Trends-in-Medicine

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Quick Pulse

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NEUROLOGY UPDATE

The American Academy of Neurology (AAN) winter meeting is an educational review, not a forum for new trial results. There were no posters and no industry exhibits at this year's meeting January 13-15, 2006, in Las Vegas. However, it was a good opportunity to talk with clinical neurologists, particularly non-academic practitioners, about a variety of issues. Twenty-five neurologists were interviewed.

Alzheimer's Disease

Several interesting points were made about treatment of Alzheimer's Disease, including:

- Integra LifeSciences' COGNIShunt, a surgically implanted shunt used to regulate the flow of cerebrospinal fluid from the brain. COGNIShunt has been implanted under a humanitarian device exemption (HDE), and several doctors at the meeting complained that it is being over-used. A speaker commented, "Patients are demanding COGNIShunt, but it should be used very rarely."
- New Medicare coding that went into effect January 1, 2006, was announced.
  - Memory loss of unknown cause is now 780.93 and can be reimbursed for mild cognitive impairment (MCI).
  - A neurological cognitive status exam is changed from 96115 to 96116, but it has to be a battery of tests, not just the MMSE, with time and interpretation documented.
  - Senile dementia (290.0) falls under mental health and is reimbursed at ~60% of a medical code, but Alzheimer's Disease is a medical code (331.0) and is reimbursed at 100% of the Medicare rate.
- The funding climate for Alzheimer's was described as "dismal," and the chance of an NIH grant approval dropped from 25% in 2004, to <15% in 2005, and <5% in 2006.
- Elan's original vaccine to treat Alzheimer's Disease (AN-1792) is dead, a speaker declared, but he said that doesn't mean another, different vaccine won't be developed, perhaps an autologous vaccine. Two passive immunization programs bear watching:
  - Wyeth/Elan have a program ongoing with AAB-001.
  - Lilly is reportedly starting a program.
- Long-term use of Pfizer's Aricept (donepezil) may not be justified by the data, but neurologists are reluctant to stop it, and families and caregivers often want the drug continued. An Alzheimer's expert said, "There can be individuals who respond more than a year or more than two years, and how to determine response is very difficult. I use the rate of decline on a cognition test as a

guide. If it is less than expected or the family thinks the patient is doing better with the drug, then I continue it… I offer families a choice. If we stop the drug, and the patient worsens, then we restart it – a temporary drug holiday. About 25% of patients continue to do well after the drug is stopped, but families are reluctant to stop because it means giving up, that there is no hope."

- Early treatment may be important. A speaker suggested that by the time Aricept or antibody therapies are used, it may be too late, "By the time we initiate them, the patient has been diagnosed, which is after clinical symptoms appear. But, in my opinion, it is too late when clinical symptoms appear. The brain has already been damaged. Sixty percent of neurons are gone by the time we make the diagnosis, so no therapy may improve a patient if the brain is so damaged. We think plaques and tangles occur many years before they produce symptoms, so for truly beneficial treatments we have to intervene earlier. About 20% of 65-year-olds have plaques, but they don't reach the prevalence (required for diagnosis) until age 75. There may be a period of a decade where the brain pathology is there before dementia occurs. So, we need biomarkers. We cannot wait for symptoms."

Botulinum toxins

Few of these neurologists currently use Allergan's Botox (botulinum toxin A), but those who do were asked about what Ipsen and its to-be-determined U.S. partner will have to do to convince them to switch to Reloxin (botulinum toxin A, formerly called Dysport) when it gains FDA approval. One doctor said a price discount of even $1 would be sufficient to cause him to switch to Reloxin, "I wouldn't switch existing patients, but a dollar is a dollar, so new patients would get Reloxin. And sometimes after a patient is getting Botox for a while, the patient develops resistance, so that is another reason to change." A South Carolina doctor said, "It is not a matter of price but of getting insurance to cover Botox. To switch, I'd need to see benefits over Botox. If it is apples to apples, and there is no difference in efficacy or side effects, then Reloxin would have to be priced 25% less to get me to switch."

Other doctors were less price sensitive. One said no price advantage would make him switch, "Allergan has done a great job of ensuring the purity of their product. I wouldn't change for any price. My confidence and experience with Allergan's Botox is outstanding." Another explained, "Price is not my issue; it is reimbursement. The biggest hurdle with Botox is insurance approval, even for legitimate causes, like hemifacial spasm. The turnaround time for insurance approval is tremendous. I'm more concerned about getting the product in a pre-filled syringe and having better storage than price."

Epilepsy

During a talk on epilepsy, Cyberonics VNS got only the briefest mention on a slide as a treatment for intractable epilepsy. The speaker reviewed some of the newer, FDA-approved drugs for epilepsy, including:

- **Elan's Zonegran (zonisamide),** which is associated with oligohydrosis, kidney stones, weight loss, and behavior changes.
- **GlaxoSmithKline's Lamictal (lamotrigine),** which is associated with drug interactions, headache, and rash that can cause patients to call their doctor.
- **Johnson & Johnson's Topamax (topiramate),** which is associated with weight loss, cognitive problems, kidney stones, and open angle glaucoma.
- **Novartis's Trileptal (oxcarbazepine),** which is associated with neurological side effects, drug interactions, and rash and requires sodium monitoring.
- **Pfizer:**
  - **Neurontin (gabapentin),** which is associated with weight gain and neurological side effects.
  - **Lyrica (pregabalin),** which is associated with mild neurological side effects, but no drug interactions. A speaker said, "The weight gain is more than with gabapentin (Pfizer's Neurontin). Many patients put on 10-15 pounds…You need to warn patients about this, so they don't call you. It is probably an appetite effect…I don't know enough to prescribe this over gabapentin…Pregabalin will have modest efficacy in patients with intractable epilepsy, but it is Tier 3, and a lot of places don't have it on the formulary. It is easy to use and okay for pain."
- **UCB Pharma's Keppra (levetiracetam),** which is associated with drowsiness and behavior changes.

Fibromyalgia

A significant number of the neurologists interviewed at the AAN winter meeting were skeptical about fibromyalgia in general. A California doctor said, "How can you say it is fibromyalgia since there is no test to prove it?" A Colorado neurologist said, "It is really a depressive disorder." A Maryland doctor said, "I send these patients to a rheumatologist." A Tennessee doctor said, "I don't treat fibromyalgia patients if I can help it. There is a lot of misdiagnosis. We thoroughly evaluate patients for neurological conditions, and if there is no evidence of a neurological condition, I am prepared to refer the patient back to the primary care physician." A Texas doctor added, "Fibromyalgia is a complex problem or a misdiagnosis."

Furthermore, sources knew little about either of the two leading drugs currently in development to treat fibromyalgia:

- **Jazz Pharmaceuticals' Xyrem (sodium oxybate, GHB),** which is FDA-approved to treat cataplexy associated with narcolepsy.
- **Cypress Biosciences/Forest Laboratories' milnacipran,** the first in a new class of agents, norepinephrine serotonin

reuptake inhibitors (NSRIs), which preferentially inhibit the reuptake of norepinephrine over serotonin. Milnacipran is approved outside the U.S. in 32 countries for non-pain indications. A pivotal Phase III trial in fibromyalgia failed to meet its primary endpoint, but the companies remain committed to the drug and plan to initiate a third randomized, double-blind, placebo-controlled pivotal Phase III study in 1Q06. The results of this trial are expected in mid-2007. In addition, changes (including an increase in the size from 800 patients to 1,200 patients) were made to another ongoing Phase III trial.

However, neurologists insisted that the key determinant of the efficacy of a fibromyalgia treatment is the effect on functional status is much more important than improvement in pain. A New York neurologist said, "I prefer functional status as an endpoint. Pain reduction is not necessarily enough." A Texas doctor said, "I'm not interested in using Xyrem…but I don't like to tell patients there is nothing to do." A Maryland doctor said, "Functional status and pain are both important." An Arizona doctor said, "Pain and functional status are inter-related, but functional status is important." A speaker added, "There are sufficient data that fibromyalgia is a real, functional disorder. Pain reduction is not enough, but the fibromyalgia inventory questionnaire would be a fine end-point. That is accepted as a standard global measure, not just pain. The FDA may accept pain for the treatment of pain in patients with fibromyalgia, but not for a broader label of fibro-myalgia…Pain may be easier to assess, but disability with fibromyalgia is not just pain, so for a fibromyalgia claim, you need to show functional improvement."

Migraine headache

With few exceptions, these neurologists are very skeptical about patent foramen ovale (PFO) closure resolving migraine headaches. Even doctors who are sending migraine patients for PFO closure are dubious about the link between PFO closure and migraines. "That's ridiculous," a doctor com-mented. A Washington DC neurologist said, "I'm involved in the PFO closure trial in stroke, but I haven't referred any patients for the migraine trial. I'm waiting to see how the data in both trials come out." Another doctor said, "I don't check for PFO." A California doctor said, "I don't ever do a trans-esophageal echo on migraine patients." A Texas doctor added, "I don't check for PFO, but I am interested in the relationship between mitral valve prolapse and migraine and syncopy."

Yet, six sources said they have or will refer patients for trials of PFO closure for migraine. A headache expert said, "I will refer patients. There is no doubt PFO is more common in migraineurs, but it is unclear what the consequences are in terms of migraine or the risk of stroke. There is no evidence on either, so I would like to see a trial with PFO closure randomized in a three-arm trial against sham and against standard of care. The MIST-II trial (of NMT Medical's StarClose) may show a decreased frequency of migraines, but not a difference vs. standard of care…Venlafaxine (Wyeth's Effexor) works in migraine, and duloxetine (Lilly's Cymbalta) is interesting." A New England doctor said, "I will refer patients to the trial, but I am skeptical of the efficacy." A Midwest doctor said, "I'll send patients with intractable pain to the PFO trial, but I'm skeptical about the efficacy." A Texas doctor said, "I've already referred patients for the trial, but I'm waiting for the data to determine if this works." Another doctor said, "I would refer patients if there were a site near me, but I am skeptical about PFO closure for migraine."

Multiple sclerosis

Two-thirds of these neurologists said they would prescribe Biogen Idec/Elan's Tysabri (natalizumab) if it came back on the market. Except for one doctor who plans to use Tysabri for most multiple sclerosis (MS) patients, sources estimated that an average of 13% of their patients would be on Tysabri within a year. Patient demand is expected to be high, and with careful and complete disclosure, the PML risk is manageable, doctors insisted. Among their comments were:

- *Texas #1:* "About 20% of my patients would be on Tysabri in a year. I had two patients on it when it was on the market, and one of those wants it back."
- *California:* "I will use it for a low percentage of patients. But I won't switch patients to Tysabri who are doing well on something else. I'd try standard of care first...You can prescribe anything if you disclose the side effects – look at chemotherapy."
- *Maryland:* "I would prescribe Tysabri, but I would wait until I could review the data and see the new label."
- *Texas #2:* "I'll probably use it, depending on the data. I have people doing poorly, and they are willing to try anything."
- *Illinois:* "About 20%-25% of my patients may be on Tysabri in a year. I let patients choose among the ABC drugs – Biogen Idec's Avonex, Schering AG's Betaseron, and Teva Pharmaceuticals' Copaxone – and Ares Serono's Rebif, and I would use Tysabri, especially in the beginning, in younger patients with extensive disease. I'd use it for all patients if I could, but I need to discuss it with patients and consider the cost. And I would use it off-label with careful documentation."
- *Ohio:* "I'll prescribe Tysabri for six months of the year, and give the patients an interferon for the other six months, but off-label use may not be paid for by insurance. And I'd use Tysabri before Zenapax (Roche, daclizumab, a monoclonal antibody approved to prevent kidney transplant rejection)."
- *Massachusetts (MS speaker):* "I expect fewer than 10% of my MS patients would be on Tysabri in a year. We will have to explain the risks and benefits. I have two patients who got it, and they both can't wait to go back on

it. But our Tysabri plan is up in the air. We would MRI every six months, but what do you do after Tysabri? And with Tysabri, you don't know the risk of PML. With years of use, the incidence may increase, and you can't monitor for PML. Patient selection will depend on price, relapsing-remitting disease, and insurance coverage. Zenapax may be as effective as Tysabri without the PML risk. We have 30 patients on Zenapax. As an MS center, we have other alternatives to Tysabri, such as Zenapax and Cytoxan (cyclophosphamide), so we may use less of it than private practitioners…The question is how to use Tysabri, and in which patients. There is no evidence the combination is worse than Tysabri alone in inducing PML. The cases were too few. Personally, I think if you give Tysabri long enough, you will see cases of PML...I think in some patients with breakthrough disease, you may want to use Tysabri for a certain period of time – maybe 6-8 months. But everyone will be afraid to use it long term."

- *New Hampshire:* "If patients are willing to accept the risk, I will use Tysabri, but I won't recommend it. There is no legal risk to prescribing it if there is full disclosure …My concern is…I don't think the PML is coincidental."
- *Texas #3, the exception:* "I would use Tysabri for almost everyone. Not that many MS patients ask for a specific drug, but I would put the pros and cons before my patients. Tysabri will be useful in short spurts like steroids or plasma exchange."

Some of the doctors who said they would not prescribe Tysabri if it became available again indicated they would refer patients elsewhere if they demanded Tysabri, but a few would not even do that. Among their comments were:

- *Minnesota:* "Patients won't ask for it. I had three patients waiting for it the first time it got approved, and I ordered it for two of them. If I had a non-responder, I would refer that patient to the Mayo Clinic. Biogen and Elan need to prove there are no cases of PML with limited use."
- *Texas:* "I wouldn't use it, and I wouldn't refer patients elsewhere to get it. I only do to my patients what I would do to my family, and I wouldn't give my family Tysabri."
- *Tennessee:* "I probably wouldn't use it. I will refer patients who insist to a tertiary site – if it seems appropriate at all – and I would do that before using Novantrone (Ares Serono, mitoxantrone)."
- *South Carolina:* "I'll take a wait-and-see approach. Most of my patients are concerned with safety. And I wouldn't use Tysabri off-label for legal reasons."
- *Washington, DC:* "I'd use zero the first year. I'd be very cautious. I didn't use it when it was on the market."

Genzyme/Schering AG's Campath (alemtuzumab), which is FDA-approved to treat B-cell chronic lymphocytic leukemia (B-CLL) also got a plug by an MS expert. She insisted it is not dead, despite the FDA putting Campath MS trials on hold and warning against the off-label use of Campath in MS after three patients developed severe idiopathic thrombocytopenic purpura (ITP), and one of these died. She said, "You have to accept a higher level of side effects and complications if you want more efficacy."

Parkinson's Disease (PD)

A speaker discussed Teva/Eisai's Agilect (rasagiline), a potent, irreversible MAO-b inhibitor that got an FDA approvable letter in 2004 but has not yet been approved. Agilect was described as possibly a good monotherapy for early Parkinson's Disease. A speaker said, "This is not a home run, but it is a single or maybe a double, and it will be a nice addition to our armamentarium…The PRESTO trial suggested that rasagiline may have some neuroprotective effect, but that has not really been established yet, and I don't think it will be an indication when the drug is approved."

Pseudobulbar syndrome

Sources estimated that an average of 4% of their patients have pseudobulbar syndrome, and this was mostly in MS patients, but it also occurs, rarely, in amyotrophic lateral sclerosis (ALS) patients. A New England neurologist said, "From 15%-20% of my MS patients have pseudobulbar syndrome. It can happen in ALS, but I have three ALS patients now, and none of them have pseudobulbar syndrome." Another doctor said, "MS patients don't get it, and it is rare in ALS." A Texas doctor said, "I only have one patient with pseudobulbar syndrome. It is really very rare." An expert on movement disorders said, "Pseudobulbar syndrome is relatively common in progressive supranuclear palsy (PSP) and other parkinsonian syndromes, ALS, MS, and patients with multiple strokes." Another speaker said, "It is more common than previously thought in the elderly, but ALS patients have more bulbar than pseudobulbar syndrome."

Most neurologists see little need for Avanir's Neurodex (dextromethorphan hydrobromide plus quinidine sulfate) to treat pseudobulbar affect. Very few sources were aware of it, and there was no excitement about it. A Midwest doctor said, "I have pretty good luck with Lexapro (Forest Laboratories, escitalopram) and Effexor, so there isn't a great need in my practice." A South Carolina doctor said, "I have MS and stroke patients with pseudobulbar syndrome, but the MS patients are too sick for Neurodex, and the pseudobulbar syndrome in the stroke patients is too transitory." A Texas doctor said, "An SNRI or a tricyclic antidepressant gives a good response in ALS patients."

However, most said they are open to learning more about it. A New Hampshire neurologist said, "I'd consider Neurodex as a second-line drug after amitriptyline." A speaker said, "I would use it if there is evidence it works. Those patients and

their families are suffering. Pseudobulbar syndrome is an unmet medical need."

Doctors also were dubious that a 12-week trial would be sufficient to convince them of the efficacy of the drug – even if it is sufficient for FDA approval. A New York doctor said, "These patients have been tried on many things already. What makes the company think they can turn this condition off in 12 weeks?" Another neurologist said, "Twelve weeks is not long enough. When you are treating a non-life-threatening condition, you need longer data." An expert said, "Twelve weeks is pretty short, but if you do an enriched trial with manifestations very, very prominent, then it would be all right. But with occasional manifestations, 12 weeks is not long enough. The company probably will be asked by the FDA for exploratory studies in a subset of patients, but potentially it could get a broad label."

One of the side effects of Neurodex is cough suppression, which could be an issue in ALS patients, but sources did not believe this would or should prevent Neurodex from getting a broad pseudobulbar syndrome label. A doctor said, "The issue on labeling is moot." Another neurologist said, "Cough suppression is not an issue. If you make ALS patients feel better, it doesn't matter if you shorten their life." A speaker said, "It would be a problem with ALS patients. Most ALS patients develop cough impairment, and impairing that even more would not be a good idea. In other pseudobulbar patients, it would not be an issue or a minimal issue. I don't think the FDA would give a broad label. You would need to know how much cough suppression there is. The concern would be indiscriminate use in ALS. A broad label would potentially concern me unless a study in ALS proved it didn't increase rates of pneumonia or hospital admissions for IV antibiotics." A movement expert said, "In patients with trouble swallowing, it could be a problem, but many times patients have suppressed cough reflex anyway. This is unlikely to be a severe problem for patients. Most ALS patients with pseudobulbar syndrome have trouble swallowing, so you would want to use it with caution in those patients."

Sources were unsure about off-label use of Neurodex in chronic cough, saying that is not an area they usually treat. They also want to see more data before making that decision.

Stroke

An expert made these points about stroke:

- Aspirin works, and studies show there is only a small additional benefit to Sanofi's Plavix (clopidogrel) – and Plavix costs a great deal more. There is little or no benefit to Coumadin (warfarin) in stroke prevention.
- PFO closure for stroke was described as of dubious benefit. The speaker said, "There are no controlled trials of the efficacy. Comparing small trials, you can get any answer you want, depending on how you choose your historical controls...The FDA criteria for PFO closure make no sense at all; you are not supposed to do it unless the patient is on warfarin or had a recurrence, even though warfarin has been shown to have no benefit over aspirin."
- Endoscopic/stereotactic evacuation of intracerebral hemorrhage appears effective, with Level I evidence of efficacy in one study and Level II evidence in another study, but a speaker said, "My neurosurgical colleagues have no interest in hearing about the positive study. There may be some role for this in some very carefully selected patients, but that remains to be determined."

Review of Stroke Therapies

Therapy	Finding	Level of evidence
Treatment of acute ischemic stroke		
tPA	No efficacy	Level I
Streptokinase	Harmful	Level I
Intra-arterial recombinant prourokinase	Effective (not available in U.S.)	Level I
Heparin, LMWH, and heparinoids	No efficacy	Level I
Aspirin within 48 hours	Effective	Level I
Mechanical embolectomy	No efficacy	Level IV
Anti-hypertensive therapy	Effective	Level I
Statins and vitamins or lowering of homocysteine	No efficacy	Level I
Prevention of acute ischemic stroke		
Aspirin for secondary prevention	Effective	Level I
Warfarin	No difference from aspirin	Level I
Warfarin in "aspirin failures"	No difference	Level II
Oral anticoagulation (e.g., Plavix)	Conflicting results	Level I
Angioplasty/stent vs. medical therapy	No difference	Level IV
PFO closure	No controlled trials	N/A
Antiphospholipid antibodies	No efficacy	Level I
Carotid endarterectomy (CEA)	Effective	Level I
CEA vs. medical treatment: men with stenosis >59%, age <75, and life expectancy ≥5 years	Surgery superior	Level I
Choice of optimal antiplatelet treatment	Conflicting	Level I
Treatment of acute intracerebral hemorrhage (ICH)		
Novo Nordisk's NovoSeven (rFactor VIIa) – FDA approved for hemophilia; stroke use is off-label.	Effective	Level II
Surgery	No efficacy	Level I
Endoscopic/stereotactic evacuation	Effective	Level I or II
Prevention of ICH		
Anti-hypertensive therapy	Effective	Level I

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