma have had inconclusive results. Therefore, the GMT group did a systematic review and meta-analysis using data from all available randomized trials that compared radiotherapy alone with radiotherapy plus chemotherapy. The main results of this paper were based on information from 12 randomized controlled trials that included more than 3000 eligible patients or 81% of patients from all known eligible randomized trials.

Overall, the results showed a significant prolongation of survival associated with chemotherapy or a 15% relative decrease in the risk of death. This effect was equivalent to an absolute increase in 1-year survival of 6% and a 2-month increase in median survival time. There was no evidence that the effect of chemotherapy differed in any group of patients defined by age, sex, histology, performance status, or extent of resection.

COMMENTARY

Prior to this meta-analysis, despite enrollment of more than 3500 patients in randomized trials, the question of whether chemotherapy was effective in the treatment of high-grade gliomas remained unclear. Because of this uncertainty, current treatment of gliomas varies intranationally and internationally. Stewart's systematic review provides an up-to-date summary of the average effect of chemotherapy in adults with high-grade gliomas and provides guidance for clinical practice and further research. Stewart showed, in this comprehensive review, that high-grade gliomas can respond to chemotherapy. The question remains as to whether the benefits of chemotherapy they detected are clinically worthwhile. As they point out, benefit is likely to vary with the clinical situation and the individual patient and his family's preferences. Tolerability of treatment and quality of life, including cognitive impairment, are major issues for patients who will survive for only a short time after their treatment has concluded. Stewart cannot answer this question because few of the trials they analyzed in their meta-analysis formally measured quality of life or undertook cognitive function tests. Nevertheless, this meta-analysis indicates that with respect to the nitrosoureas, chemotherapy is fairly well tolerated and easily administered and, therefore, is of practical use for treatment of individuals who wish to extend their likely survival time if only by a modest amount. Obviously the modest benefit of treatment and the remaining uncertainty about quality of life still allows clinicians to limit treatment to surgery and radiotherapy alone in patients whose quality of life is poor and in whom prolonging survival would be a burden both to them and to their families. Nevertheless, the small but definite improvement in survival from chemotherapy should encourage the use of available agents for the treatment of high-grade gliomas and encourage further studies of new chemotherapy agents. **—JOHN J. CARONNA**

Optimal Dosing of Interferon in MS

ABSTRACT & COMMENTARY

Source: Durelli L, et al. *Lancet.* 2002;359:1453-1460.

In this open-label Italian study, 188 patients with relapsing-remitting multiple sclerosis (MS) at 15 centers were randomly assigned to either interferon (IFN) beta-1b (250 mcg, 8 MIU, Betaseron) SC QOD, vs. IFN beta-1a (30 mcg, 6 MIU, Avonex) IM Q weekly. The primary clinical outcome measure was the proportion of patients free from relapses during the 24-month study period, with secondary measures of annualized relapses, treated relapses, and sustained progression of disability. All clinical outcomes were assessed in an open-label manner. The primary brain MRI outcome measure from yearly scans, which were analyzed in a blinded manner, was the proportion of patients free from new proton density/T2 hyperintense lesions, with secondary MRI outcomes of gadolinium-enhancing lesions and burden of disease.

The proportion of patients free from relapses at 24 months was 36% for IFN beta-1a vs. 51% for IFN beta-1b ($P = 0.03$). Patients with sustained and confirmed progression of disability of 1 EDSS point at 24 months was 30% for IFN beta-1a vs. 13% for IFN beta-1b ($P < 0.01$). The percentage of patients free from new T2 lesions was 26% in the IFN beta-1a group vs. 55% in the IFN beta-1b group. Similarly, the percentage of patients free from enhancing lesions in the IFN beta-1a group was 49% vs. 76% in the IFN beta-1b group ($P = 0.001$). There was, however, a higher incidence of adverse effects, especially injection site reactions, in the IFN beta-1b group, as was the incidence of neutralizing antibodies approximately 4-fold higher in the IFN beta-1b group (6% vs 22%).

COMMENTARY

Evidence-based medicine can provide helpful comparisons about the relative efficacy of treatments and provide practical information about benefits and risks of therapy. This trial showed better primary and secondary outcome measures for the patients treated with IFN beta-1b every other day, than in patients treated

weekly with IFN beta-1a. These effects were more apparent at month 24 than at 12 months. A significant and incontrovertible limitation of these data is the unblinded, open-label study design, not only for the patient, but also for the evaluating clinician. This introduces unavoidable investigator and patient bias which can drive an anticipated result. Further, there were more male patients with longer disease duration and more PD/T2 brain lesions at baseline in the weekly IFN beta-1a group, arguably a more difficult patient group to treat. It remains to be seen to what extent the added therapeutic benefit of more frequent SC IFN beta-1b injections is offset by the higher incidence of neutralizing antibodies. **—BRIAN R. APATOFF**

Analgesic Options Using Antiepileptic Medication

DRUG SUMMARY

Source: Burton AW. *Internet Journal of Pain, Symptom Control & Palliative Care.* 2001;1n2. http://www.ispub.com/ostia/index.php?xmlFilePath=journals/ijpsp/front.xml.

IN THE FOLLOWING TABLE, 13 ANTIEPILEPTIC agents that may be considered for long-term pain control are listed with dosage and side effect profile. We hope our readers will find this Table convenient and useful. **—MICHAEL RUBIN**

Table

Antiepileptic Drugs for Pain Management

Drug	Mechanism of Action	Side Effects	Maximum*
Carbamazepine	Slows recovery rate of voltage gated Na+ channels	drowsiness, diplopia, unsteadiness aplastic anemia (1:200,000)	1600 mg/d
Phenytoin	Similar to carbamazepine	nausea, diplopia, dizziness, confusion, gingival hyperplasia, Stevens-Johnson syndrome	600 mg/d
Valproic Acid	Similar to carbamazepine, also increases levels of GABA by decreasing degradation	nausea, vomiting, sedation ataxia, rash, alopecia, appetite stimulation elevated transaminases in 40%	60 mg/kg/d
Clonazepam	Enhancement of the GABA-induced increase in chloride conductance	sedation, lethargy, ataxia, dizziness	20 mg/d
Gabapentin	Uncertain, may have its effect at a central voltage dependent L-type Ca++ channel	drowsiness, somnolence, fatigue	3600 mg/d
Pregabalin	gabapentin analog	not yet approved for clinical use	
Lamotrigine	Inhibitor of voltage gated Na+ channels; may suppress glutamate release may inhibit serotonin reuptake	dizziness, diplopia, drowsiness, rash	900 mg/d
Topiramate	Potentiates GABA responses, increasing CNS GABA levels, blocks the AMPA kainate excitatory receptor, weak carbonic anhydrase inhibitor	abnormal thinking, psychotic thinking, delusional	400 mg/d
Oxcarbezapine	Similar to carbamazepine, may modulate voltage activated Ca++ currents	drowsiness, diplopia unsteadiness	2400 mg/d
Felbamate	Decreases glutamate synthesis blocks NMDA receptors	rare hepatotoxicity aplastic anemia	3600 mg/d
Zonisamide	Na+ channel blockade T-type Ca++ channel blockade carbonic anhydrase inhibitor		600 mg/d
Tiagabine	GABA reuptake inhibitor future potential for the treatment of painful conditions		60 mg/d
Vigabatrin	GABA metabolism inhibitor future potential for the treatment of painful conditions		4000 mg/d

*N.B. Only carbamazepine, phenytoin, gabapentin, and lamotrigine have been evaluated in double-blind trials (*JAMA.* 1998;280:1837-1842; *Pain.* 1997; 73:223-230). Always begin with a low dose, preferably at bedtime. Increase gradually until side effects occur. Maximum dose may be exceeded if patient is tolerant. Pain relief may be gradual; wait 4-8 weeks at therapeutic dosage before moving to a different agent.

Can a Protective Interstitial CNS Drug Prevent or Slow the Damage of ALS?

ABSTRACTS & COMMENTARY

Sources: Tikka TM, et al. *Brain.* 2002;125(Pt 4):722-731; Shaw PJ. *Brain.* 2002;125(Pt 4):693-694.

MOTOR NEURON DISEASES (MND) IN THESE 2 ARTICLES are the same as lower motor neurons (LMN) in amyotrophic lateral sclerosis (ALS) in the United States. Both above reports emphasize that LMN deterioration usually begins and develops in particular body areas such as the distal area of one upper or lower limb or of the lower cranial nerves. It then advances gradually and steadily, part by part in disintegrating LMN in ipsi- or contra-neuromuscular zones. Thus far, no medication has been able to seriously slow down or halt this most vicious illness which usually strikes middle adult or lower elderly patients (some familial cases, however, can start as young as the late teens). Approximately 10% of ALS cases are familial and some 20% of those show indications in the CuZn-superoxide dismutase (CuZn-SOD) gene. Many cases reflect dysfunctional glutamate homeostasis. Recent studies also have identified glutamate as playing a large, abnormal part of genetic somatomotor dysfunction in all somatic motor activity. Riluzole acts as a modest glutamate release/inhibitor and appears to be the only treatment to have even a modest protective effect in the early days of ALS.

COMMENTARY

Shaw clearly emphasizes in her editorial that Tikka and colleagues took the clear CSF of each of 3 different ALS patients and added each sample to a cell culture of a neurological disease different from ALS. Each of the 3 functional CSF cultures gave way to produce apoptotic degeneration of both neurons and microglia. The CSF samples from the other non-MND neurological disorders did not have that lethal touch. When N-methyl-D-asparate (NMDA) and AMPA receptor antagonists were applied to the ALS patients, they prevented the microglial damage of ALS. Minocycline also added to the cultures and prevented death to either assault.

Through a somewhat complicated set of experiments, Tikka et al conclude that all motor neuron cases are susceptible to cytotoxic action that can be identified by specific testing of CSF. Whether or not minocycline will turn out to be clinically effective remains to be seen. —**FRED PLUM**

CME Questions

24. All of the following statements regarding hypothermia for the treatment of cardiac arrest are true *except*:

a. treatment is effective when used for only 12-24 hours.
b. relatively mild hypothermia (33ºC) may be used.
c. complications such as pneumonia and thrombocytopenia occurred significantly more frequently in the treatment group.
d. patients must be paralyzed and sedated to facilitate therapy.
e. similar treatment might be considered for large strokes or head trauma.

25. Which one of the following statements is true?

a. The presence of cerebrovascular disease on CT or MRI studies precludes the diagnosis of AD.
b. Galantamine was shown to improve cognition and function, but not behavior, in patients with VaD.
c. Gastrointestinal symptoms are the most common side effects in patients treated with cholinesterase inhibitors.
d. Cholinesterase inhibitors are safe for all patients.

26. Which of the following statements about the use of chemotherapy in adult gliomas is true?

a. Chemotherapy is of no benefit in prolonging survival in high-grade gliomas.
b. Chemotherapy prolongs survival only in patients with low-grade gliomas.
c. Chemotherapy improves survival and quality of life in patients with high-grade gliomas.
d. Chemotherapy prolongs survival only in patients with gross total resection of tumor.
e. Chemotherapy produces a small improvement of survival by its effect on quality of life varies with the individual case.

Readers are Invited. . .

Readers are invited to submit questions or comments on material seen in or relevant to *Neurology Alert*. Send your questions to: Neill Larmore, *Neurology Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. For subscription information, you can reach the editors and customer service personnel for *Neurology Alert* via the internet by sending e-mail to neill.larmore@ahcpub.com. We look forward to hearing from you. ■

In Future Issues:

Can IVIG Ameliorate Diabetic Neuropathy?

PHARMACOLOGY WATCH

HRT: Position Paper Places Benefits in Question

A soon-to-be published position paper will call into question the benefits of hormone replacement therapy (HRT) for women. The "International Position Paper on Women's Health and Menopause" will go to press in June, but newspapers coast to coast are already publishing the recommendations of the document, which concludes that an evidence-based review of HRT does not support the use of HRT in preventing coronary artery disease, Alzheimer's disease, depression, or urinary incontinence. The position paper was the product of an international group of 28 doctors and scientists and was funded by the National Institutes of Health and the Giovanni Loren Zini Medical Science Foundation of Italy. The recommendations reflect a shift in opinion for most physicians and epidemiologists who feel that HRT's risks, which include increased risk of blood clots, cholelithiasis, and breast cancer do not outweigh the potential benefits. The thought process doctors must go through with patients when considering starting or discontinuing HRT is well laid out in a recent "Clinical Crossroads" paper in the *Journal of the American Medical Association*. Dr. Deborah Grady reviews the current literature, and dilemmas faced by both physicians and patients alike when trying to wade through conflicting studies. A self-avowed former proponent of HRT, Dr. Grady now feels that it should be reserved for treatment of vasomotor symptoms, and that it is second-line therapy to bisphosphonates for the treatment of osteoporosis (*JAMA*. 2002;287:2130-2137).

Alosetron Set for Comeback

Eighteen months after it was withdrawn from the US market, alosetron (Lotronex) GlaxoSmithKline's irritable bowel syndrome (IBS) drug, may be making a limited comeback. The FDA's Gastrointestinal Drugs and Drug Safety Advisory Committees approved the drug for patients with severe IBS symptoms. The drug was initially approved in February 2002 for the treatment of women with IBS characterized by diarrhea. However, soon after the drug was marketed, cases of severe constipation were reported along with several cases of ischemic colitis. Of the 7 deaths, alosetron was possibly a factor in all of them. The drug was effective in selected patients, however, and the FDA was inundated with requests to re-release the drug in a limited fashion. The current plan is to restrict the drug to patients with the most severe symptoms, and to require patients to sign a patient-physician agreement and to receive counseling about the potential risks of the drug. The FDA is also considering limiting the use of alosetron to gastroenterologists. GlaxoSmithKline is working out the plan for re-release of alosetron with the FDA and hopes the drug will be available before the end of the year.

Losartan Could Receive Expanded Indication

The angiotensin receptor blocker (ARB) losartan may soon be approved for prevention of renal disease in type 2 diabetes. The FDA is considering granting losartan the expanded indication based on a favorable vote by the FDA's Cardiovascular and Renal Drugs Advisory Committee early in April. Angiotensin converting enzyme inhibitors (ACEIs) have long been considered first-line treatment of hypertension in type 2 diabetics because of studies that suggested that blockade of the renin-angiotensin system delays progression to end-stage renal disease. Whether this benefit extends to ARBs was debatable until 3 articles were published in the

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Sept. 20, 2001, *New England Journal of Medicine* confirming the benefit of ARBs in protecting patients with Type 2 diabetes from developing renal disease.

Merck supplied additional data to the FDA in April, which eventually led to the recommendation. The FDA is expected to endorse the committee's recommendation, granting losartan the indication for reno-protection in type 2 diabetes, the first drug to receive such approval.

Viagra Shown Beneficial in Intensive Care Unit

Viagra (sildenafil) in the ICU? It may not be so far-fetched, and the benefit may be lifesaving for those with severe pulmonary hypertension. Sildenafil has been shown to cause pulmonary vasodilation along with its other well-known effects. German researchers looked at 30 patients with severe pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension, or pulmonary hypertension due to aplasia of the left pulmonary artery. Patients were randomized to receive sildenafil alone or in combination with iloprost, a long-acting inhaled prostacyclin analogue. Maximum pulmonary vasodilatory potency (maximum reduction of pulmonary vascular resistance and increase in cardiac index) occurred with the combination of sildenafil 50 mg plus inhaled iloprost (-44.2%, 95% CI, -49.5% to -38.8%). This compared with a drop of 14.1% with inhaled nitric oxide. The combined effect of sildenafil with iloprost lasted longer than 3 hours and had minimal effect on systemic arterial pressure and arterial oxygenation. It was concluded that sildenafil is a potent pulmonary vasodilator that acts synergistically with inhaled iloprost (*Ann Intern Med*. 2002;136:515-522).

Smallpox Vaccination Needs Consideration

Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases, has kicked off "an open and public dialogue" on the need for a national preemptive smallpox vaccination program (*N Engl J Med*. 2002;346:1319-1320). Nearly unthinkable a year ago, the events of Sept. 11 have focused the national health-care community on the real possibility of bioterrorism. And of all the potential bioterrorism pathogens, which include anthrax, plague, and even tularemia, it is smallpox that stands out as a true threat. Declared eradicated from the world in mid-1970s, routine vaccination for smallpox in this country was discontinued 30 years ago. As a result, more than half the American population is susceptible to smallpox infection. Samples of variola virus, the cause of smallpox, were stored at the CDC and were actually produced and stored in the former Soviet Union as part of a biologic warfare program. Those stores were reported destroyed by the current Russian government, but it is unknown whether samples of the deadly virus may have fallen into the hands of potential bioterrorists. Smallpox is a uniquely deadly bioterrorist weapon. Once infected, victims are most contagious prior to the development of symptoms, thus becoming unwitting agents of the bioterrorist, especially in our highly mobile society. Plus smallpox infection carries a relatively high mortality rate, from 5 to 20% based on 30-year-old data. Current CDC policy for an attack focuses on a "ring-vaccination" strategy in which suspected or confirmed cases and their contacts are isolated and immediately vaccinated. This is the method that successfully eliminated smallpox 30 years ago. The CDC currently is advocating the strategy in the event of a bioterrorists attack. But critics, such as William J. Bicknell, MD, from Boston University School of Public Health, argue that ring-vaccination was effective against natural outbreaks of the virus but may not be effective against a deliberate bioterrorist attack. He makes the case for widespread voluntary smallpox vaccination, which would achieve protection for the majority of Americans and also act as a deterrent to attack (*N Engl J Med*. 2002;346:1323-1325). There is a risk to the vaccine including encephalitis and vaccinia, and vaccination of the majority of Americans would be expected to result in approximately 180 deaths. This debate would have been moot 2 months ago because it was felt that CDC did not have enough vaccine for a nationwide vaccination program. However, researchers from the National Institute of Allergy and Infectious Diseases Smallpox Vaccine Study Group have tested dilutions of a recently discovered cache of smallpox vaccine produced in 1982. The randomized single-blind trial of 680 adult volunteers showed that both 1:5 and 1:10 dilutions of the vaccine were as effective in conferring immunity as the full strength vaccine, with at least 97% of those vaccinated developing protective antibodies (*N Engl J Med*. 2002;346:1265-1274). The common side effects from the vaccine included formation of satellite skin lesions, regional lymphadenopathy, fever, headache, nausea, and other signs of a viral infection. But the true upshot of the study was the realization that as a nation, we suddenly have the ability to vaccinate the entire population. But with this realization comes the debate as to whether we should. The turning point in this deliberation may depend on our government's ability to truly characterize the risk of a bioterrorist attack. ■