Connecticut Parkinson's Working Group Newsletter June 2004

==========

Support for this newsletter comes from **Pfizer Corporation** and the donors to **CPWG**.
Editor: Stan Wertheimer stan.Wertheimer at gmail.com
Interview Editor: Jeff Lincoln jeffrey.Lincoln at yale.edu
Distribution: Pam Lincoln, Pat Gerace

==========

CPWG Annual Summer Picnic

The date is Saturday 10 July 2004, it starts at 11 a.m. and ends when we all leave or the Ks kick us out. Bring your own 'main course' and also a salad, snack or dessert to share, and a lawn chair. (Danielle and Skip have some but not enough.)

CPWG or the Ks will provide two grills, paper plates, cups, napkins, plastic utensils, condiments, soda, juice (in general the non-alcoholic beverages) and ice. There is a small above ground pool, and room for a bocce/croquet court.

This is an event for the whole family, so bring as many members of your family as want to come – grandchildren are especially welcomed.

Directions: Cheshire is at the intersection of routes 10 (N-S) and 68 (E-W). When you arrive at the intersection, proceed north on route 10 for a short distance (less than 100 feet) to Spring Street; turn left. Proceed on Spring Street for slightly more than 1/2 mile to Warren Street; turn right. The next street on your right is Kristen Court; the Ks are at the end. Another option: You can also travel a bit further north from Cheshire on route 10 (500 feet) to the continuation of route 68 (west), also called the Waterbury Road, onto which you turn left. Proceed to Warren Street and make another left. Kristen Court is a left from Warren Street.

If there are questions contact Jackie, Skip/Danielle, or Terry Deshefy-Longhi who is helping with the picnic.

{The next two articles attest to the therapeutic benefits of the Placebo Effect in PD. Are these reports telling us "it is all in our minds?" We already know that it is surely, if not all – significantly, in our brains. Stan}

Placebo effect strong in Parkinson's treatment by Susan Aldridge, Ph.D.

Patients who believed they had received a brain cell transplant for PD report improved quality of life. Previous research has suggested that transplantation of DA-producing neurons can be an effective treatment for PD. Now researchers at the University of Denver have come up with a rather surprising result. Patients participating in 'sham' surgery – where no neurons were actually transplanted – reported an improved quality of life 12 months later.

The improvement was noted in those who believed they had received the neurons. The trial was double-blinded so no one knew who'd had the transplant and who had not. One woman even reported a resumption of full physical activity, having been inactive for many years before surgery. The power of the placebo effect has been seen before in PD – but never to this extent. Clearly the mind-body connection is very strong in this condition and it's to be hoped that ways can be found to exploit this to benefit the patient.

Source: Archives of General Psychiatry April 2004

Placebo alters individual neuronal activity in Parkinson's disease **May 17, 2004**

NEW YORK (Reuters Health) - Administration of a sham treatment after several injections of the anti-PD medication apomorphine decreases electrical activity in individual neurons in patients with PD, a study in Italy suggests.

Previous research had shown that placebo could induce release of DA in the striatum, Dr. Fabrizio

Benedetti, at the University of Turin, and associates note in a brief communication in Nature Neuroscience, published online May 16. Up until now there has been no evidence that neurons are affected individually. The group therefore studied intraneuronal responses in patients who were undergoing electrode implantation into the subthalamic nucleus (STN) for treatment of PD.

Eleven patients had already been given several subcutaneous injections of apomorphine prior to surgery. In the operating room prior to electrode implantation, the patients were given a subcutaneous injection of saline "along with the verbal suggestion of a motor improvement" and the researchers recorded neuronal activity. Six patients exhibited a placebo response, consisting of reduced arm rigidity and a reported feeling of well being; in one patient, the placebo response lasted less than 15 minutes. Among the sustained placebo responders, significant reductions in frequency of neuronal discharge ($p < 0.001$) were recorded after placebo treatment, along with a reduction in bursting activity.

There were no significant changes measured in the neurons of the five patients who exhibited no placebo response or in the patient who had only a short-lived response. In a natural history group of 12 patients not treated with apomorphine or placebo, there were no significant differences in neuronal discharges or bursting activity.

"The tight correlation between reduction of rigidity on the one hand and reduction of STN frequency discharge and bursting activity on the other" suggests that "these STN neuronal changes are likely to be induced by the placebo-activated DA," Dr. Benedetti's group concludes.

Nat Neurosci 2004.

{These next two articles speak to the effect of Permax on the heart, the valves in particular. They are meant for information only; if you have questions about your treatment/medications you should always consult your physician. However, they do seem to post a warning for some of us. Stan}

Parkinson's Drug Linked to Heart Valve Disease

By Jennifer Warner WebMD

*April 28, 2004 -- A drug commonly used to treat the early stages of PD may damage the heart and increase the risk of heart valve disease, according to new research. The study showed that 89% of PD patients treated with the drug Permax had leaky heart valves, called valvular insufficiency, a form of heart valve disease that occurs when the heart valves don't close properly. The condition forces the heart to work harder to meet the body's blood circulation needs and could lead to serious complications, such as heart attack or heart failure. Researchers say cases of heart valve disease **have** previously been reported anecdotally among PD patients treated with Permax.*

Permax is a member of a class of drugs known as DA agonists and stimulates nerves in the brain that would normally be stimulated by DA. People with PD suffer from a shortage of this brain chemical. The results of the study were presented today at the American Academy of Neurology 56th Annual Meeting in San Francisco, Calif.

To determine whether these anecdotal reports represented isolated incidents or a common side effect of Permax that had gone unnoticed, researchers sent letters to 200 people with PD who were known to be taking Permax. Those who wished to continue taking the drug were urged to have a heart ultrasound, called an echocardiogram, to detect any heart valve problems.

Echocardiograms were performed on 46 PD patients, and researchers compared the results to an age-matched healthy comparison group.

The study showed that 89% of the patients treated with Permax had evidence of leaky valves, and patients taking the drug were up to 18 times more likely to have significant leakage in at least one of their heart valves compared with the comparison group. "Our study demonstrates that [Permax] may injure cardiac valves and, since they are available, consideration should be given to switching patients to an alternate DA agonist," says researcher Richard B. Dewey Jr., MD, associate professor of neurology at the University of Texas Southwestern Medical Center in Dallas, in a news release.

Symptoms of heart valve disease include:

- Shortness of breath and/or difficulty breathing
- Weakness or dizziness
- Chest pain or pressure
- Heart palpitations
- Swelling of ankles, feet, or abdomen
- Rapid weight gain

People with PD using Permax or experiencing these symptoms should discuss the issue with their doctor.

SOURCES: American Academy of Neurology 56th Annual Meeting, San Francisco, April 24 - May 1, 2004. News release, American Academy of Neurology. WebMD Medical Reference provided in collaboration with The Cleveland Clinic: "Heart Valve Disease." WebMD Medical Reference from Healthwise: "DA agonists for PD."

Treatment of PD with Pergolide and relation to restrictive valvular heart disease

By Guy Van Camp (lead author) Lancet volume 363 page 1179 10 April 2004

Summary

Background: Restrictive valvular heart disease (scarring or fibrosis of the heart valves) has been reported in patients with PD treated with pergolide (or Permax). However, few data are available on the frequency (in what percent of patients it appears), severity (is the scarring minor or potentially life-threatening), dose dependency, and reversibility of pergolide-induced disease (will the scarring go away if the drug is stopped) nor on the pulmonary pressures of these patients. We aimed to clarify these characteristics in a large group of patients.

Methods: 78 patients with PD treated with pergolide (an ergot derived DA agonist) and 18 never treated with an ergot-derived DA agonist (Mirapex or Requip) were evaluated by echocardiography (a test to visualize the heart valves). A valvular scoring system (a means of evaluating the severity of the scarring was used, ranging from 1 (proven ergot-like restrictive valvular heart disease) to 4 (no disease).

For the mitral valve: (the valve between the right atrium where blood enters the heart and the right ventricle where blood is pumped from the heart into the lungs) tenting areas and tenting distances were measured.

For Systolic pulmonary artery pressures: (the pressure in the artery that carries blood from the right ventricle to the lung) were derived from the tricuspid regurgitant jet

Findings: Restrictive valvular heart disease of any type was present in 26 (33%) patients in the pergolide group and none in controls, the patients on Mirapex or Requip (this is statistically significant). Important, or potentially serious disease or scarring (score 1 or 2) was present in 15(19%) patients in the pergolide group and none in controls (this is significant).

There is a statistically significant correlation between the cumulative doses of pergolide (the daily dose times the number of years the patient was on pergolide) and the scarring or narrowing of the mitral valves.

Mean systolic pulmonary artery pressures were 39.3 mm of mercury (range 25-71) in the high-dose group versus 38.5 mm of mercury (range 20-65) in the low-dose group (this difference is not significant) and 31 mm of mercury (range 25-40) in controls (this is significant versus all patients in the pergolide group). An elevated pulmonary artery pressure, called
pulmonary hypertension makes it harder to get blood from the heart into the lungs.

In six patients, pergolide treatment was stopped because of restrictive valvular heart disease, in two of whom regression of disease was shown.

Interpretation: Restrictive valvular heart disease is NOT a rare finding in patients treated with pergolide. Clinicians should consider changing to a
non-ergot drug if this disease is diagnosed. Comment: This study shows that up to 1/3 of patients who are treated with pergolide may over time (after a few years) develop scarring of one or more heart valves. The symptoms of such scarring may, in the extreme cases, result in heart failure. Patients who are on pergolide should go for an echocardiogram to see if there is any scarring (there may not be) and should have repeat echocardiograms at the discretion of their doctors. The echocardiogram is the way to detect the scarring early. Early scarring probably cannot be detected by listening with a stethoscope to the heart. Lancet 2004; 363: 1179-83
{This article was modified by DR. Abraham Lieberman to make it more readable for lay people}

What Doctors Do Not Know

Stan Wertheimer

We all want a relationship with our physicians, especially our neurologist that is comfortable. This can mean a partnership, or a paternal (maternal) hierarchy, or perhaps a dictatorship. If you want your doctor to tell you what you have to do and you accept unquestioningly, that you may be not doing yourself the most good even if you are the most comfortable. In this situation it is a good bet that you feel that your doctor has all the answers, and sometimes even the questions. However there are bound to be things your MD does not know, either about the methods used to treat you, or your life with PD.

For example, I was recently brought up short in conversations with two excellent and respected neurologists when I mentioned that I could save $500 a year on one of my medications if my prescriptions were written for quadruple the dosage I needed taken 1/4 as often. An example: Suppose you need 1 mg of Requip twice a day. Your MD could prescribe four 0.25mg tablets, one 1.0mg tablet, or one-half a 2.0mg tablet twice a day. The costs are: 4 ($0.49 per 0.25mg) x twice/day = $3.92 per day
1 ($1.38 per 1.00mg) x twice/day = $2.76 per day
1/2 ($1.50 per 2.00mg) x twice/day = $1.50 per day
so your yearly costs are $1431, $1007, and $548. Your potential saving is almost $1000 a year for the worst case, and about $500 for the expected case. By the way, these are Canadian prices.

I got similar results for Parlodel, Permax, Mirapex, and levodopa/carbidopa. The most dramatic one was Permax, where the difference ratio of costs is as much six to one. The reason is that, for some reason, drug companies stop increasing their prices even though they increase the dosage, usually after a certain limit is reached. Mirapex costs about twice as much for 0.5mg as for 0.25mg, which seems logical; it costs exactly the same for 1.0mg and 1.5mg as for 0.5mg however!

This got me thinking about what else my MD might not be aware of, and it didn't take me long to realize that even the most caring physician can sympathize with a patient without necessarily being able to empathize. If one has never experienced a situation, you can only use your brain, not your body, to understand it.

Can you explain to your doctor how it feels to wake up in the morning with a pillow, which is moist with saliva? Or how you find yourself falling when there is nothing apparently

in your way, and even though you know you are falling you don't seem to be able to do anything about it to protect yourself? Or how you cannot coordinate your muscles to carry out a simple task even though you have the strength? Or how you spend several hours awake at night when everyone else is sleeping even though you are dead tired.

PWP are surely not unique in this regard. Can a sighted person really know what it is like to be blind? Can a person who has never experienced the death of a loved one feel how another does who has? The part we may not consider is that the same holds for PD. We shouldn't expect our MDs to have powers that the rest of us do not have. Conversely, the doctor must not think that he or she fully understands how a patient is feeling.

I believe the lesson I took away from this thought excursion (gedanken experiment) is that I must work a little harder in communicating with my doctor, and hope the same holds for the doctor. We may not be able to tell the MD exactly how we feel, but it is important to try, and to have the time to talk about it. It is up to both of us, PWP and MD, to make the effort and the time.

My next cogitation will be on what the PWP does not know, and how the MD can best inform him or her. Here we are the ones that must make the larger effort. If we want to benefit the most from our interaction with our MD we must prepare, just as we expect the MD to prepare. Call it doing your homework.

M N I

Jackie Dorwin

As I sit here in the lobby of the Institute for Neurodegenerative Disorders (IND) waiting for my annual brain imaging process to begin, the receptionist answers "Good morning, IND." There is nothing unusual about that. A minute later the telephone rings again but she answers this call with "Good morning, MNI." That greeting raised a few eyebrows, and I wondered if the others waiting here with me knew about MNI? They may have noticed these initials used on the welcome board by the elevators, as part of an email address for some of the staff, in the promotional literature available in this lobby, but are they aware of the impact MNI has on their Parkinson disease (PD)?

MNI translates to 'Molecular NeuroImaging.' For our purposes molecular neuroimaging can be defined as a technique that permits visualization (imaging) of different brain functions. Add 'LLC' to the end of this phrase and you have the name of a growing medical research company with its base here in Connecticut. Both the process and the company are deeply involved in researching neurodegenerative disorders. Studies conducted in the specialty of nuclear medicine have given scientists the means to deliver a specific radiopharmacological biomarker to a chosen part of the brain. This biomarker hooks up with certain specific neuroreceptors and gives us pictures of these chemical messengers. Scientists can use this method to estimate how many of these neuroreceptors are present, and how many are not. This is particularly important to those who have PD, as this can indicate the extent of loss of DA neurons, causing the symptoms.

Dr. Paul Hoffer led this research at Yale for 1987 – 1992; he chaired the nuclear medicine department. Dr. Hoffer recognized the talents of Dr. John Seibyl who at the time was focusing his studies on psychiatry. Their ensuing relationship has not only been good for nuclear medicine but good for Parkinson disease patients as well. Dr. Seibyl eventually became the head of Yale's NeuroSPECT Lab when Dr. Hoffer retired, ironically due in part to his own diagnosis of PD.

In 1992 Dr. Ken Marek was opening the Yale Movement Disorder Center where he and his staff studied PD, Huntington's disease, and dystonia. The two scientists successfully collaborated on several projects; in 2001 Drs. Seibyl and Marek formed the two entities now known as IND and MNI. IND is a not-for-profit research institute, responsible for the clinical research, while MNI develops new brain targets and applies them to speed the development of medications for PD and related disorders.

To be able to provide optimal services to the medical community, Dr. Seibyl and his staff

determined that the imaging process would be more efficient if they synthesized the necessary biomarkers right here in New Haven. To this end they have built a state of the art radiochemistry laboratory on site, and in 2003 over 1000 research studies were performed. The staff is also developing protocols and biomarkers for other neurological and psychiatric disorders such as Alzheimer's, dystonia, depression, and Huntington's disease.

Although headquartered in New Haven, the impact of MNI is global. Scientific collaborators in Europe and Japan are using the techniques developed in New Haven. An important product of the research is the scientific knowledge that is disseminated in publications and discussed in scientific symposia around the world. Similarly, scientists regularly come to New Haven to visit MNI's facility.

Creativity is a word not usually associated with printouts, radiotracer targets, or imaging, but at MNI it fits. In PD research they are developing new tools. Their excitement is infectious. We hope the road to a cure is shorter because MNI is traveling with us.

FDA Approves New Parkinson's Drug

4/21/2004 *Associated Press/AP Online*

WASHINGTON The FDA has approved a new drug to treat PD patients who develop periods of immobility. The problem, called hypomobility or "freezing," affects about 10 percent of people with PD. The drug, apomorphine, to be sold under the name Apokyn, was given priority as an orphan drug. It is the first drug to treat these episodes, which affect about 112,000 people.

The FDA said that within 3 to 5 years of treatment with standard PD drugs, about 10 percent of patients develop these episodes, when they are unable to rise from a chair, to speak or to walk. The episodes can occur toward the end of a dosing interval with standard medications or at unpredictable times. Apokyn, which is injected, can cause severe nausea and must be taken with an anti-nausea drug. Certain anti-nausea drugs, such as ondansetron, must be avoided because the combination can lead to very low blood pressure and loss of consciousness. Apokyn is manufactured for Bertek Pharmaceuticals of Research Triangle Park, N.C., by Draxis Pharma Inc. of Canada.

Putting A Patch On Parkinson's Disease

Mary Ellen Egan, 04.23.04

NEW YORK - Mornings were the worst part of the day for Michelle Lane. In June 2000, the 41-year-old mother of three was diagnosed with PD, a progressive disease that attacks the central nervous system. As the disease progressed, Lane lost the ability to button her shirts or brush her daughter's hair. More troubling were the mornings Lane would awaken frozen and have to wait up to an hour before her medication kicked in so she could get out of bed.

A new drug, rotigotine, has changed the way Lane approaches her day. It works by acting like DA, a neurotransmitter lacking in PD patients. This type of drug is called a DA agonist. The three most prescribed versions on the market are **Eli Lilly**'s Permax, **Pfizer**'s Mirapex (from its Pharmacia acquisition) and **GlaxoSmithKline**'s Requip. But rotigotine has a distinct advantage: It's the first DA agonist to be delivered via a patch, thereby allowing patients to have a consistent dose of the drug in their systems at all times.

Over 1 million Americans suffer from PD; they spend over $2 billion on medications each year, including $400 - $500 million for DA agonists. Patients are diagnosed by four primary symptoms: tremor, rigidity, postural imbalance and the slowing or freezing of voluntary movement.

For over 30 years, levodopa, the chemical precursor of DA, has been the primary medication for PD patients. Long-term use can result in dyskinesia (jerky, involuntary movements) and levodopa can lose its beneficial effects over time. Since DA agonists have fewer side effects, they are currently the first line of defense against PD.

Two years after Lane was diagnosed, her doctor put her on Mirapex. Lane says she stayed on the drug for just three months because it made her "extremely sleepy." At that time, her doctor, Jayaraman Rao, director of the PD and Movement Disorder Clinic at Louisiana State University Health Sciences Center, told Lane about a clinical trial for a new PD drug. In May 2002, Lane enrolled in the rotigotine trial.

The drug was developed by Aderis Pharmaceuticals, a privately held biotech based in Hopkinton,

Mass., and Schwarz Pharma, the North American affiliate of Germany-based Schwarz Pharma AG. The two companies joined forces in August 1998 to finish the work on the agonist molecule that had begun in the late 1980s. Their goal was to have rotigotine delivered via a patch, since one of the biggest problems plaguing PD patients is keeping the right amount of medication in their systems throughout the day. Too much medication can cause dyskinesia, and too little can result in paralysis.

"Some patients set the alarm clock for 3:00 A.M., and then take a pill so they can get out of bed in the morning. With the patch, patients can now sleep through the night," says Aderis Chief Executive Peter Savas.

Rotigotine comes in four patch sizes and dosages. Lane, whose clinical trial ended in November 2002, opted to stay on the medication and now wears two patches a day. "Mornings are now the best part of my day. I can wake up, clean the house, and get my kids off to school on my own again," she says.

Schwarz is currently compiling the data from three separate rotigotine trials--two on early stage patients and one on late-stage patients--and the company expects to file for U.S. Food and Drug Administration approval by this fall. If all goes well, the PD patch could be on the market by 2006.

Trial Results on SCHWARZ PHARMA's PD Patch Published by PSG 7 January 2004

The Parkinson Study Group (PSG) reports the results of a major multi-center clinical trial of rotigotine CDS (constant delivery system) in PD in the December 2003 issue of the "Archives of Neurology". Rotigotine CDS delivered by a once-a-day skin patch, compared with matching placebo, improved disease signs and symptoms in patients with early PD.

Rotigotine CDS, a novel D2-DA receptor agonist, which has been developed as a silicone-based transdermal system, or skin patch, was tested in this trial as a single treatment for PD. In 2001 and 2002, research physicians at 36 PSG sites in the USA and Canada evaluated 242 patients with early PD in an 11-week study. Unaware of treatment assignments, investigators measured the severity of patients' PD. The highest two of the four active rotigotine CDS dosages tested --- 13.5 mg per day and 18 mg per day --- were clearly superior compared with placebo. Rotigotine CDS was well tolerated overall, with a side effect profile similar to that of other DA agonists. Skin reactions occurred commonly at the site of the patch applications in patients receiving both active and placebo patches; however, the prevalence was higher in patients receiving rotigotine CDS.

The primary prespecified outcome of the study was the average change from baseline in the sum of motor and activities of daily living sections of the Unified PD Rating Scale (UPDRS). The UPDRS is a standardized measure of patients' abilities to perform basic motor skills, as well as activities of daily living and mental abilities.

Dr. Karen Blindauer, Director of the Movement Disorders Program at the Medical College of Wisconsin, and co-principal investigator and corresponding author of the study states, "This study shows that a DA agonist for the treatment of PD can be successfully delivered by a skin patch. This experimental drug provides clinical benefit, and the transdermal approach may offer a needed alternative for PD patients unable to take oral medications."

SCHWARZ PHARMA's multinational phase III clinical studies with the once-a-day PD patch rotigotine CDS in early PD patients have been successfully completed in the fourth quarter 2003. The first results of the double blind, placebo-controlled studies demonstrate the efficacy and safety of the PD patch. Detailed results will be available in the first quarter of 2004. The approval applications for the U.S.A and Europe are planned for the third quarter of 2004.

The PSG (www.PD-Study-Group.org) is a non-profit, cooperative group of PD experts from medical centers in the United States and Canada who are dedicated to improving treatment for persons affected by PD.

Connecticut Parkinson's Working Group
132 Highwoods Drive
Guilford CT 06437

DISCLAIMER: Articles in this newsletter are for information only. Any questions of treatment should be discussed with your physician.

WRITE! your representatives in congress.

Christopher Dodd
Russell Senate Office Building
Washington, D.C. 20510

Joseph Lieberman
Hart Senate Office Building
Washington, D.C. 20510