



Parkinson's Disease
UPDATE

A newsletter devoted to the most current medical, social and psychological aspects of Parkinson's Disease

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THE SEARCH FOR BIOMARKERS

Imagine undergoing a lab test to determine if you harbor pathological processes in your brain leading to Parkinson's disease. With this information, your clinician hands you a prescription for a medication that scrambles the degenerative decline, providing a dozen or more years of symptom-free living. Ever so slowly, we inch towards this day.

Biomarkers, according to the Biomarkers Definitions Working Group, are characteristics that may be measured as indicators of normal biological processes, pathogenic processes, or pharmacological responses. Research in this area is a hotbed of promise and all those involved need to accept the ground rules, or definitions, hence the 'Group'. Biomarkers are typically invisible signals or signs that underlie or antedate the clinical manifestations of the disease. Using specific biological, chemical or physical methods, the invisible markers can be made visible, be used to predict onset of PD, to follow its natural course or to measure the effects of a medication. To be a marker of PD the specific indicator must be normal for all diseases other than PD. With the increased sensitivity and specificity harnessed from biomarkers, clinical drug trials will be able to target a more defined population with fewer questions or suspicions about whether participating subjects truly suffered from PD.

For convenience, we can shuffle the vast array of potential biomarkers into three categories; imaging studies, clinical tests and biochemical and genetic

tests. Imaging studies are the most widely investigated and encompass the well-known functional images of PET and SPECT scans, ultrasound, and the lesser known MIBG scintigraphy. Both PET and

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SPECT scans have the potential to follow the decline in neurotransmitter function, examine metabolic activity and monitor cerebral blood flow. New ligands, or chemicals that signal when they attach to certain membrane receptors, may have the potential to provide pathological information, for example the accumulation of proteins such

alpha-synuclein or beta-amyloid, or the microglial response to cell death-they transform into phagocytes, meaning cell eaters.

Compared with the other types of scans, ultrasound has received less investigation. In 2001, Dr. Berg used ultrasound to investigate how the substantia nigra responds to sound frequency, determining the echogenicity of the brain structure. Patients with PD tend to have increases or hyper-echogenicity on both sides of the brain, as do psychiatric patients using neuroleptic drugs with severe motor symptoms. Elderly people without a diagnosis of PD, but with substantia nigra hyper-echogenicity had more frequent and more severe slowing of movements than age-matched control subjects. Yet researchers have identified this trait in approximately 9% of apparently healthy adults, and whether they will develop PD is questionable.

Though interesting, such studies have not yet identified a biological factor that relates solely to those with PD. Neither did work on autonomic dys-

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This newsletter explores the social, psychological, and medical picture of a puzzling disease that affects over 1.5 million Americans. It is our hope that the information contained here will be helpful and enlightening to those with Parkinson's disease, and to their families, as an expanding network of individuals maintain contact to help bring about relief and hopefully a cure.

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function. Many PD patients report autonomic nervous system symptoms such as bladder irritability, sweating or constipation, prior to developing the typical motor signs of PD. In addition, post-mortem exams have found Lewy bodies scattered diffusely within the autonomic system, leading researchers to question its role in PD and search for tools to access it. MIBG is short for metaiodobenzylguanidine. The substance is a neurotransmitter that acts as a tracer when labeled with radioactive iodine, is transported into neurons, and is detected by scintigraphy. Images of 246 PD patients and 45 patient cases with Multiple System Atrophy, suggested the reduced pattern in which the heart takes up dye, correctly identified cases of PD with 94% specificity, from cases of MSA. However, similar responses in the heart are evident in people suffering from dementia with Lewy bodies, and exactly what reduced intake of MIBG by the pulsing muscle means, remains unclear.

Clinical testing in PD relies on the outward manifestation of disease; however idiosyncratic individual cases may be, so in the years prior to symptoms examinations may be problematic. Sensitive testing might be able to detect changes in the earliest of signs, in populations with higher risks of contracting the illness. Patients who ultimately develop PD frequently suffer years earlier, from a wide range of nonspecific symptoms, for example, depression, anxiety, loss of smell, visual changes and musculoskeletal pain, which may be signs heralding impending illness. Studies have discovered evidence of early cognitive decline, before any apparent motor signs develop, that passes undetected by fam-

ily members. Tests can monitor progression of such maladies but depression rating scales and other standard exams lack the specificity needed for the unique disease of PD. Complex neuropsychological tests may pick up some deficits early, though they have been unsuccessful in reliably detecting PD. Medications given to relieve symptoms will affect biomarkers measuring apparent expression of illness, making such findings unreliable. Researchers rely on clinical testing when trying to gauge response to treatment or monitor fluctuations, but test results can also categorize the various types of PD, by recognizing patterns of presentation and progression of illness. Breaking the patient PD population into smaller groups can be helpful in targeting those who will benefit from certain treatments. New research data has suggested specific subgroups of patients respond better than others to novel treatments, for example cell transplantation.

Although the ideal biochemical biomarker would be easily measured and accurately reflect the ongoing degeneration occurring within the basal ganglia, many researchers and clinicians would settle for less. The pursuit for PD biomarkers has focused on blood tests in which investigators have explored the role of oxidative stress using platelets as peripheral biomarkers. PD patients have reduced mitochondria complex I in their substantia nigra, and in the late eighties, some research findings suggested platelets exhibit a similar reduction. Not all investigations arrived at this conclusion, casting doubt on whether platelets could monitor changes in the central nervous system. Other chemicals in the blood were scrutinized, though none were sufficiently robust to be used as a diagnostic biomarker. Researchers explored dopamine metabolism in the peripheral nervous system (as opposed to the central nervous system; brain and spinal cord) identifying sluggish lymphocytes (white blood cells), and several other aberrations in chemical activity.

Exploring the composition of spinal fluid is trickier. Extracting cerebral spinal fluid (CSF) requires a long needle to pass carefully between bony vertebrae, pierce the dural sheath encasing the spinal column while avoiding nerve roots. In 1997 researchers found reduced levels of beta-phenylethylamine in cerebral spinal fluid were negatively related to the Hoehn and Yahr clinical stage of disease; the lower the chemical level the higher the stage of disease score and the more debilitated the patient. In 1999, other scientists discovered significantly elevated levels of the reactive oxygen

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While it is the purpose of this newsletter to report and explain current information on Parkinson's Disease, it is not intended to furnish medical answers to individual problems. This is best done by your own doctor.

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species, malondialdehyde. Laboratories exploring CSF found the biochemical compound orexin, reduced; alpha-synuclein and insulin hovered near normal levels, while homovanillic acid, 5-hydroxy-indoleacetic acid and acetylcholinesterase differed only slightly from the levels of the control population. Though all the findings are chemically provocative, they lack functional application in real-life terms. An investigative group from the Karolinska Institute in Stockholm, Sweden, synthesized the information about CSF biomarkers, reached conclusions, and published their work in 2005.

“Three cerebrospinal fluid biomarkers (the 42 amino acid form of β -amyloid (A β), total tau, and phospho tau) have been evaluated in numerous scientific papers. These CSF markers have high sensitivity to differentiate early and incipient AD from normal aging, depression, alcohol dementia and Parkinson's disease, but lower specificity against other dementias, such as frontotemporal and Lewy body dementia.” A German research group continued exploring the 42 amino acid form of β -amyloid (A β) trying to uncover the meaning of A β peptide patterns in CSF for Alzheimer's disease (AD), dementia with Lewy Bodies (DLB) and Parkinson's Disease dementia (PDD). They found peptide patterns displayed variations specific to each disease, and certain ratios discriminated the three diagnostic groups from each other, except in cases of dementia with Lewy Bodies and Parkinson's disease dementia. However, they noticed a novel peptide present in the CSF of all 88 patients. The pronounced increase of the new peptide in the spinal fluid of those with DLB provided a way to discriminate it from the spinal fluid of patients with PDD. They published their findings in the journal, *Brain* in 2006 concluding that though peptide patterns failed to meet requirements for a sole biomarker, their strength combined with the contribution of other biomarkers is promising in the diagnosis of dementia.

No genetic quirk can be identified and held responsible for the vast majority of people diagnosed with idiopathic PD, though the list of mutations associated with the disease continues to grow. Some specialists argue there may be a genetic susceptibility in families where PD presents in clusters or in identical twins where illness affects a single sibling. Though rare, there are families where PD is an inherited characteristic, while having a family history of PD increases the risk of contracting the disease by two to four times. In cases of apparent

idiopathic PD or sporadic PD, studies have attempted to identify specific genes with PD using familial linkage analysis, direct DNA sequencing and allelic association. No dramatic associations exist yet, but new ideas rise from past explorations. For example, single nucleotide mutations and haplotype maps (gene maps) could be used to explore slight genetic differences in cellular drug receptors and explain differences in how patients respond to drugs, the molecular basis for the variety of clinical presentations, and eventually serve as biomarkers predicting clinical response.

Searching for biomarkers is hot. As researchers identify biological barometers, our understanding of PD increases and influences how clinicians diagnose the disease. Additionally, biomarkers may prove useful in stratifying the forms in which PD finds expression, and evaluating and monitoring drug treatments and disease progression.¹

BEHIND THE WHEEL

Alone in the driver's seat with the wind in your hair, doing seventy miles per hour as the green scenery whips past; your illness hangs by mere shreds of memory, but Parkinson's disease affects physical movement beyond the standard bodily sense. When the sun sinks and you are late for dinner, your crying grandchild is in the back car seat, your stockbroker is on the phone and you are braking repeatedly in five o'clock traffic, PD impacts upon how you respond to challenges. Investigations into the driving ability of people with PD found patients had more simulated driving collisions than did control subjects, with increasing number of accidents linked to more severe levels of impairment as indicated by Hoehn and Yahr scores. Both patient and clinician were likely to over-rate driving ability.

A team of investigators from Melbourne Australia examined the driving behavior of people with PD to uncover any differences between that population and a group of age-matched control subjects. They also measured how performing a distracting task while driving affected the execution of both activities. Rather than conduct the experiment on the city streets of Melbourne, the investigation used a driving simulator equipped with three traffic signals, 16 curves and automatic style transmission. Drivers drove on the left side of the street, as Australian custom dictates. The distracting task consisted of 19 different sounds, approximately one second in length, occur-

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ring somewhat randomly every 80 to 100 meters. Three target sounds had a jungle theme; a lion roar, a monkey screech and a bird-call. When two of the jungle-theme target noises sounded one after another, subjects responded as quickly as possible, by pressing the turn signal downward. Sixteen other noises occurred randomly among target sounds; these included a cash register, chimes, and various electronic racket.

In general, people with PD tended to drive more conservatively than did their able-bodied counterparts. They took longer to decelerate, came closer to traffic signals while frequently overshooting the optimal stopping location, and slowed significantly later when preoccupied with concurrent tasks. On curves, PD subjects traveled more slowly, though they decreased their rate of speed at a similar rate to control subjects. Though the differences were not statistically significant, control subjects drove with greater variability in speed. When performing a second task while driving, both groups limited their variation in speed. As to position in the lane, cars from both groups shifted towards the middle of the road when performing the secondary task. Comparing the ability to respond correctly to target sounds; PD subjects took consistently longer to react and missed more auditory cues than controls.

The authors were surprised to find both subject groups responded similarly when performing a secondary task while driving. Both slowed and shifted towards the middle of the street. The investigators speculated participants with PD sacrificed their performance on the concurrent task to maintain adequate driving ability, while controls did not.

To some, driving represents independence. They would prefer have their teeth torn from their gums then lose their car keys. The Australian study provides evidence people with PD should avoid multitasking when driving. Turn cell phones off, pacify grandchildren and avoid rush hour traffic if possible. Driving requires complete attention from people with PD, who must compensate for deficiencies brought on by illness, specifically slowed reaction time and possible extraneous movements. Think and plan ahead. As illness progresses compensatory strategies need to grow; for example by limiting driving to daylight hours, planning travel routes, and investing in extra wide mirrors.

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When questioning whether one should still be driving, a professional driving evaluation provides an objective assessment of skills and abilities. Giving up one's car keys need not shrink one's living circle when dependable contacts and family members are willing to act as chauffeurs. Emotionally the change may be hard to swallow. It is advisable still, to err on the side of caution, since your car may be regarded a deadly weapon in accidental circumstances.²

POSTPRANDIAL MOTOR BLOCKS: IMMOBILITY AFTER EATING

Do not be intimidated by the word postprandial. Prandial is an adjective coming from the Latin word prandium, describing a meal. Postprandial then, describes something after a meal. Motor blocks, or the inability to move, occur most often after eating, because large amino acids in protein-rich foods compete with levodopa medications for passenger space on cell membrane transporters where they are guided from the blood into the brain. Patients most often find the time between 1pm and 5pm the most difficult to move in, due to lunch. An Italian team of investigators studied a pool of PD patients to determine how efficiently a special diet of low protein products decreases 'off' periods occurring after meals.

The guidelines for management of PD endorsed by the Italian Neurological Society and described in a treatment algorithm by American investigators Olanow, Watts and Koller, recommend the protein redistribution diet for patients with advanced disease. Transferring protein-rich foods to the evening meal, while restricting protein intake during breakfast and lunch, increases movement capacity during daylight hours, and improves the quality of life. The dietary regimen calls for shifting of the recommended daily allowance of protein, not eliminating or reducing it. The diet does not alleviate the competition between proteins and levodopa. The motor set back still occurs, but it happens later in the day, not during periods of peak productivity. Patients may enjoy meat, fish, dairy products, eggs and legumes during dinner, while breakfast and lunch are rich in breads, pastas, vegetables and fruits, which have relatively sparse quantities of protein.

The Italian investigative group went one step farther. To ensure participants in the study had the lowest levels of protein during breakfast and lunch, they

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ate specially formulated products originally intended for people with chronic kidney failure. A low protein diet delays end stage kidney disease. The group wished to evaluate whether strict control of protein intake, not exceeding the recommended daily allowance, improved motor function without causing protein malnutrition in patients with advanced PD. Specifically, people typically consume 8.3% of the daily recommended allowance of protein at breakfast, 51.8% at lunch and 39.8% at dinner. The low protein diet provided 2% of the total allowance for breakfast, 12.6% at lunch and 85.3% at dinner.

Twenty-one participants enrolled in the study, twenty completed it and eighteen had data usable for statistical analysis. After two months on the protein redistribution diet, postprandial 'off' periods were significantly shorter for the low protein group, averaging 49 minutes versus 79 minutes for those on the balanced diet. Postprandial 'on' time was significantly longer on the protein-shifted diet; 250 minutes versus 220 minutes, and total 'on' time was also significantly longer; 852 minutes versus 738 minutes. Investigators asked participants for their clinical impression of the dietary change. Half the subjects, nine people, felt marked to moderate improvement and wished to continue using the low protein foods. Six of these subjects reduced their mid-day dosage of levodopa by an average of 45.8 mg. The other nine subjects reported minimal improvement, with either no change or worsening of conditions. Though their experience was more negative, diary records of these subjects also documented significant reductions in total 'off' time, while on the diet, 198 minutes (3.3 hours) versus 282 minutes (4.7 hours) while on the balanced menu plan.

Most importantly, researchers found no significant changes in blood or biochemical tests, though subjects lost a modest amount of body weight, averaging 1.8% of their total weight. Weight loss greater than five percent raises suspicions of malnutrition. The authors attributed the weight loss to increased mobility and ease of movement when the amount of 'off' time decreased. They failed to plan for this increased energy consumption in dietary plans hence, subjects shed pounds.

All participants in the investigation benefited by having decreased 'off' episodes and increased times of mobility, but only half reported an overall beneficial effect. The authors fail to provide reasons for this. Several possibilities exist. How does it feel to adhere to such a strict dietary protocol for two months? Do subjects yearn for omelets in the morn-

ing? How does the motor block occurring after a dinner of mostly proteins compare to the block after a balanced meal? What do the low protein products provided by Aprotin Heinz-Italia taste like?

The curious must know specialized low protein foods are expensive. A box of Kraft macaroni and cheese has nine grams of protein per serving and costs .97 cents at the supermarket; the imitation variety made by Dietary Specialties has less than a gram of protein per serving and costs \$7.99. Other items are just as costly, for example a 13 ounce box of Loprofin cereal costs \$ 6.50, and four servings of flavored porridge made by Dietary Specialties costs \$9.99. Aside from the benefits of having close to zero protein, the products are highly refined, tend to be high in corn syrup and sugars and offer little fiber. Personal assessments are required here. Some budgets may not allow the specialized products; other people may depend on the fiber in Albran cereal. Explore your possibilities.³

FERTILIZING BRAIN CELLS

Risking bloody assault on the reader by the cruel teeth of scientific jargon, one must attempt to describe promising animal research with the cellular fertilizer, neurturin. The cardinal signs of PD, the tremor between the fingers and thumb, slowness, rigidity and standing instability, result from insufficient dopamine within the substantia nigra pars compacta. Visualizing this area in the brain, the 'black substance' or substantia nigra becomes progressively lighter as dopamine-containing cells, containing melanin (dark pigment) gradually die away. Medications provide symptomatic relief for most PD symptoms, though with time drug-induced side effects such as dyskinesias and motor fluctuations, plague patient function. Deep brain stimulation provides an alternative treatment for some. Our arsenal of options lacks proven ways to protect existing dopamine-rich cells and ways to alter the natural progression of disease.

For this reason, research in cellular trophic factors is important and holds promise. Trophic factors act as shields to cells under toxic onslaught, providing sustenance and support in an otherwise noxious environment. Some researchers describe trophic factors as cellular fertilizers that enhance the growth and well-being of brain cells. Our own cells produce some of these compounds. Glial cells emit glial cell line-derived neurotrophic factor and the analog, neurturin.

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Both of these enhance the function of dopamine-containing cells in animal models with PD.

An investigative group headed by Jeffrey Kordower, of Rush University Medical Center in Chicago published his findings in the December edition of *Annals of Neurology*. Performing preliminary testing with rodents, the group induced an artificial state of PD by treating animals with MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). When motor deficits became apparent, the creatures received treatment with AAV2-NTN. In the subsequent months, the animals regained a great deal of their prior function.

AAV2-NTN is an adeno-associated virus based vector, which provides the genetic code for human neurturin, and is formulated by the company Ceregene. The viral counterpart supposedly produces no diseases or clinical symptoms, and most people have been exposed to it through daily living circumstances. When introduced into the brain the vector enhances secretion of neurturin in other cells. In the reported study, investigators injected MPTP into one side of the brain of twenty male rhesus monkeys and they became parkinsonian on that side of their body. They divided the population into two groups, one to form the control group for comparison sake, and the other to receive the active compound. Four days later both groups of monkeys got injections with either AAV2, or phosphate buffered saline, the placebo. The injection sites were located with the aid of an MRI; the caudate nucleus got two injections, the putamen got three and the substantia nigra got one.

Researchers noted functional improvement in the group that received AAV2, a month after treatment. The changes advanced until the fourth month, where enhanced function plateaued and remained for ten months. Four of five monkeys recovered complete motor ability. None in the control group spontaneously recovered. Technicians anesthetized and sacrificed all the monkeys after ten months. They removed the brains, immersed them in saline, and sectioned them while frozen before staining. In microscopic studies, investigators detected the presence of neurturin in the caudate, putamen and substantia nigra. The distribution was limited mostly to the target regions, around the injection sites and anatomically related areas; though there was evidence that cells transported neurturin to other more

distant brain structures. Researchers found no evidence of any abnormal pathology amidst the stained brain sections of monkeys who received AAV2.

The fifth monkey, who exhibited incomplete motor recovery, had several different findings on microscopic anatomic study. The brain had the least amount of neurturin evident in the nigro-striatal system, suggesting a less accurate injection into the striatum, compared with the other monkeys. Staining displayed the greatest amount of dopamine-containing cell loss, apparent from the density of the substantia nigra, ordinarily darkly pigmented with melanin-rich cells. Brain tissue in the affected half of this individual indicated 30% of the cerebral hemisphere was intact, while the other monkeys functioned with an average of 70% of their cerebral hemisphere intact. Researchers inferred percentages from TH positive cells; tyrosine hydroxylase indicates the presence of cells containing dopamine.

Given the functional benefit neurturin provides, is improved motor performance due to restoration of dopamine neurons or their protection? The authors state they cannot differentiate between the two and perhaps neurturin has a dual function. However, harnessing AAV2 in an effective and practical treatment for those with PD remains a formidable challenge. Past efforts to diffuse similar substances into the brain using implants or hardware elicited inconsistent results and safety concerns. The beauty of gene transfer is that once it is inside the brain it continuously expresses the therapeutic protein. How to get it inside is another question. I wonder how many PD patients would consent to having it injected into their brains.⁴

ZELAPAR

On June 16 2006, the FDA approved a new form of selegiline hydrochloride. In the mouth, the technologically enhanced tablet dissolves in seconds, where it is absorbed through the soft tissue lining. Comparing it to the standard swallowed variety, Eldepryl, the new tablet provides a larger dose of bioavailable drug. Patients use the drug as an adjunct when combinations of levodopa-carbidopa alone become inadequate in controlling motor symptoms of PD. A monoamine oxidase inhibitor, the drug inhibits the breakdown of dopamine in the body, allowing increased quantities

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of neurotransmitter to the brain.

The effectiveness of Zelapar underwent scrutiny in a 12 week, multicenter, double-blind, randomized, placebo-controlled, parallel group study—the cream of scientific investigations. Participants received either 1.25 mg of Zelapar, or a placebo (no active drug, i.e. sugar pill) substitute daily for six weeks, then either 2.5 mg of Zelapar or placebo daily for an additional six weeks. After one week, subjects taking the grapefruit-tasting tablet had significantly reduced periods of “off” time. After 12 weeks, “off” time fell by 2.2 hours daily, while those taking placebo experienced reductions of a mere .6 hour; a statistically significant difference, indicating Zelapar’s ability to enhance the effects of levodopa and carbidopa.

Of the 140 participants, 94 made up the active treatment group and 46 received placebo. Subjects experiencing dyskinesias, or involuntary and uncontrollable movements due to the addition of Zelapar could reduce their dosage of levodopa. Sixteen people or 17% of 94 in the Zelapar group elected to decrease their medications, by an average of 24%. A smaller percentage of subjects, 4%, experienced hallucinations. Occurrence of these episodes in one percent of the population, led to withdrawal from the study and cessation of Zelapar. Other adverse reactions, comparable in number to placebo, included nausea, dizziness, pain, headache, insomnia and rhinitis (drippy nose). For those interested in Zelapar caution is advised, as the MAO inhibitor must be avoided when taking other medications: all tricyclic antidepressants, and selective serotonin re-uptake inhibitors Luvox, Paxil, Prozac, and Zoloft. The combination of medications has dire outcomes, including coma and death.⁵

ZONISAMIDE

In 2001, Dr. Murata of the University of Tokyo published the results of his research in the journal, Neuroscience Research. He reported treating a PD patient who also suffered from intractable epilepsy, with 300 mg of zonisamide and found the patient’s convulsive attacks ceased and parkinsonian symptoms dramatically improved. Soon after, he recruited nine subjects with advanced PD to participate in an open trial of zonisamide, ranging in dose from 50mg to 200mg per day. Seven of the nine subjects experienced lessening of motor symptoms, alleviation of dyskinesias and decreased problems with ‘wearing off’.

The investigative team subsequently enlisted 347 patients in a larger, more scientifically rigorous

study. The double-blind, placebo controlled investigation involved 58 medical centers across Japan and studied three doses of zonisamide; 25mg, 50mg and 100mg. Those enrolled had lived with PD for an average of 8.6 years and their response to levodopa had diminished. Patients added the new drug while maintaining their regular medications. Using the UPDRS motor examination, investigators documented improvements in areas of speech, facial expression, resting tremor, and neck rigidity. Though all participating subjects improved in motor function while in the study, the 25mg and 50mg daily doses produced the greatest changes. While receiving 100mg per day, subjects failed to show significant improvement. The 50mg dose had the largest effect, with participants exhibiting at least a 30% reduction in UPDRS scores (indicating impairment), from baseline to final assessment.

Though the typical dose used to treat epilepsy is 300-600mg/day, the PD patients experienced improved motor symptoms with much less. To the scientific mind, this suggests the mechanism of action in epilepsy is different from what occurs in PD. In epilepsy, Zonisamide’s major effect is to quiet the firing of high frequency neurons, though it increases the release of neurotransmitters GABA and glutamate and has multiple other actions. At therapeutic levels, between 20-50 mg/daily, animal models showed increased levels of dopamine within and between cells in the striatum (area affected by dopamine-rich cell loss) of the brain.

While providing some undeniable benefits, zonisamide produced significant unwanted effects in the majority of patients. In this case, the adverse events of the 25mg and 50mg doses were comparable; 70.9% and 72.9% of subjects respectively, experienced somnolence, apathy, weight loss, and constipation. A higher percentage, 79.5% of subjects reported reduced appetite, somnolence and apathy while taking the maximum dose.

Will the drug find a new use for people with PD? Past drug trials have proven it may be useful, though not overwhelmingly so, and not without negative fallout. If nothing else proves fruitful, it may find its niche in the unfortunate population of those diagnosed with both difficult epilepsy and PD.⁶

A DAUGHTER'S VOICE

The first time I really realized my father had Parkinson-like symptoms was when I visited him after a knee replacement surgery.

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I had thought that something was going on with him that was not being addressed by his doctors, but seeing him walking just as slow and stiff as before his surgery confirmed it.

All along, he had been saying it was the pain in his leg that was limiting his mobility, but the surgery was not going to help him walk any faster.

He was also beginning to shuffle and have marked changes in his facial expressions.

I was pretty depressed at all of this. I had come to help my father through his knee rehab but I was feeling like I was facing something much bigger, with more lasting repercussions and no one was talking about it. Actually, it is not so much the fact that my father has this disease that has become so hard for me but the fact that it has been so difficult to get him to acknowledge that he has a problem, which is apparent to everyone else around him.

He filters out anything he doesn't want to hear

and doctors tend to be so diplomatic with patients that even the worst news is packaged in such a way that if you are someone like my father, you can choose not to get the message.

The whole point of acknowledging the problem is so he can seek appropriate treatment and have the best quality of life as possible. Over time, he has opted out of activities like hikes, painting outside with his watercolor class, and visits to family because it is getting harder for him.

Putting on a seat belt is sometimes impossible.

So I am hoping that with some encouragement and support from his family my father will realize it is worth the risk and try medication.

After all, it is not enough to just be here, but we should be able to enjoy the things we love to do in life for as long as possible.

~~ Sarah O'Neill Bonilla

EDITOR'S POSTSCRIPT

PDUPDATE finally has a Web-site: www.pdupdate.com It is still under construction, but is available for perusal. Individuals with current subscriptions and who have email can chose to have each issue sent directly to their email address in Adobe pdf format. Subscribers who want this service, please send your email address to: editor@pdupdate.com.

PDUPDATE will now be published by Zenografia, Inc a medical consulting and publishing company based in Tampa, FL. The new management will include Dr. Sanchez-

Ramos as managing editor and will retain the staff employed by Medical Publishing Company of Philadelphia.

Although there will not be any dramatic changes in format, we would like to include more personal anecdotes and experiences from patients, family members and caregivers. Please submit your personal views and stories by email to: editor@pdupdate.com or by regular mail to the new address.

Please note the new address and phone number: Zenografia, Inc., P.O. Box 47315, Tampa, FL, 33647. Toll-free Number: 866-424-0622.

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All articles written for PD Update by Kate O'Neill, unless otherwise noted.