

## A Year in Neurology

a report by

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The growing attention on the burden of neurological disorders continued in 2008, with the European Brain Council launching the first multidisciplinary forum on major brain disease, with a special focus on Parkinson's disease (PD). There is increasing recognition that greater resources and co-ordinated research strategies are required to tackle the major neurological disorders. In the interim, data presented at international professional society meetings continue to add to the growing knowledge of disease pathology across several disciplines.

### Multiple Sclerosis

In multiple sclerosis (MS), 2008 has been a big year in terms of disease-modifying therapies. Results from key clinical trials presented at the 60th annual meeting of the American Academy of Neurology (AAN) revealed that high-dose interferon beta-1b (Betaferon®/Betaseron®, Bayer Schering Pharma) had little advantage in efficacy over its low-dose counterpart, and no clear superior efficacy could be discerned between interferon beta-1b or glatiramer acetate (Copaxone®, Teva Pharmaceuticals). Nor have any greater clinical benefits been found by doubling the standard dose of glatiramer acetate. Significantly, very strong evidence has been presented in support of early treatment with interferons and glatiramer acetate immediately following the initial MS attack. This strategy has been proposed as potentially delaying progression to clinically definite MS.

Also presented at the AAN meeting were updates on new and current therapeutics. The anti-CD52 monoclonal antibody alemtuzumab (Campath®, Genzyme/Bayer Schering Pharma) has been under investigation for the treatment of relapsing–remitting MS (RRMS). At three years, alemtuzumab was associated with significant reductions in relapse rate (73%) and risk for sustained accumulation of disability (71%) compared with the interferon beta-1a comparator; clinical trials continue that will help to define the role of alemtuzumab in RRMS. Positive results have also been reported for daclizumab (Zenapax®, Biogen Idec) and rituximab (Rituxan®/Mabthera®, Genentech/Biogen Idec/Roche). Natalizumab (Tysabri®, Biogen Idec/Élan), approved for monotherapy in MS patients who were unresponsive to or intolerant of alternate MS therapies, has been associated with an increased risk for progressive multifocal leukoencephalopathy (PML). With more than 40,000 natalizumab-experienced patients and no cases of PML, there was hope that the previous cases were due to interaction with concomitant therapies, controllable by natalizumab monotherapy. Sadly, two cases of PML have emerged this year in patients receiving natalizumab monotherapy for approximately 14 and 17 months. While the current indication for natalizumab remains unchanged, physicians are urged to be extra vigilant about any adverse effects observed.

As all currently approved MS medications are available only as injectable formulations, there has been much interest oral agents and positive results from clinical trials have been reported this year for the following: vitamin D<sub>3</sub>, rolipram, ibudilast (MN-166, Avigen), laquinimod (Teva Pharmaceutical Industries and Active Biotech), cladribine (Leustatin®, Merck Serono), fingolimod (FTY720, NovartisPharma), and BG-12 (dimethyl fumarate, Biogen Idec).

### Alzheimer's Disease

Researchers who evaluated the consumption of fish and the appearance of lesions in the brain scans of 3,660 people 65 years of age and over have found that a diet of broiled or baked tuna and other fish high in omega-3 fatty acids three times or more each week can reduce the appearance of the lesions that can cause dementia and stroke by nearly 26% compared with those who did not. This benefit was not seen with a regular diet of fried fish.

Definite diagnosis of Alzheimer's disease (AD) is only possible *post mortem*, and the current methods of diagnosis via brain scans, blood tests, and interviews hold an accuracy of about 85%. However, researchers have shown that computers can be programmed to distinguish the scans of patients with AD from those of healthy individuals and patients with other forms of dementia with an accuracy as high as 96%—an attractive option in terms of cost- and time-efficiency.

Regarding risk factors, a maternal history of AD has been found to confer a predisposition to impaired glucose metabolism in regions of the brain that are associated with the disease. The likelihood of developing AD differs between the sexes, with one in six women and one in 10 men at risk, but studies have recently reported that there are critical sex-based risk factors in the progression from mild cognitive impairment to dementia: depression in women and stroke in men. Observational studies and primary prevention trials suggest that antihypertensive treatment can reduce the risk for AD.

Various trial results presented at the Alzheimer's Association International Conference on Alzheimer's Disease (ICAD) 2008 present new potential future therapies. Levels of an intravenously administered experimental monoclonal antibody LY2062430 that targets amyloid- $\beta$  (A $\beta$ ) were found to be increased in the cerebrospinal fluid (CSF) of patients with AD, leading scientists in this phase IIb study to believe that this is due to a dissolution of brain plaques by the antibody. Researchers have also proposed a role for the antihistamine dimebon in sustaining clinical benefit in mild to moderate AD; dimebon is believed to work by preserving mitochondrial function, which may have a neuroprotective effect. The six-

month open-label extension trial following the positive results from a one-year placebo-controlled trial showed that patients who continued on the drug over the extension period maintained preserved memory, ability to perform activities of daily living (ADL), and cognitive and behavioral functions close to baseline. New trial data presented at the American Neurological Association (ANA) 133rd Annual Meeting suggest that once-daily dosing of extended-release memantine (Namenda®, Forest Pharmaceuticals) may be safe and effective in treating moderate to severe AD; when used in combination with a cholinesterase inhibitor, extended-release memantine confers significant benefits on cognition, behavior, and verbal fluency. However, results from a phase III study presented at ICAD have confirmed that the gamma-secretase inhibitor tarenfluril (Flurizan™, Myriad Genetics) has no effect in early AD, with no improvement in cognition or ADL.

Research had previously shown that atypical antipsychotic drugs can increase the risk of stroke, particularly in patients with dementia. Despite a lack of clear evidence, the UK's Committee on Safety of Medicines issued a recommendation in 2004 that patients with dementia should not use these drugs. It is now known via a review of the General Practice Research Database containing clinical information of over six million patients in the UK that patients with dementia are twice as likely to have a stroke while taking any antipsychotic.

### Chronic Pain

Results from a new study presented at the American Academy of Pain Medicine 24th Annual Meeting suggest that people suffering from chronic neuropathic pain are twice as likely to smoke cigarettes than people with chronic nociceptive pain. Clinical studies had previously shown that nicotine could produce a modest analgesic effect, and although there is an association between nicotine and neuropathic pain, no direct causative effect is apparent. However, the adverse risks of smoking still outweigh any potential benefit as a perceived treatment for neuropathic pain. The study investigators concluded that further evaluation of the physiological relationship between smoking and development of chronic neuropathic pain is necessary.

There is new evidence that suggests an association between rewiring of the brain and pain. Anatomical magnetic resonance imaging (MRI) and diffusion tensor MRI scans of the brains of patients suffering from complex region pain syndrome (CRPS) have found the first biological underpinning for the chronic pain condition. In addition to an apparent reorganization of white matter, the brains of CRPS patients displayed an atrophy of gray matter similar to previous observations in other chronic pain patients. In another study, functional MRI brain scans of people with chronic low-back pain and pain-free volunteers were monitored while they performed a visual task. While an equilibrium of activation and deactivation was maintained in the cortex of the volunteers, this resting state was not observed in the chronic pain group, where regions of the brain maintained a constant firing of neurons. These results suggest that suffering from chronic pain could trigger the onset of other pain-related symptoms.

### Migraine and Headaches

New research from an observational study presented at the 50th Annual Meeting of the American Headache Society (AHS) states that vitamin D

deficiency is common in patients with chronic migraine. Vitamin D deficiency is known to be a cardiovascular risk factor, supporting the link between migraines and cardiovascular disease. Recent evidence from Italy also suggests that migraine sufferers may be more prone to venous thrombosis or thromboembolism, although the study also found that, contrary to another current theory, these people were not more likely to have any hardening or narrowing of the arteries.

A survey of 24,000 people in the US on their use of medications for treating headaches has linked the overuse of narcotics and barbiturates to an increased likelihood of developing chronic migraines. These results, presented at the AAN, imply that physicians and patients should limit the use of these drugs in order to prevent migraines becoming more frequent and painful. Alternatively, the investigational sumatriptan/naproxen sodium combination (Trexima™, GlaxoSmithKline) has shown high and consistent efficacy in relieving symptoms if taken within one hour of the start of a migraine. Phase III trials of telcagepant (MK-0974, Merck) have shown that the investigational calcitonin gene-related peptide (CGRP)-receptor antagonist has comparable efficacy to the highest recommended dose of zolmitriptan (Zomig®, AstraZeneca), with fewer adverse effects. Investigators say that if approved, telcagepant could provide an important alternative to patients who are non-responsive to or intolerant of triptans.

There is good news for women who suffer from migraines: a new study has found a 30% lower risk for breast cancer for women with a history of migraines compared with women who did not have such a history. In particular, a history of migraines appeared to reduce the estrogen-receptor- and/or progesterone-receptor-positive breast cancers—the most common subtypes. Researchers propose that this association between migraines and breast cancer is related to fluctuations in the levels of circulating hormones, as some known migraine triggers are associated with hormones and migraines occur more frequently in women than in men.

### Sleep Disorders

Improvements in neuroimaging techniques have revealed that the brains of patients with untreated obstructive sleep apnea (OSA) undergo extensive changes in white matter. Not only has OSA been associated with cognitive and mood changes including sleepiness, fatigue, and memory difficulties, but OSA also significantly increases the risk for cardiovascular disease, hypertension, stroke, clinical depression, obesity, car crashes, and sudden death during sleep.

The association of OSA with increased mortality, particularly in stroke victims with OSA, is of interest because OSA is a wholly treatable condition; the treatment of OSA could then confer protective effects, especially against cardiovascular death. The continuous positive airway pressure (CPAP) device is currently used as treatment for OSA, and has been found to be beneficial in patients with both AD and OSA by increasing the total sleep time. These results presented at SLEEP 2008: the 22nd Annual Meeting of the Associated Professional Sleep Societies described an improvement in apnea, as well as cognition. An alternative option in treating OSA may lie in pharmacotherapy. Preliminary data on BGC20-0166—an oral combination of two serotonin-modulated drugs—has shown that treatment with the drug can reduce the apnea–hypopnea index (AHI) by a mean of 40% within 28 days. ■