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Do Dietary Antioxidants Prevent Alzheimer's Disease?

ABSTRACT & COMMENTARY

Sources: Engelhart MJ, et al. Dietary intake of antioxidants and risk of Alzheimer disease. *JAMA*. 2002;287:3223-3229; Morris MC, et al. Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. *JAMA*. 2002;287:3230-3237; Morris MC, et al. Vitamin E and cognitive decline in older persons. *Arch Neurol*. 2002;59:1125-1132.

THERE IS A LARGE BODY OF EVIDENCE, WHICH IMPLICATES oxidative damage as playing a role in the pathogenesis of Alzheimer's disease (AD) and other neurodegenerative disorders. As yet, however, most of this evidence is correlative, and a strong case for a cause and effect relationship has not been established. Three recent studies have provided epidemiologic data that increased intake of antioxidants may be associated with a reduced risk of developing AD. The evidence has been most convincing for increased intake of vitamin E from dietary sources. The first study was that of Morris and colleagues, which studied the dietary intake of antioxidant nutrients in the Chicago Health and Aging project. Morris et al examined patients prospectively from 1993 to 2000. There were 815 residents 65 years and older who were free of AD at baseline and who were followed up for a mean of 3.9 years. They completed food frequency questionnaires at an average of 1.7 years after baseline examination. Morris et al made adjustments for numerous risk factors for AD including age, education, sex, race, ApoE4, and length of follow-up. The patients in the highest quintile of vitamin E intake from food were 70% less likely to develop AD than those in the lowest quintile of intake. This was a significant trend. The protective effect of vitamin E was observed only among patients who were ApoE4-negative. There appeared to be no association with dietary intake of vitamin C, beta-carotene, or intake from dietary supplements.

The second prospective study was that of Engelhart and colleagues. This is the Rotterdam Study, which is a population-based prospective cohort study conducted in The Netherlands. Engelhart et al examined a total of 5395 participants who at baseline were approximately 55 years of age. At that time, they were free of

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dementia, noninstitutionalized, and had reliable dietary assessment. They were subsequently reassessed at 2 further time points approximately 3 and 6 years after the initial evaluation. After a mean follow-up of 6 years, 197 participants developed dementia, of whom 146 were diagnosed as having AD. After an adjustment of multiple other risk factors, Engelhart et al found that vitamin E and C intake reduced the risk of AD to 0.82. The effect appeared to be largely confined to smokers in which the reduced incidence was much more profound being 0.58, and in this subpopulation, there was also a significant effect of beta-carotene being 0.49 relative risk and flavonoids being 0.54 relative risk.

The third study was again conducted in the Chicago cohort mentioned above. In this study, 2889 community residents age 65 and older were questioned 18 months after baseline. They were followed for an average of 3.2 years. They were examined with a number of cognitive tests, including the East Boston Memory test, the Mini-Mental State examination, and the Symbol Digit Modalities test, both at baseline and 3 years for all participants. Morris et al observed a 36% reduction in the rate of decline among patients in the highest quintile of vitamin E intake as compared to those from the lowest quintile. This was true of intake from both supplements or foods. They also observed an independent effect of vitamin E intake from foods.

COMMENTARY

These studies are of considerable interest and provide "food for thought." There, however, are a number of caveats about these studies and their interpretation. In the initial 2 prospective studies, there was no identified association between incidence AD and the use of vitamin E and C supplements, although in the third, there did appear to be an association with vitamin E supplements. The fact that in the initial Chicago study there was no effect in ApoE-4 positive patients suggests that this genetic factor may override any potential protective effect of antioxidants. In that study, the dietary assessment occurred on average 1.7 years after the participant has been ascertained to be at risk, meaning that a number of the patients were studied essentially cross-sectionally, which has the potential for a number of biases that could have affected the results. The Rotterdam Study had a longer mean follow-up of 6 years. The patients were considerably younger by approximately 10 years than those in the Chicago Study. The effect in the Rotterdam Study, however, appeared to be largely confined to smokers. This is consistent with a number of other observations that smokers have a markedly increased risk of oxidative damage. This has been clearly demonstrated by measurement of a number of markers of oxidative damage in smokers. For instance, plasma markers of cholesterol hydroperoxides and urinary measurement of oxidative damage to DNA are significantly increased in smokers. In the Honolulu-Asia Aging Study, vitamin E and C supplements reduced the risk of vascular dementia, but not that of AD.[1]

Previous cross-sectional studies have suggested that increased plasma levels of vitamin E may also be associated with reduced risk of developing AD. Another epidemiological study suggests that increased dietary intake of flavonoids, another antioxidant, which is found in foods, is also associated with a reduced risk of developing AD.[2] In contrast, increased plasma homocysteine levels, which may be associated with increased oxidative damage, are associated with an increased incidence of developing AD.[3] When one assesses the evidence obtained thus far, it is both intriguing and worthy of further investigation. As yet, it cannot be said to be definitive. Prior studies have suggested that antioxidants might reduce the incidence of cancer and arthrosclerosis but the interventional studies thus far have not sustained these predictions. The present observation that dietary intake of vitamin E-rich foods may reduce the incidence of AD is similar to prior observations that foods rich in fruits and vegetables reduce the risk of cancer. Ultimately, the issue will have to be resolved with a well-designed primary prevention clinical trial. This is well

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justified considering the increasing age of the population and the increasing incidence of AD along with its consequent cost to society. — **M. Flint Beal**

References

1. Kraft E, Trenkwalder C, Auer DP. *Neurology*. 2000; 54:1265-1272.
2. Commenges D, et al. *Eur J Epidemiol*. 2000;16: 357-363.
3. Seshadri S, et al. *N Engl J Med*. 2002;346:476-483.

Fibrates, Statins, and Myopathy

ABSTRACT & COMMENTARY

Source: Wortmann RL. Lipid-lowering agents and myopathy. *Curr Opin Rheumatology*. 2002;14:643-647.

Nicotinic acid, fibrates, and statins (HMG CoA reductase inhibitors), by lowering serum lipid levels, reduce cardiovascular morbidity and mortality. Myopathy has been associated with these agents, ranging from myalgias to rhabdomyolysis, myoglobinuria, renal failure, and death, and appears dose-related rather than idiosyncratic or allergic. Impaired renal function and combining different types of lipid-lowering agents may increase myotoxicity. Symptoms, which may be focal, proximal, or generalized, include weakness, myalgias, and muscle tenderness or cramping sensations. Creatine kinase (CK) may be normal or elevated and muscle biopsy is nonspecific, showing variation of fiber diameter, fiber splitting, internal nuclei, fibrosis, necrosis, and hypercontracted fibers.

Fibrates and statins are associated with a 42-fold and 8-fold increased risk of myopathy, respectively, compared to normal controls, but the incidence remains low, at 6 per 100,000 and 1 per 100,000, respectively. Overall mortality from statin-associated fatal rhabdomyolysis is 0.15 per million prescriptions, but this includes cerivastatin (Baychol), which was withdrawn from the market with 3.16 deaths reported per million prescriptions.

Etiology remains unclear. Complicating factors, including concomitant hypothyroidism and increased exercise, may contribute to CK elevation and myalgia. By inhibiting HMG CoA reductase, mevalonic acid synthesis is also impaired. Mevalonic acid is an isoprenoid precursor, necessary for RNA synthesis, glycoprotein synthesis, heme A, and ubiquinone (coenzyme Q10), both the latter involved in the electron transport chain, the last containing 10 isoprenoid units. Coenzyme Q is an antioxidant in lipid membranes and low levels may predispose to membrane damage and myopathy. Indeed, coenzyme Q supplementation may be beneficial for statin-associated myopathy,[1] but not universally so, suggesting that pathogenesis of statin-myopathy is likely multifactorial.

COMMENTARY

Axonal polyneuropathy may also be associated with statin usage.[2] In a population-based study in Funen, Denmark (population 465,000), 1084 patients with a diagnosis of polyneuropathy were registered between 1994 and 1998. After record review, 166 were found to have no other concomitant diagnoses associated with neuropathy, including diabetes, renal failure, alcoholism, thyroid disease, cancer, monoclonal gammopathy, AIDS, Lyme disease, collagen vascular disease, vitamin deficiency, familial polyneuropathy, heavy metal intoxication, or chronic inflammatory demyelinating polyneuropathy. All 166 fulfilled clinical criteria for polyneuropathy, including distal sensorimotor symptoms and abnormal nerve conduction studies. Each patient was matched with 25 age-, sex-, and date-matched Funen citizens without a diagnosis of polyneuropathy as controls. Analysis of prescription records revealed that patients with idiopathic polyneuropathy were 16.1 times more likely to have been on statins, with increased duration and dosage associated with increased risk. Does this mean that statins cause neuropathy? Not necessarily. As the underlying disease, atherosclerotic peripheral vascular disease may be causative or contributory.[3] Patients with chronic idiopathic axonal polyneuropathy (CIAP) or peripheral vascular disease, n = 97 each, and 96 age- and sex-matched controls were investigated in this incidence case-control study. CIAP patients were more likely to have cardiovascular disease or risk factors compared to controls that included stroke, heart disease, or family history thereof, hypertension, hypercholesterolemia, or current smoking history. Correspondingly, those with peripheral vascular disease were 3.3 times as likely to have CIAP than controls. Statins, cardiovascular disease, and polyneuropathy are inter-related but which comes first remains to be clarified. — **Michael Rubin**

References

1. Shults CW, Schapira AH. *Neurology*. 2001;57:375-376.
2. Gaist D, et al. *Neurology*. 2002;58:1333-1337.
3. Teunissen LL, et al. *J Neurol Neurosurg Psychiatry*. 2002;72:590-595.

Dopamine Agonists for Parkinson's Monotherapy

ABSTRACT & COMMENTARY

Source: Clarke CE, Guttman M. Dopamine agonist monotherapy in Parkinson's disease. *Lancet*. 2002;360: 1767-1769.

THE AVAILABILITY OF NEW DOPAMINE AGONISTS, pergolide (Permax), ropinirole (Requip), and pramipexole (Mirapex) in the United States, and cabergoline in Europe has radically changed the treatment of patients with early Parkinson's disease (PD). Ropinirole and Mirapex, the two nonergot dopamine agonists, were introduced to the US market in late 1997. Most neurologists are familiar with these drugs and use them in their routine practice. In this thoughtful, well-balanced review, Clarke and Guttman review the evidence for using these drugs to treat patients with early PD.

Ropinirole, pramipexole, pergolide, and cabergoline have been studied in early PD patients in large, multicenter, double-blind trials. In the pramipexole trial, 301 patients were randomized to receive pramipexole or levodopa, with adjuvant open-label rescue with levodopa if needed. Fifty-two percent of the pramipexole group developed motor complications after 4 years compared to 74% of the levodopa group, chiefly dyskinesias. However, those patients who received levodopa enjoyed greater improvements in motor performance, with fewer adverse events. In the ropinirole trial, 268 patients were treated over 5 years with either ropinirole or levodopa. Dyskinesias were less common in the ropinirole group, but again at the expense of less-robust motor improvement and increased side effects. Similar trials have been performed with pergolide and cabergoline.

Two imaging studies have examined the possibility that, in addition to their beneficial effects on symptoms, pramipexole and ropinirole may be neuroprotective (ie, they may reduce the rate of loss of dopaminergic neurons in the substantia nigra in affected patients). An imaging study of 82 patients who took part in the larger randomized, controlled trial of pramipexole in early PD used single-photon emission computed tomography and the radiotracer beta-CIT to measure the presynaptic dopamine transporter. The integrity of the dopamine transporter is a marker of the nigrostriatal dopaminergic projection. This study demonstrated a reduction in beta-CIT uptake of 16% in patients treated with pramipexole vs 25.5% in those treated with levodopa. A similar study performed in Europe examined 186 early PD patients enrolled in the ropinirole trial, using the presynaptic tracer 18-fluro-dopa and positron-emission tomography. Examining fluro-dopa uptake in the putamen (again, a measure of the integrity of the nigrostriatal projection), a 13% reduction was seen in the group treated with ropinirole vs a 20% reduction in those patients treated with levodopa. Both studies seemed to support the idea that treatment with a dopamine agonist (vs levodopa) results in slowing of loss of the dopaminergic projection from the substantia nigra to the striatum.

COMMENTARY

These data were widely publicized by the pharmaceutical manufacturers of pramipexole and ropinirole as evidence that early treatment with the new, nonergot dopamine agonists is neuroprotective. However, the possibility exists that drug treatment itself affects the radioligand binding, compromising the ability of these methods to evaluate progression in PD. What evidence is there to support this possibility? Clarke and Guttman examined 30 untreated PD patients using PET and a related radiotracer that measures the dopamine transporter. They then repeated these evaluations 6 weeks after patients began treatment with either pramipexole or levodopa. Presumably 6 weeks is too short a time to see evidence of neuroprotection; nevertheless, they observed a 16% reduction of radiotracer uptake in the levodopa group vs a 7% reduction in the pramipexole group. This suggests that drug treatment affects the results of these neuroprotection studies and casts serious doubt on the imaging studies that are widely touted by the pharmaceutical manufacturers of these drugs.

How are neurologists to make sense of these data in their practice? Who should be treated with a dopamine agonist vs levodopa? There are no firm answers to these questions; however, movement disorder neurologists at Columbia-Presbyterian make every attempt to treat young (younger than 70 years old) PD patients with dopamine agonists first. Levodopa is then added, if and when it is needed. Patients with dementia, hallucinations, or orthostasis tolerate dopamine agonists poorly. The agonists are also extremely expensive, and it takes time to build up to an effective dose. These considerations should be weighed in the decision to treat with agonist or levodopa, an important question that remains unanswered. — STEVEN FRUCHT

Alzheimer's Vaccination Re-Examined

ABSTRACTS & COMMENTARY

Sources: Hock C, et al. *Nature Medicine*. 2002;8(11): 1270-1275; McLaurin J, et al. *Nature Medicine*. 2002; 8(11):1263-1269; Pfeifer M, et al. *Science*. 2002;298:1379.

When trials of Elan's AN1792 vaccine for Alzheimer's disease (AD) were halted this past year owing to the development of an inflammatory encephalitis in 15 study participants, the future of this novel therapeutic approach came into doubt. Although no further injections of AN1792 are being performed on patients, follow-up studies of surviving subjects are in progress, as well as animal studies designed to further characterize the effects of amyloid immunization. The results of 3 recent investigations suggest that immunotherapy still has the potential to become a treatment for AD but that the road to its successful development is likely to be a long one.

Hock and colleagues in Zurich, Switzerland, reported limited results from the Elan beta-amyloid (A-beta) vaccination trial in humans, including examinations of sera from 24 of the participants. They documented the presence of antibodies in sera obtained an average of 55 days after the second injection of AN1792. These antibodies were found to react against diffuse and neuritic amyloid plaques as well as vascular amyloid. The antibodies appeared specific for A-beta and did not cross-react with amyloid precursor protein (APP) or soluble amyloid monomers and oligomers. Approximately 20% of those tested had high antibody titers (greater than 1:10000) after only 2 injections. They conclude that vaccinating humans with A-beta can produce antibodies with a high degree of selectivity for the type of amyloid found in neuritic plaques.

McLaurin and colleagues sought to further define the effects of immunization by identifying the range of peptides within A-beta to which antibodies most avidly bind. In studies using a transgenic mouse model of AD, they used multiple independent methods to demonstrate that high-affinity binding involves the 4-10 peptide region of A-beta. Moreover, antibodies targeting this region were shown to inhibit amyloid fibrillogenesis and amyloid cytotoxicity in mouse brains without eliciting an inflammatory response of the type seen in the human immunization trials. This suggests that vaccines engineered to react with smaller regions of the A-beta molecule might exert therapeutic benefits without the inflammatory side effects associated with AN1792.

Pfeifer and colleagues encountered a problem using amyloid immunotherapy in transgenic mice that had not been previously reported.. They passively immunized 21-month-old APP23 mice (a transgenic line that develops human amyloid AD-like neuropathology) by weekly intraperitoneal injections of a monoclonal antibody against a 4-amino-acid portion of the human A-beta. After 5 months there was a 23% reduction in neocortical amyloid load, with the majority of the clearance affecting the 42-peptide form of A-beta in diffuse plaques. Amyloid deposits in blood vessels in the form of congophilic angiopathy (CAA) were not significantly reduced by vaccination, yet more than twice the number of hemorrhages occurred in immunized animals than placebo-treated controls. The severity of hemorrhage in immunized animals was also increased in comparison to controls. The distribution of hemorrhages suggests that passive immunization increases the risk of cerebral hemorrhage by weakening the walls of amyloid-laden blood vessels associated with CAA, a common condition in the brains of AD patients.

COMMENTARY

These studies highlight several interesting issues relating to amyloid immunotherapy for AD. The Hock et al study establishes that high titers of antibodies against A-beta can be produced by humans after active immunization with the 42-peptide form of A-beta. The McLaurin et al study suggests that immunization targeting a smaller component of the A-beta molecule may reduce inflammatory side effects. A striking difference, however, between the antibodies produced in humans and those found in mice is that the human antibodies did not react against soluble forms of A-beta. Soluble oligomeric forms of A-beta are thought to be important to the pathogenesis of AD, and the lack of reactivity of the human antibody against soluble A-beta could compromise the therapeutic effect of this approach. More work needs to be carried out to address this issue.

The occurrence of cerebral hemorrhage in older animals passively immunized against A-beta is another potentially serious blow to the immunization approach. CAA is virtually ubiquitous in the brains of AD patients, and potential therapies that target A-beta in plaques are likely to have some effect on amyloid in blood vessels. It is unclear whether the occurrence of cerebral hemorrhage is related to the use of passive, rather than active, immunization or a consequence of treating older animals with a significant vascular amyloid burden. Future approaches may need to incorporate strategies that minimize effects on vascular amyloid or stabilize blood ves-

sel walls after amyloid inclusions have been removed. Clearly, there is a considerable amount of additional research that needs to be carried out before the immunization approach can be safely retried in humans. Nevertheless, the problems identified to date do not appear to be insurmountable, and the basic approach is still quite viable. — NORMAN R. RELKIN

Warfarin vs Aspirin in AF: A Meta-Analysis

ABSTRACT & COMMENTARY

Source: van Walraven C, et al. Oral anticoagulation vs aspirin in nonvalvular atrial fibrillation: An individual patient meta-analysis. *JAMA*. 2002;288:2441-2448.

PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION (AF) have an increased risk of stroke and other vascular events. Treatment with warfarin decreases the risk of stroke by more than 50%. Aspirin (ASA) also decreases stroke risk but to a lesser extent.[1] Several clinical trials have randomized patients with AF to an oral anticoagulant or a regimen containing ASA. Three of these studies determined that warfarin was significantly more effective than ASA at reducing thromboembolic events.[2,3,4] Nevertheless, considerable concern exists among clinicians regarding the risk-benefit ratio of long-term anticoagulation compared to antiplatelet treatment.

In order to compare the risk of vascular events and bleeding complications in patients with AF, van Walraven and associates analyzed data from 6 randomized clinical trials.[2-7] More than 4000 AF patients were assigned randomly to receive oral anticoagulants, in ASA alone or in combination with low-dose oral anticoagulants. Six possible outcomes were studied: ischemic or hemorrhagic stroke, myocardial infarction, systemic embolism, cardiovascular death, major intracranial or systemic bleeding, and death from any cause.

Compared with ASA, oral anticoagulants significantly decreased the rate of all stroke and cardiovascular events (*see Table*). The decrease in the rate of all stroke was due to a large decrease in ischemic stroke with only a small absolute increase in hemorrhagic stroke.

The use of oral anticoagulants significantly increased the rate of major bleeding, and 15% of all major bleeding episodes were fatal. Hemorrhagic stroke accounted for one-quarter of all major bleeding but one-half of fatal bleeding events. Overall mortality, however, did not differ between the oral anticoagulant and ASA patient groups.

The relative benefit of warfarin vs ASA in ischemic stroke prevention was greater for patients younger than 75 years. The absolute risk reduction in ischemic stroke with warfarin was greater in patients at the highest risk of stroke, namely those with a history of previous stroke or transient ischemic attack. Such patients had an absolute risk reduction of 6% per year while patients without previous cerebrovascular events had an absolute risk reduction of 1.2% per year. The increased risk of major bleeding for patients taking warfarin was consistent in all patient subgroups.

COMMENTARY

The meta-analysis of van Walraven et al supports the use of warfarin as first-line preventive therapy for patients with nonvalvular AF. For patients at higher risk of ischemic strokes, the absolute risk reduction in ischemic stroke with warfarin outweighed the associated bleeding risk. Therefore, clinicians must determine baseline risk in order to identify AF patients most likely to benefit from oral anticoagulants.

The present results differ from those of a previous meta-analysis,[8] which found no strong evidence to support the clinical practice of long-term anticoagulation in patients with nonrheumatic AF. The previous study[8] excluded 2 studies[3,7] that showed significant benefits of oral anticoagulants over ASA for strokes and cardiovascular events.

The meta-analysis of van Walraven has clarified the trade-off between the potential harm and benefit of warfarin prophylaxis in AF patients. In high-risk patients, the benefits of warfarin exceed the therapy-associated bleeding events. — JOHN J. CARONNA

Table.
Comparison of Warfarin and ASA

Outcome	Events Warfarin	Events ASA	Hazard Ratio	*P* Value
Stroke				
All	2.4	4.5	0.55	< .001
Ischemic	2.0	4.3	0.48	< .001
Hemorrhagic	0.5	0.3	1.84	NS
Cardiovascular Events				
All	5.5	7.8	0.71	< .001
Major Bleeding	2.2	1.3	1.71	.02
Lethal Bleeding	0.4	0.2	2.15	NS
Death	4.9	5.2	0.93	NS

References

1. Hart RG, et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: A meta-analysis. *Ann Intern Med*. 1999;131:492-501.
2. Petersen P, et al. The Copenhagen AFASAK Study. *Lancet*. 1989;1:175-179.
3. European Atrial Fibrillation Trial (EAFT) Study Group. *Lancet*. 1993:342:1255-1262.
4. Stroke Prevention in Atrial Fibrillation Study. *Circulation*. 1991;84:527-539.
5. Hellemons BS, et al. *BMJ*. 1999;319:958-964.
6. Gullov AL, et al. *Arch Intern Med*. 1998;158: 1513-1521.
7. The SPAF III Writing Committee for the Stroke Prevention in AF Investigators. *JAMA*. 1998;279: 1273-1277.
8. Taylor FC, Cohen H, Ebrahim S. Systematic review of long term anticoagulation or antiplatelet treatment in patients with non-rheumatic atrial fibrillation. *BMJ*. 2001;332:321-326.

While clearly effective, aripiprazole's side effect profile is what differentiates it from the typicals and atypicals. In the pivotal data set there was no difference from placebo with respect to prolactin levels, extra-pyramidal symptoms, weight gain, or QTc prolongation. Mild headache, insomnia, agitation, and nervousness were the only significant side effects vs placebo. Only 2 cases of NMS were reported in the entire premarketing worldwide database comprising about 6000 patients. The efficacy and safety data are provided by the package insert.

There are 2.2 million Americans with schizophrenia. It is estimated that 33% switch or discontinue antipsychotic medication and most cite side effects issues as the reason. Given the problem of EPS side effects from the older, typical antipsychotics and with the growing concern for diabetes, weight gain, and QTc prolongation caused by the newer atypicals, aripiprazole is a welcome addition to the neuropsychopharmocologist armamentarium. We also look for additional postmarketing studies to assess aripiprazole's efficacy in bipolar, Alzheimer's disease, and even migraine.

Late Breakers

FDA New Drug Approval Watch

Aripiprazole (Abilify), a new drug for schizophrenia, received FDA approval November 15, 2002. Aripiprazole is a joint product of both Bristol-Myers Squibb and Otsuka Pharmaceutical Co. Aripiprazole is the first of a new generation of atypical antipsychotics with a complex mechanism of action that involves partial agonism at dopamine D2, and serotonin 5-HT1A and antagonism at serotonin 5-HT2A receptors. In animal models of dopamine hypoactivity, aripiprazole has the properties of a functional agonist and in models of dopamine hyperactivity, it functions as an antagonist. Therefore, it has been referred to as a "dopamine-serotonin system stabilizer"—more of a dopamine "dimming switch" as opposed to an "on-off switch" that we have seen with the current typicals and atypicals. It was approved as an oral, once-daily drug and will be marketed in the 15-mg and 30-mg dosages. The pivotal data included 4 short term (4- and 6-week) placebo-controlled trials of acutely relapsed inpatients with DSMIV criteria for schizophrenia. In all the studies, aripiprazole was superior to placebo and equal to comparators (risperidone or haldol) on the Positive and Negative Syndrome Scale (PANSS). In a longer-term 52 week, 1294-subject study, aripiprazole 30 mg was found superior to haldol 10 mg in responders demonstrating a 30% improvement in PANSS.

More Progress on New Sleep Drug

In a previous *Neurology Alert* we reported on a development of a new sleep drug now named indiplon, which is currently under investigation, and we continue to follow its clinical progress. On November 14, 2002, Neurocrine Biosciences Inc. announced positive results from its first phase III clinical trial with indiplon-IR achieving primary and secondary end points of sleep initiation. Indiplon-IR is an immediate-release formulation of a nonbenzodiazepine GABA-A agonist. In the current randomized, double-blind, placebo-controlled, parallel group trial, both doses of indiplon-IR (10 mg and 20 mg) proved effective on primary end points of latency to persistant sleep (LPS) as measured by polysomnography. Mean improvements over placebo were 36% and 50% for both dosages, respectively ($P < 0.0001$). Safety profile was undifferentiated from placebo. The full data set are expected to be presented at the yet undisclosed scientific meeting of spring 2003. A new drug application for FDA submission is likely by the end of 2003 for both the immediate-release and modified formulations.

December CDC Highlights

The Center for Disease Control and Prevention reports that the death rate from brain injuries in the United States has fallen 11% from 1998. Over the past decade, the death rate stemming from brain injury lowered from 21.9 deaths per 100,000 people to 19.4 per 100,000. The CDC attributes this positive trend to stricter seat belt laws. — JEFFREY REICH

CME Questions

1. **Which statement is true?**
   a. Statins are contraindicated in patients with peripheral neuropathy.
   b. Statins are associated with a 42-fold increased risk of myopathy.
   c. Mortality from statin-associated fatal rhabdomyolysis is 1.5 per million prescriptions.
   d. It remains to be determined whether statins or cardiovascular disease are the more proximate cause of peripheral neuropathy.
   e. None of the above

2. **Antibodies produced by humans inoculated with the AN1792 "Alzheimer vaccine:"**
   a. react with soluble amyloid.
   b. react with amyloid precursor protein (APP).
   c. react with beta amyloid in diffuse plaques.
   d. react with all forms of amyloid.

3. **Compared to ASA, warfarin therapy in AF did not significantly reduce the rate of which one of the following?**
   a. All strokes
   b. Ischemic strokes
   c. Hemorrhagic strokes
   d. Cardiovascular events

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PHARMACOLOGY WATCH

FDA Approves Claritin For OTC Use For Seasonal Rhinitis

After years of legal wrangling, the FDA has approved loratadine (Claritin, Schering-Plough) as an over-the-counter (OTC) product for the treatment of seasonal rhinitis. Loratadine is considered a nonsedating antihistamine, and its OTC approval was linked with the FDA's work with the National Transportation Safety Board to improve public awareness about the concerns of drowsiness while driving associated with older antihistamines. The OTC switch also comes within months of loss of patent protection for loratadine and the entry into the market of generic equivalents. The OTC switch applies to all 5 formulations of Claritin, and at least 1 generic house plans to market "Reditabs." Meanwhile, Schering-Plough continues to aggressively market desloratadine, the active metabolite of loratadine under the trade name Clarinex, in an attempt to protect its $3 billion Claritin market.

Simpler Atrial Fibrillation Management

Management of atrial fibrillation (AF) may be simpler in the future based on the results of 2 studies published in the December 5, 2002, *N Engl J Med*. The larger of the 2 studies (AFFIRM) enrolled more than 4000 patients in the United States and Canada with AF and at least 1 other risk factor for stroke such as hypertension, coronary artery disease, diabetes, congestive heart failure, or age older than 65. Patients were randomized to a rhythm control strategy with cardioversion followed by amiodarone, sotalol, propafenone, or older antiarrhythmics such as procainamide or quinidine; or a rate control strategy with digoxin, beta-blockers, and/or calcium channel antagonists. All patients in both groups were anticoagulated with warfarin. The primary end point was overall mortality. The 5-year death rate was 23.8% in the rhythm control group and 21.3% in the rate control group (P = 0.08). Rhythm control was associated with more hospitalizations and more adverse drug effects. In the second study from The Netherlands, 522 patients with persistent AF after electrical cardioversion were randomized to treatment aimed at rate control or rhythm control. Both groups received oral anticoagulation, and the composite end point was death from cardiovascular causes as well as bleeding, implantation of a pacemaker, or severe adverse effects of drugs. After a mean duration of nearly 2.5 years, the primary end point occurred in 44 patients in the rate control group (17.2%) and 60 patients in the rhythm control group (22.6%) (P = 0.11). Although both studies showed trends toward adverse outcomes with rhythm control, neither study reached statistical significance. The authors of both studies suggest that a rate control strategy for the treatment of AF is at least as good as the rhythm control strategy. In an accompanying editorial, Michael D. Cain, MD, states that "on the basis of these data, rate control can now be considered a primary approach to the treatment of atrial fibrillation." He also suggests that nonpharmacologic treatments for AF will still be pursued with the goal toward maintaining

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sinus rhythm (*N Engl J Med*. 2002;347:1825-1833; 1834-1840; 1883-1884).

Oral Anticoagulation Vs Aspirin in AF

In a related study, oral anticoagulation was found to be superior to aspirin in preventing stroke in patients with atrial fibrillation (AF) or paroxysmal AF. The study was a pooled analysis of 6 trials of more than 4000 patients who were randomized to receive therapeutic doses of oral anticoagulant or aspirin with or without low-dose oral anticoagulants. Patients receiving oral anticoagulation were significantly less likely to experience stroke (2.4 vs 4.5 events per 100 patient years; hazard ratio [HR], 0.55), ischemic stroke (HR, 0.48), or cardiovascular events (HR, 0.71) but were more likely to experience major bleeding (2.2 vs 1.3 events per 100 patient years; HR, 1.71). Anticoagulant therapy also showed benefit on all-cause mortality but only after 3 years of therapy. Interestingly, more benefit was seen for anticoagulation vs aspirin in patients younger than 75 compared to those 75 years or older. A lesser benefit was also seen for women compared to men. The authors suggest that oral anticoagulation is more effective than aspirin in decreasing the risk of stroke and other cardiovascular events in patients with nonvalvular AF (*JAMA*. 2002;288:2441-2448).

Immunization Does Not Cause Autism

A new study should put an end to concern regarding the MMR (measles, mumps, and rubella) vaccine and its possible link to autism. Researchers in Denmark looked at the records of all children born between January 1991 and December 1998, representing a cohort of almost 540,000 children. Of those, 82% (440,655) received the MMR vaccine. In the cohort, 316 children were diagnosed with autism and 422 were diagnosed with other artistic spectrum disorders. After adjustment for potential confounders, the relative risk for artistic disorder in the vaccinated children compared to the unvaccinated was 0.92 (95% CI, 0.68 to 1.24). The relative risk for other artistic spectrum disorders was 0.83 (95% CI, 0.65 to 1.24). The authors also looked for a possible association between age at the time of vaccination, the time since vaccination or the date of vaccination, and development of artistic disorder and found no relationship. They also found no temporal clustering of cases of autism at any time after immunization (*N Engl J Med*. 2002;347:1477-1482).

Statins May Lower CRP Levels

C-reactive protein (CRP), an inflammatory marker, has shown to be a strong predictor of cardiovascular events, perhaps even more predictive then LDL cholesterol levels (*N Engl J Med*. 2002; 347:1557-1565). Most physicians have looked at these studies with interest but have been unsure what to do with an elevated CRP level in an individual patient. Perhaps even more importantly, it is unclear whether lowering CRP affects cardiovascular outcomes. Until an answer is found to this important question, an increasing body of evidence is suggesting that statins may lower CRP levels.

Simvastatin Reduced CRP Plasma Levels

A recent study reviewed the use of simvastatin in 130 patients with mixed hyperlipidemia and 195 patients with hypertriglyceridemia in a placebo-controlled, double-blind trial. After 6 weeks of treatment with simvastatin 20, 40, and 80 mg, significant reductions in CRP plasma levels were noted vs placebo ($P < 0.05$) (*Am J Cardiol*. 2002;90:942-946). CRP lowering by statins appears to be a class effect with multiple reports of benefit with various statins in the last 2 years.

FDA Actions

Roche's pegelated interferon alfa-2a (Pegasys) has been approved for use in combination with a ribavirin for the treatment of hepatitis C. The drug was approved in October 2002, but Roche has been eagerly awaiting the approval for combination treatment in order to compete with Schering-Plough's Peg-Intron/ribavirin combination for the same indication.

Eli Lilly has received approval to market atomoxetine (Strattera) for the treatment of attention deficit hyperactivity disorder (ADHD). Unlike other drugs for this indication, atomoxetine is not a stimulant and is not listed as a controlled substance. Rather, the drug is a selective norepinephrine reuptake inhibitor, which seems to play a role in regulating attention, impulsivity, and activity levels. Strattera is approved for treatment of ADHD in children, adolescents, and adults.

Eli Lilly has also received approval to market teriparatide injection (Forteo) for the treatment of osteoporosis in postmenopausal women who are at high risk for fracture. Teriparatide is a portion of human parathyroid hormone, which stimulates new bone formation in the spine and hip. The drug is given by daily injection in the thigh or abdomen. ■