Maine PD News

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Maine PD News is a quarterly newsletter about Parkinson's disease in and out of the state, and is intended for PD patients and their caregivers. This is not a site for medical advice. Instead, I hope as editor to bring thought-provoking and helpful information about treatment, resources, specialists, affiliated health care providers, data from new published studies, news items in PD and science at large as it may pertain to PD. There is a great deal out there that is science-based, and there is a great deal that is not. Science is spoken here.

This is a unique time because movement disorders has grown in our state in the last few years and we will very soon have five fellowship trained movement disorders subspecialists: Drs. Poulopoulos and Unia in Bangor, myself in Brunswick, Dr. Kleinman, and soon Dr. Dodwell, in the Portland area. We have also seen a growth in related PD care with exercise classes and programs directed at patients. physical therapy is much more widespread, patients are reporting more involvement in the support groups, and networking is bigger and better in our PD community, in no small part due to all who have come before us. We may be hearing from some of them in future editions of this newsletter as I think their perspective is important. Enough for now; let's get started. Articles may be accessed on the website also and you may print, email, or share an article by clicking the "share" button with each article. Subscribe and receive new articles or posts by email, or get to Maine PD News through Facebook.

-Bill Stamey, M.D.

NEW DRUG: Pimavanserin Approved by the FDA

Pimavanserin, trade name Nuplazid, was approved by the FDA for the treatment of hallucinations and delusions in PD, per press release April 29. Pimavanserin was granted an FDA breakthrough therapy designation, which is a program "designed to expedite the development and review of drugs intended to treat a serious condition and where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint." The drug was also granted a priority review, which provides for an expedited review of drugs that offer a significant improvement in the safety or effectiveness for the treatment, prevention, or diagnosis of a serious condition.

Pimavanserin is an atypical antipsychotic, which is meant to bind to the serotonin receptor 5-HT2A in the brain and thus avoid exacerbation of motor symptoms seen with older typical antipsychotics (1). Older antipsychotics are generally avoided and relatively contraindicated in PD due to blockade of dopamine receptors (the target of multiple drugs meant to improve motor

symptoms). Pimavanserin exploits data that 5-HT2A serotonin receptors are specifically associated with visual hallucinations (2).

Phase II trial participants progressed to an average daily dose of 44.5 mg, and by day 28 revealed no impairment of motor function compared to placebo, nor did the drug cause sedation or hypotension (3). There were significant reductions in both hallucinations and delusions.

Phase III trial data showed an improvement in the quality of sleep and daytime wakefulness during a six-week period with 199 participants. The drug was shown to be superior to placebo in decreasing the frequency and/or severity of hallucinations and delusions without worsening the primary motor symptoms of Parkinson's disease. An open-label extension study presented at the 17th International Congress of Parkinson's Disease and Movement Disorders reportedly showed that pimavanserin is safe and well-tolerated with long-term use.

Per the FDA press release (4), the most common side effects reported by participants taking Nuplazid were swelling, usually of the ankles, legs, and feet, nausea, and confusion. The FDA points out that "as with other atypical antipsychotic drugs, Nuplazid has a Boxed Warning alerting health care professionals about an increased risk of death associated with the use of these drugs to treat older people with dementia-related psychosis. No drug in this class is approved to treat patients with dementia-related psychosis."

-Bill Stamey, M.D.

1. Neurochem Res. 2014 Oct;39(10):2008-17
2. Arch Neurol 2010;67:416–421
3. Neuropsychopharmacology 2010;35:881–892
4. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm498442.htm

What is LSVT?

A commonly chosen option for physical therapy in Parkinson's disease (PD) is Lee Silverman BIG and LOUD, offered at several centers around the state. This program, like much of physical therapy, takes into account that one of the major issues underpinning the problems with PD results from dysfunction of the part of the brain called the basal ganglia. An important role of the basal ganglia is to serve as a sort of quality control center for the brain, checking movement and speech to make sure each is being carried out properly. However, in PD, the basal ganglia often reports that things are fine when they are not. This misinformation is why sometimes patients are unaware of the abnormal movements or speech patterns. Thus, one of the big goals of physical therapy is to make the patient aware of what they are doing wrong. Following this, the person is taught a new way to perform an old activity such as speaking or walking. Repetition is key so that the new way of doing something is reinforced. In doing this, the brain uses synaptic plasticity to form a new pathway. Those new connections lead to new ways of doing things, and essentially bypass the bad circuits.

Lee Silverman Voice Treatment, now known as LSVT LOUD is a speech treatment specifically designed for patients with PD, and is named after Lee Silverman, a PD patient who was treated in the 1980s. Since the 80s, there have been multiple studies showing at least short term benefit with

What is LSVT?, continued…..

LSVT, and patients have found the treatment very helpful for volume of speech, intonation, articulation, and facial expression (1). The basic gestalt is to first help people with PD recognize that the voice is too soft. Following this, one strengthens muscles of speech through a series of progressive exercises in four 60-minute sessions per week for one month. This motor learning stimulates the brain to form new pathways (2). People with PD learn that the louder voice is normal, and eventually will feel normal about the new speech pattern (3). LSVT LOUD has been successfully taught to people in all stages of PD, and is usually most effective in early or middle stages of PD.

In the last few years the same approach has been used to develop improvements in limb movement and gait with a program known as LSVT BIG (4). Training tends to focus on increased amplitude of limb and body movement. Studies have shown improvements in movement, speed, balance, and quality of life. LSVT BIG can be delivered by a physical or occupational therapist certified in this treatment, and is also taught to patients in four 60-minute sessions per week for a month. Usually BIG and LOUD are done on the same day. The exercises are built upon in a repetitive pattern meant to improve the movements used in activities of daily living, again forming new connections in the brain.

Sandi Merrill

Sandi Merrill, a person with PD, notes LSVT BIG and LOUD has been "very beneficial and I have more freedom of movement. It's improving my health." She says when talking with others, "they notice a change." Her husband George notes "several people have commented how much easier it is to have a conversation with her. And, BIG is helping her with everyday things she used to find frustrating, like getting out of a chair in a restaurant."

I had the chance to discuss LSVT with Tina Phillips, PT at Mid Coast Hospital in Brunswick. She tells me that within her group there are four clinicians certified in BIG and two certified in LOUD, all busy treating patients. Tina notes "people seem to really enjoy the program and get a kick out of learning to train their brain." She tells me that LSVT is most effective for people who are very motivated. If they do the exercises they make improvements, get excited, and feel a lot of encouragement. She emphasized to me that carrying on exercise after the class is very important to have a continued benefit. Some patients keep this up very well at home and some do not. Fortunately, this May on Thursdays from 11 a.m. to noon there will be a new graduate LSVT program at the Landing YMCA in Brunswick. The program will incorporate all four Mid Coast BIG instructors, who will go through exercises with graduates from any LSVT program. There will also be new activities including Argentine tango dancing, yoga, and Tai Chi. Tina will be there May 19th. The Landing YMCA is located in the old Naval Air Station, 24 Venture Avenue, Brunswick, ME, 207-844-2801.

-Bill Stamey, M.D.

1. Journal of the International Neuropsychological Society, 2014;20(3):302-12.
2. Seminars in Speech and Language, 2006;27, 283-299.
3. Expert Reviews in Neurotherapeutics, 2011;11(6), 815-830.
4. Phys Ther. 2014;94(7):1014-23.

Awareness Day 2016

Saturday, April 2, we had a great turnout for the PD Awareness Day meeting at the Clarion Hotel in Portland. We were very fortunate to introduce Dr. Sarah Dodwell, who will be joining the Maine Medical Partners Neurology group this fall. She spoke on the psychiatric & cognitive complications of Parkinson's disease and introduced "the friendly elephant in the room." Dr. Bill Stamey discussed alpha-synuclein, the little molecule that goes bad in PD, and trials that target it for diagnosis and treatment (see article in this edition for summary). Dr. Michael Kleinman covered the complex issues of PD medications. All three held a panel with neurosurgeon Dr. Anand Rughani and questions from the crowd were diverse and interesting.

PD PEARLS

–**Take levodopa** one hour before, or two hours after meals containing protein. Levodopa and proteins are absorbed in the first part of your small intestine and if consumed together may compete to get into the bloodstream like passengers trying to get through a turnstile before a train leaves. If you eat a cheeseburger for example, and take levodopa at the same time, you may not absorb your medication. And, the problem does not stop there. Proteins are broken down into amino acids that will compete with levodopa to get through the blood brain barrier, a two-hit problem. If you have to eat something when you take levodopa, have crackers or a piece of fruit.

–**Most patients with PD will have hyposmia** (loss of sense of smell), constipation, and/R.E.M. sleep behavior disorder (RBD) for years before motor symptoms of tremor, stiffness, and slowness develop.

–**A third of all PD patients don't have tremor.** The most important diagnostic sign of PD is actually bradykinesia, or slowness of movement.

–**Work on balance** daily, even if it is not yet a problem. Balance will almost certainly be a problem later on, and the more you do now, the better off you are likely to be.

–**Melanoma** is a little more common among PD patients than the general population and regular skin exams with a doctor should take place, along with heightened concern for any new unusual lesions.

-**Exercise** has been shown again and again to improve motor function, sense of well being, quality of life, and mood in people with Parkinson disease.

Should you adjust your own Parkinson's meds?

The short answer is "No."

The medications used to treat Parkinson's disease are primarily meant to deal with the issue of low dopamine in the brain. This seems like a fairly straightforward proposition and over time many people seem to get the hang of what I am doing when I adjust meds. They note that I may have started them on a very low dose and slowly increased the strength and/or the frequency. Major advances or changes in medication dosing should always be directed by a physician trained in movement disorders. There are some exceptions. Sometimes my colleagues will make adjustments if covering on call. It is possible that an emergency room physician might change the dose. If this happens, please let me or your normal PD doc know as soon as possible. Otherwise, these are the only times in which your medications should be changed. However, some patients take it upon themselves to change dose strength or timing. This is generally not a good idea. Advancing doses on your own can lead to unwanted side effects. In the case of carbidopa/levodopa (Sinemet), lightheadedness, nausea, confusion, worsening constipation, impulsivity, and hallucinations are only some of the potential problems.

There is also a less obvious issue of taking too much too soon early in disease, which can result in several issues, including the early appearance of unwanted involuntary movements such as dyskinesia. Patients who take too much medication early in disease may be causing irreversible damage and advance of disease. This is only one example.

In the case of dopamine agonists such as the drugs pramipexole (Mirapex), ropinirole (Requip), and rotigotine (Neupro patch), excess dosing can result in problems such as confusion, hallucinations, impulse control disorder, foot swelling, excessive daytime sleepiness, and sleep attacks. With each of the drugs used to treat Parkinson's disease excess dosing can be quite serious.

Under dosing is also an issue. Some patients decide they don't like the way they feel taking the medications, or perhaps they are just "not a pill person." They will sometimes decide to take lower doses or with less frequency than prescribed, which can result in the reemergence of symptoms over time. Sometimes this is obvious within a day or two. What many patients do not realize is that there is a longer term effect that may take weeks to show itself. This is a so-called steady-state effect of drugs. Any change in dosing may take up to 28 days to show full effect.

Some patients will abruptly stop drugs. This can actually be dangerous and in some rare cases life-threatening, especially when taking relatively high doses of PD medications. Don't do it.

What if my pharmacist doesn't think I should take it? Always call your PD doc to discuss before changing any medication, even if the pharmacist has raised concerns. Please understand that pharmacists are very well educated and intent upon helping you. Still, they are not physicians. Pharmacists dispense thousands of different medications written by every type of prescriber, and cannot possibly know the intimate details of each drug. They often raise concern about a so-called class effect, related to the family of a medication and not a specific warning related to a specific drug. For example, Azilect (rasagiline) is in the class of monoamine oxidase inhibitors. There are warnings for the class of drug which were specifically removed by the FDA for the drug Azilect after extensive demonstration of safety with this particular drug. Some of the warnings pharmacists have provided patients have wound

up in my office, and appear to be generated by third-party software vendors. These sheets may not be up-to-date and may occasionally be inaccurate. Conversely, most doctors tend to be very familiar with the 50 or so drugs they commonly prescribe. I don't mean to claim we never make mistakes, or that we don't need the very valuable help of pharmacists, just that it is a complex situation. We all need to work together, so don't put aside that prescription, call and let your doc know what's going on.

-Bill Stamey, M.D.

Movement Disorder Neurologists/Neurosurgeons in Maine

Dr. Michael Kleinman graduated from the University of New England College of Osteopathic Medicine, completed an internship at St. Vincent Hospital, and neurology residency at Boston University Medical Center Neurology. He completed movement disorders fellowship at Boston Univeristy. Dr. Kleinman is Co-Director of the Movement Disorder Program at MMP Neurology.

Dr. Markos Poulopoulos completed medical school in Greece and an additional four years of training in medicine in England. He completed his neurology training at the University of Connecticut and fellowship at the Center for Parkinson Disease and Related Disorders at Columbia University in New York City. He is practicing with Eastern Maine Medical Center's Neurology Specialists in Bangor, Maine.

Dr. Anand Rughani was born and raised in Eugene, Oregon. He studied Cognitive Science at McGill University before attending medical school there. After neurosurgery residency he obtained subspecialty fellowship training in functional neurosurgery, with a particular interest in movement disorders surgery and is experience in deep brain stimulation of STN, GPi, VIM as well as thalamotomy, pallidotomy, and gamma knife and focused ultrasound.

Dr. William Stamey is originally from Memphis, Tennessee and completed medical school at East Tennessee State University Quillen College of Medicine, Johnson City, TN where he also completed an internal medicine internship. He spent a year in the neurology program at University of South Florida, Tampa. He completed neurology residency and fellowship in movement disorders at Baylor College of Medicine in Houston, Texas. He is a diplomate of the American Board of Psychiatry and Neurology. Dr. Stamey has been in practice in Maine since 2007. He is a member of Mid Coast Medical Group Neurology.

Dr. Roople Unia is from Halifax, Nova Scotia and attended Dalhousie University where she graduated with a degree in neuroscience. She then completed medical training in Krakow, Poland, neurology residency and vascular neurology fellowship at the University of Rochester, followed by a movement disorders fellowship at New York University's Parkinson and Movement Disorders Center. She has been practicing with Eastern Maine Medical Center's Neurology Specialists in Bangor, Maine since 2015.

What's so bad about alpha-synuclein?

Alpha-synuclein is a tiny protein found in the neurons of your brain. One of its important jobs is to stabilize tiny bags of dopamine so that they may be released at the synapse where one nerve communicates with another. This makes it a very important little protein. The problem is that alpha-synuclein, like any protein, has a three-dimensional shape and must be folded correctly. If it is not, bad things happen. One of the bad things that we have learned in recent years is that "misfolded" alpha-synuclein appears to be able to spread by causing other normal alpha-synuclein to also misfold. I think of it like one bad apple spoiling whole bunch. Once misfolded alpha-synuclein accumulates it cannot be used and cannot be broken down and forms Lewy bodies. Lewy bodies, clumps of proteins in the affected neurons, are the pathologic hallmark of PD.

Diagnosis

The good news is that in recent years studies have shown that alpha-synuclein may be used to diagnose Parkinson's disease. These misfolded proteins have been detected on biopsies of the GI tract and in the salivary glands. It appears that the FDA may soon approve a test to diagnose PD by needle biopsy of the salivary gland. Studies of early and advanced Parkinson's patients have shown positivity in about 75% of patients (1).

Therapy

Alpha-synuclein is also a target for therapy. After multiple animal trials, there have been three human studies involving monoclonal proteins targeting alpha-synuclein. These monoclonal proteins are antibodies which target alpha-synuclein. Antibodies are little Y-shaped proteins that our immune system produces to fight virus, bacteria, and any foreign protein. The idea with this drug was to target alpha-synuclein as a foreign protein. The first trial was with healthy subjects and was able to completely bind all alpha-synuclein found in the blood. The drug was very well tolerated. To learn more about this visit www.clinicaltrials.gov and type in the search bar NCT02095171. An ongoing trial with six PD patients in multiple centers around the country will measure alpha-synuclein and the antibodies in cerebrospinal fluid (NCT02157714). A third study with a different monoclonal protein produced by Biogen is being tested and 40 healthy volunteers in Texas and Indiana. There are also vaccines under trial. It should be noted that animal studies have shown removal of Lewy bodies and resolution of abnormal behaviors in animal models of PD, making vaccine a very attractive possibility (2). AFFiRis has done the only human trial with vaccine in Vienna, Austria. The first phase I study with a vaccine called PD01A was given to 32 early PD patients and, as this was a safety study, was tolerated quite well (3). Patients were entered into long-term follow-up and the data is not back on that yet.

Other Drugs

There was a press release a few months back about the drug Nilotinib reporting marked improvements in a few PD and LBD patients. Nilotinib is already FDA approved for the treatment of chronic myelogenous leukemia, and was shown in a mouse model to reduce the activity of an enzyme called c-Abl (4). c-Abl is activated in PD patients and is associated with overproduction of alpha-synuclein. Animal studies have shown that injection of either alpha-synuclein or c-Abl will increase levels of the other; excess of either can lead to LB formation and cell death. Nilotinib is currently in a phase I clinical trial for the treatment of PD and DLB (NCT02281474) at Georgetown U. The study will measure changes in alpha-synuclein and the protein tau as the primary outcomes, and will include 36 iPD patients.

A phase III study of 86 patients with a form of parkinsonism called MSA at University of Munich is currently recruiting participants (NCT02008721) for the compound EGCG, a polyphenol found in green tea and

widely used in dietary supplements. It has been shown to inhibit the formation of toxic alpha-synuclein (5). There is no data as yet.

What's so bad, continued….

There are other trials targeting alpha-synuclein, which should give patients hope. I think we are standing in the doorway to a new era of treatment. For a copy of the slides to the talk I gave on this visit www.mainepdnews.org

-Bill Stamey, M.D.

1. Movement disorders. 2016:31 (2) 250-56
2. Neuron 2005;46:857-68
3. Park Relat Disord 2012;18(Suppl 1): S11-13)
4. Sci Rep 2014;4:4874
5. Proc Natl Acad Sci USA 2010;107:7710-7715

Parting Thoughts

We have a growing deep brain stimulation community in Maine and that is pretty exciting for several reasons. Until three years ago, DBS was not implanted here (with a couple of notable exceptions by Dr. Florman remotely) and we were sending patients to Boston for implantation. The trip down meant lots of driving back and forth, navigating Boston and the medical centers, etc. I hear parking was a particular challenge. I am so glad to have said goodbye to those issues because I think it makes life easier for patients. DBS has always been of interest to me and was one of the main reasons I trained at Baylor, where I had exposure to a huge population of cases. Here in Maine, I started out small with a few cases and slowly built up until Dr. Ed Drasby retired, (then I built up a lot faster). And, we now have a neurosurgeon trained in DBS (Dr. Rughani) and a team of docs across the state who collaborate on these cases. For the past three years Drs. Rughani, Kleinman, and I have held monthly meetings to discuss potential cases and outcomes. We are joined now by Anne Herrick, NP, Sarah Vreeland, MS, CNRN, and two neuropsychologists, Dr. Thomas Miller and Dr. Heather McClelland on the DBS committee. Next edition I will interview Dr. Rughani and review the DBS program. Dr. Rughani is an interesting and articulate person and I look forward to the conversation.

We will read about psychosis in PD, as Dr. Markos Poulopoulos is contributing that article. I heard Dr. Poulopoulos speak at the PD Awareness Day in Brewer, Maine in April, 2015 and was impressed with the depth of his interest in the history and science of PD.

I plan as well to contribute additional articles in the next issue, covering a range of topics. If there is some particular area you would like to read about, let me know via the website or Facebook.

- Bill Stamey, M.D.