



VIAGRA AND PD

As one begins to feel and move less like a PD patient and more like a regular person, one's interest in sex may rekindle. Patients, spouses and caregivers have a myriad of questions regarding the safety of sexual supplements like Viagra. This brief entry is in response to those questions. For others, sexual pleasure may be the only source of enjoyment in an otherwise very limited lifestyle. Wherever one lies on the spectrum of carnal interest, sexuality can present dilemmas. The easiest answers generally concern the safety of adding another medication to those already being taken. Whether or not the patient will benefit from the medication is a more complicated issue. Some individuals experience increased sexual fantasies as part of a levodopa-induced side effect, and the provision of a drug like Viagra may result in more problems than benefits. For such an individual preoccupied with sexuality but unable to maintain an erection, or have a satisfactory orgasm, is it preferable to decrease the dosage of levodopa to decrease sexual fantasies, or should he be given Viagra so he can fulfill himself?

The most difficult answers encompass layers of social functioning, where prescribing a drug for sexual enhancement may encourage the patient to act on a compulsive fantasy, threatening the safety of caregivers and youthful neighbors and ultimately bringing the patient into the web of law enforcement, where shame and lack of compassion must be endured by an entire family. Perhaps this is not vivid enough. One patient dressed only in his wife's ivory silk slip is stuck between palm trees, a victim of a sudden "off" episode. The thirteen-year-old neighbor calls her mother at work when she notices the masturbating figure outside her bedroom window. Mother, alarmed at her office, calls the police. The police amble through the landscaping carefully regarding the shoeless, but

fancy-clad man wedged between vertical trunks, whose voice is little more than a hoarse whisper. The wife wonders about divorce as she pays the bail costs. Sighing, she covers her husband's thin form with her raincoat directing her gaze to the hairs on his feet, unable to meet the curious eyes riveting toward them as they make their way through the gravel parking lot.

In smaller steps, an individual with a moderate level of parkinsonism may require an attendant during the day. Will the caretaker respect the patient's need for privacy and not regard him as a 'dirty old man'? Has the patient the mental acuity to know, care and act within our societal rules regarding sexuality? Or will the patient make advances and lewd remarks to the attendant, who finding her working conditions intolerable, quits? Decisions in scenarios more confusing and multi-dimensional than these, need to be made with slow deliberation with more minds than one.

Addressing the safety of medications has an easier answer. It has been three years since Viagra made its debut on the market. More than 10 million people have received prescriptions. The drug has shown to be effective in a variety of diagnoses including Parkinson's disease. Most side effects of the medication are temporary, of mild to moderate intensity and rarely lead to its discontinuation; they include facial flushing, upset stomach, bluish or blurred vision or sensitivity to light. A study of ten male PD subjects in a 2-month period, each using 50-100 mg sildenafil citrate (Viagra) found a statistically significant improvement in sexual fulfillment, satisfaction with sexual desire, ability to achieve and maintain erection and ability to reach orgasm. No changes were noted in either their depression level or their level of functional ability as measured by the Unified Parkinson Rating Scale (UPDRS). One subject reported having a headache, the most common side effect.

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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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A larger study enrolled twenty-four patients, half with Parkinson's disease and half with multiple system atrophy. For those with PD, the medication significantly improved the ability to maintain an erection and improved the quality of their sexual life. There was minimal change in blood pressure of subjects with PD, however, three subjects with multiple system atrophy (MSA) experienced severe postural hypotension (a drop in blood pressure when bringing the head above the heart) an hour after swallowing the pill. All those with MSA reported a good erectile response and were reluctant to stop using the medication. In some patient cases, PD can be difficult to distinguish from multiple system atrophy. The authors of the study recommend systematically measuring and monitoring blood pressures over time and in various positions prior to prescribing sildenafil to patients, as the drug has been shown to aggravate postural hypotension.

The male subjects in these studies were not the only ones to applaud the effects of the medication. Nine hundred and thirty partners agreed to participate in a survey reporting personal responses while their partner received treatment with sildenafil. The partners reported their mate had significantly more frequent erections and increased ability to maintain them, irrespective of age. While undergoing treatment the partners reported more frequent intercourse satisfaction. The partner's assessment confirmed the subject's evaluation of his own sexual functioning, both indicating treatment with sildenafil significantly improved erectile function.

For individuals for which sildenafil is inappropriate there may be another option. Investigators induced penile erections by intermittent subcutaneous injections of apomorphine in five patients with PD compli-

cated by motor fluctuations. Four of the patients reported erectile dysfunction before beginning apomorphine, and two reported a significant improvement of sexual function resulting from use of injections. In a Greek study published this year in the International Journal of Impotence Research, investigators compared sildenafil with apomorphine injections. The overall success rate of sildenafil was 67% compared with 32.1% for apomorphine. Apomorphine usage resulted in a higher number of negative events and two of 19 subjects stopped treatment. A larger British study conducted this year had similar results, a 75% successful intercourse rate for sildenafil versus a 35% for apomorphine. Ninety-six percent of the men in the study expressed a preference for sildenafil as a treatment for their erectile dysfunction. Surely, all will appreciate inserting a needle into the skin of one's penis is not a pleasant event, yet for a set of patients, there may be no other alternative. The benefits of apomorphine on sexual function for these patients suggest it has a possible role in the treatment of impotence.¹

APOMORPHINE TREATMENTS

Apomorphine injections are currently being marketed for people with Parkinson's disease suffering from sudden "off" episodes. The drug and its injection delivery have been available for some time in Europe. The medication is limited to incidents where the person suddenly finds himself incapable of movement. These situations are predictable to some degree, by being aware of the feelings preceding the freezing episode. Injected apomorphine bypasses metabolism by the liver—all drugs taken orally pass through and are broken down by this organ. By avoiding the liver, the drug disperses quickly into the blood stream where it circulates and reaches the brain. The clinical effect is fast, from 8 to 12 minutes and the effects are transitory. Apomorphine delivered directly through the skin by means of a microinfuser has been used successfully in patients with advanced disease to reduce motor fluctuations and guarantee a continuous flow of dopaminergic stimulation when levodopa therapy is interrupted or when the patient requires a drug holiday. Continuous microinfusion avoids the peaks and troughs of high and low blood levels, thought to be the cause of dyskinesias. Yet side effects, specifically nausea, sleepiness and hallucinations prevent this mode of use for extended periods.

However, other clinicians obtained opposing results. An Italian group conducted a study to ascertain whether an increase in psychiatric symptoms accompanied prolonged apomorphine use. Investigators compared conventional oral treatment with continuous apomorphine infusion for twelve months for PD patients with severe motor fluctuations. No increase in psychiatric events was evident when com-

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Publisher..... Sylvia A. Sack

Managing Editor..... Juan R. Sanchez-Ramos, PhD, MD

Production Manager John Paone

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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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pared with baseline. Daily “off” duration was shortened significantly and levodopa dosage was reduced significantly in infused patients. Neuropsychiatric assessment noted a significant improvement of mood in the apomorphine group. A year earlier a British team treated 64 patients with apomorphine pumps; 45 successfully converted to apomorphine monotherapy, managing to discontinue all other forms of dopaminergic medications during day hours. Patients were followed for an average of 33.8 months and their clinical data was analyzed afterwards. The mean maintenance dose of apomorphine did not significantly increase at final follow-up. Dyskinesias were reduced by an average of 64% in the monotherapy group, compared to 30% in those continuing on polytherapy.

Another Italian team analyzed the sleep patterns of 12 parkinsonian patients. All received a single night's treatment of apomorphine emulsion, assuring a constant release of drug over several hours. Sleep analysis revealed a 16% increase of total sleep time, a 12% increase of sleep efficiency, a 16% increase of stage 3 and 4 non-REM sleep, and a 22% reduction of arousal index. They concluded apomorphine emulsion may be able to diminish abnormal nocturnal movements, akinesia (not moving), and rigidity in Parkinson's disease, thus reducing the disturbed sleep typical of Parkinson's disease. This same Italian research group published their findings on absorption, efficacy and tolerability of an apomorphine emulsion applied to the skin in the August edition of *Movement Disorders*.

Their study involved twenty-one PD patients who averaged 7.9 years since diagnosis. All who received apomorphine took domperidone to allay nausea and began a dietary regimen to minimize protein interference with drug uptake. Ten grams of cream was applied to an area over the front of the chest and covered with foam tape to avoid evaporation of the components. The patch remained in place for 12 hours while blood samples measuring apomorphine concentration were drawn at regular intervals for 24 hours. Heart rate, blood pressure, the UPDRS III (Unified Parkinson's Disease Rating Scale-measures functional ability), and tapping and walking tests were conducted at the same time as the daytime blood draw. The drug was effective in reducing the duration of “off” periods and disability rather than improving motor performances in “on” conditions. It took an average of 45 minutes for apomorphine to reach therapeutic levels. Stable blood levels were maintained while the patch was on the subject's body; when it was removed blood concentration of the drug decreased at a rate comparable to the injectable variety. A majority of subjects-71.4% had redness and inflammation along the patch border. In two subjects, it persisted longer than 3 days and required treatment. 53% of the subjects reported side effects that included sleepiness during

treatment, mild orthostatic hypotension (transient low blood pressure while moving from lying to sitting, or from sitting to standing), and nausea. One subject experienced nausea that was unresponsive to domperidone and was withdrawn from the study.

While the investigators concluded that apomorphine tolerability was good they state chronic side effects require further investigation if the cream will be used on a consistent basis. The ointment may prove too caustic if used daily, though it is unclear whether subjects reacted to the cream or to the dressing covering it. Because of the 45 minute average lag time before clinical improvement of symptoms, the injection variety is still superior for sudden “off” episodes. Whether an experimental fluke or human variation in how the drug preparation penetrates the skin, no detectable apomorphine was discovered in the blood of two subjects. Several variables influence how medications are absorbed across the skin barrier. Concentration of the ointment and the area of application are important, as well as skin temperature, pH and local blood flow. Stronger active ingredients placed in warm areas with active blood flow are absorbed more quickly. Can we expect some individuals not to absorb drugs through the skin? If researchers could predict who would respond clinically, they might spare time, energy, supplies and hopes.²

A SUBJECT WITH PARKINSONISM DRAMATICALLY IMPROVES FOLLOWING SMOKING

Clinical researchers documented a PD subject who improved following cigarette smoking. The patient underwent genetic investigation and was found to harbor the parkin mutation, a well established factor exerting influence in acquisition of early-onset PD. The role of the genetic mutation is still unknown and its function is apparently complex. Both retrospective and prospective (examining the past and examining the present) studies have consistently revealed an inverse relationship between cigarette smoking and PD. Those who smoke appear to suffer less with PD and theories abound as to why this is so. One theory poses smoking in general and nicotine in particular may have neuron-protecting effects. The investigators examined the individual sequentially when “off” prior to smoking, when un-medicated after smoking, and when “on” following levodopa/benserazide medication. The individual, then 33 years old, had suffered from rigidity, bradykinesia; slowness of movement, gait and postural problems since the age of 18, though responded dramatically to levodopa/benserazide therapy. During “off” phase examination and prior to smoking, the

individual showed severe slowness of movement, rigidity, gait and postural difficulties. After smoking a filtered cigarette all symptoms improved, but did not resolve. Improvement was noted though not as dramatic as that seen with dopamine replacement medication. The authors noted the role of nicotine in PD is a subject of much discussion. Transdermal nicotine patches were found useless as add-on therapy, in strictly performed trials. It may be that nicotine is useful in a specific subset of people afflicted with PD.³

THE NOSE AND PRE-CLINICAL SYMPTOMS OF PD

The scientific community has known patients with Parkinson's disease have had problems with their sense of smell since a 1975 study conducted in the Netherlands discovered decreased olfaction in this population. Other scientific work has reinforced the finding, establishing that people with PD have profound olfactory disturbances, including impaired odor detection, identification and differentiation. In August's edition of *Neurology*, Dr. Ponsen and his colleagues published a study investigating smell ability, or olfactory sense. They set out to ascertain whether unexplained olfactory (smell sense) dysfunction is associated with an increased risk of PD. If they could establish certain people were at risk for PD, steps could be taken to protect the neurons at risk. Medications providing neuroprotection could be incorporated into a lifestyle with few side effects, thus either postponing and/or decreasing the severity of illness. The major pathological characteristic of PD is degeneration of dopamine neurons in the substantia nigra, pars compacta and those projections to the striatal regions in the brain. Extent of degeneration can be visualized using by using PET (positron emission tomography) or SPECT (single-photon emission computed tomography). There appears to be dopamine neuron loss 4 to 6 years before the individual presents any clinical indication of illness; the preclinical phase of disease extending between onset of dopamine neuron loss and clinical diagnosis of PD accounts for the death of 58% to 64% of dopamine-containing neurons. Certain researchers have proposed that PD-related pathology first occurs outside of substantia nigra and striatal regions in areas that include the olfactory bulb and anterior olfactory nucleus (areas of the brain in which olfaction or smell is located). If identifying those who lack a hearty sense of smell allows us to make predictions about the inevitability of disease, clinicians can administer neuro-protective drugs and study neuro-degeneration, with aims to halt or cause regression of the pathological process. The recent work involved 361 first-degree relatives: 285 children, 73 siblings, and 3 parents of those with diagnosed cases of idiopathic PD. Two years after tests of baseline olfactory ability, 10% of those who had low

smelling ability had developed PD. SPECT scan suggested subclinical degeneration of the nigrostriatal system in an additional 12% of the relatives, indicating the risk of developing PD in those with impaired olfaction to be as high as 22%. Follow up studies of this group of relations may reveal the risk of PD associated with decreased smell sense is actually considerably higher than the figures obtained.⁴

GDNF STUDY HALTED

The North American clinical trial of glial-derived neurotrophic factor (GDNF) stopped due to safety concerns. Rather than traditional pharmacological prescriptions replacing lost dopamine, the surgically implanted mini-pump attempted to preserve and or revive dying dopamine-producing cells by slow infusion of the nourishing protein into the brain. Hopes for the new intervention soared when the first five people treated with the substance exhibited dramatic improvement of symptoms.

On Tuesday October 5th, Anthony Lang of Toronto Western Hospital in Canada announced the end of an extensive clinical trial of GDNF at the annual meeting of the American Neurological Association in Toronto, Canada. Six months after beginning the study, no difference was apparent between those who had received the mini-pump and those who received the placebo. The study compared Parkinson's Disease rating scores, walking tests, dyskinesia scores, medication doses, quality of life measures, and "off" time. The current setback brings to mind other disappointing results from another promising experimental therapy conducted in 2003. Neuroscientists found implants of fetal brain tissue had little effect in large trials.

Glial-derived neurotrophic factor was expected to have a significant impact on the disease according to many leaders in the field. Amgen, the pharmaceutical company sponsoring the trial, announced in June that patients did not appear to benefit from GDNF after the first six months of the trial. Doctors continued to track patients who were receiving the drug. Anthony Lang of Toronto was first to report detailed results. Of the 34 people in his study, four began producing antibodies to the GDNF protein. Essentially, the body recognized the treatment protein as foreign matter and initiated defensive steps against it. This was surprising because the protein was derived from actual human neurotrophic factor and should have been compatible with all people. Apparently, our current understanding of the immune system and neurotrophic factor is limited. Though the patients are asymptomatic and appear healthy, they risked developing dangerous immune reactions if treatment had continued. Additionally concurrent studies using monkeys have developed unusual cerebellar cortical pathology. Whether this is related to GDNF treatment is unknown. As a

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result, doctors took all patients off the therapy earlier this month.

Several dozen research groups involved with GDNF around the world will endure the scientific repercussions of this news. Alternatives and less invasive methods than neurosurgical implantation of pumps for delivery of GDNF to the brain, as done in the study by Dr. Lang, are being refined; gene therapy and implantation of protein-secreting cells may still yield promising results.

The biggest fear in the scientific community is Amgen may lose complete interest in the field. Since the company holds patents on GDNF, further research studies may go unfunded.

Questions remain about the discrepancy between an earlier five-patient trial, performed in the UK, and the larger North American trial. The improvement seen in the first set of patients may be explained as the placebo effect, since all knew that they were undergoing treatment. In contrast, patients in the second trial were randomly assigned to receive infusions of GDNF or a placebo, and they did not know which they were taking; they were "blinded". Dr. Clive Svendsen of the University of Wisconsin suggests there may be other explanations for the different results. Dr. Lang's trial used smaller doses of GDNF and larger plastic tubing to supply treatment to the putaminal area of the brain. Wider tubing diameter will increase the area of tissue damage.

Brain scans carried out in both studies showed dopamine-producing cells had increased vitality compared with prior to treatment; specifically fluorodopa uptake near the drip tip was mildly but significantly improved in the GDNF-treated group. Side effects were similar between the two groups, except for a slight increase in frequency of paresthesias (unusual sensations in the limbs), headache, and upper respiratory infection in GDNF-treated patients. There remains hope that with refined techniques the neurotrophic factor will be of benefit to PD patients. Researchers in the field plan to meet and discuss the issues. For now, it is premature to sound the death bells for GDNF therapy, since there are few experimental therapies ready to take its place.⁵

NET NEWS

M. J. Fox Grant to University of Lund for GDNF producing Cells

The Michael J. Fox Foundation for Parkinson's Research (MJFF) announced it has awarded a grant to a research team led by Olle Lindvall, MD, PhD, of the University of Lund, Sweden. The team is developing a neuroprotective therapy based on the implantation of encapsulated cells that produce growth factor GDNF (glial derived nerve growth factor) within the brain. Awarded under the Linked Efforts to Accelerate

Parkinson's Solutions (LEAPS) program, the project will receive funding totaling approximately \$3 million over four years, assuming all milestones are met. Because GDNF does not cross the blood-brain barrier, it cannot be given orally or by injection. While still experimental, encapsulated cell technology, if successful, will enable localized, long-term sustained delivery of GDNF to the brain; its primary aim to protect dopamine neurons and stimulate their regeneration. Prior studies of GDNF in Parkinson's disease have shown positive effects in animal models as well as in early clinical trials. Recently, preliminary results from a phase II trial employing another delivery system showed no clinical improvement after six months. However, the ability of GDNF to protect dopamine neurons and stop the progression of the disease was not tested. This LEAPS project will help resolve and advance understanding of GDNF's therapeutic potential as well as potential delivery system variables. Full funding for the project is contingent upon the achievement of predetermined scientific milestones. The team's first milestone is to generate human cell lines capable of steadily secreting small amounts of GDNF and place these cells in retrievable fiber capsules. Once created, these capsules will be tested to assess cell viability, level and duration of GDNF secretion and diffusion into the brain, along with general safety issues such as inflammation and retrievability. In addition, the neuroprotective and regenerative effect of this type of delivery of GDNF will be studied in disease models. Should this therapy prove effective, 12 patients will be enrolled in clinical trials in Sweden, Switzerland, Germany and the U.K. and assessed clinically for at least 24 months.

@bio.com/industryanalysis July 4, 2004

M. J. Fox Foundation Grant for Genotyping PD

The Mayo Clinic in Rochester and a California biosciences firm have received a \$2.8 million grant from the Michael J. Fox Foundation for Parkinson's research. The money will be used to try to create a map based on more than 200 million typings of DNA. This data might eventually help create a DNA profile that can be used to find individuals who have a more than average chance of getting Parkinson's disease.

@bizjournals.com June 14, 2004

Vaccine for PD?

For the first time, researchers have shown that an experimental vaccine can reduce the amount of neurodegeneration in a mouse model of Parkinson's disease. The finding suggests a similar therapy might eventually be able to slow the devastating course of Parkinson's disease in humans. The experimental treatment in this study is

Safinamide – an experimental neuroprotectant

among the first to show potential for slowing brain degeneration in this disease. Currently available therapies can treat symptoms of the disease, but they do not prevent loss of brain cells. Studies in the last decade have shown that inflammation is common to a variety of neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease, HIV-1 associated dementia, and amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease). The inflammation in these diseases involves activation of microglia -specialized support cells in the brain that produce immune system signaling chemicals called cytokines. Although inflammation can be damaging, Michel Schwartz, Ph.D. and colleagues at the Weizmann Institute in Rehovot, Israel, have pioneered research, showing that activating immune cells in specific ways also may lead to neuroprotective responses in animal models of spinal cord and brain injury. In the new study, Howard E. Gendelman, M.D., of the University of Nebraska Medical Center in Omaha, along with graduate student Eric Benner and colleagues, experimented with a drug called copolymer-1 (Copaxone). Previous studies have shown that Copaxone-commonly used to treat multiple sclerosis, increases the number of immune T cells that secrete anti-inflammatory cytokines and growth factors. The researchers extracted immune cells from mice that had received Copaxone immunization and injected them into mice, which had received injections of a drug called MPTP. MPTP leads to Parkinson's-like neuronal degeneration in the brain. Mice who received the Copaxone-treated immune cells had significantly less degeneration of dopamine-producing neurons in their brain than mice who received none of the treated cells. These mice lost fewer dopamine-transmitting nerve fibers than control mice and had only a small decrease in their levels of dopamine produced in the brain. Dopamine is a nerve-signaling chemical (neurotransmitter) that involves movement; a loss of dopamine-producing neurons is the central problem in Parkinson's disease. Researchers found T cells in the treated mice migrated to the damaged area of the brain, in what is interpreted as a neuroprotective response, reducing the harmful reactions of the microglia. In addition, the vaccine dramatically increased the amount of growth factor called GDNF (glial-derived neurotrophic factor) that helps prevent neuro-degeneration. The vaccination modified the behavior of glial cells so that their responses are beneficial to the nervous system rather than harmful. The researchers are now planning follow-up studies to confirm their results and to identify the specific cytokines, nerve growth factors, and other proteins that play a role in the protective response. Other work is needed to determine how to translate the study results into a therapy for humans and to make sure the treatment is safe for patients with Parkinson's, who may not react to the drug in the same way that MS patients do.

@scienceblog.com August 13, 2004

Phase three clinical trials recently published on the new drug Safinamide show promising results. Before the medication donned its popular name it was called PNU 151774E. Newron Pharmaceuticals organized the clinical trials in Europe and have their headquarters in Bresso, Italy. The Italian Ministry of Productive Development's Innovation Technology Fund awarded Newron Pharmaceuticals a 2.7 million euro grant-partial support, for the development of safinamide in Parkinson's disease. The company focuses on ion channel-based therapies for diseases of the central nervous system-particularly epilepsy, Parkinson's disease, neurodegeneration and pain.

Safinamide is a unique molecule with multiple mechanisms of action, including sodium channel blocking activity, calcium channel modulation, glutamate release, selective and reversible inhibition of monoamine oxidase (MAO)-B, without a MAO-A effect and dopamine re-uptake inhibition. The sodium channel blockade selectively affects only the neurons with abnormal firing patterns leaving normal activity unaltered. Safinamide is chemically unrelated to current anti-epileptics, though its potency is comparable or superior to that of most classic anticonvulsants. It possesses a wide protective index and a low potential to induce tolerance, motor or cognitive side effects. The absorption of safinamide was rapid with peak plasma concentrations occurring within 2 to 4 hours. Food prolonged the rate and did not affect the extent of drug absorption. In a dose regimen of one pill daily, a steady therapeutic state was reached on the fifth study day.

Benefits of safinamide treatment in Parkinson's disease include

- dopamine uptake inhibition
- potential neuroprotective activity due to multiple mechanisms of action
- reversible MAO-B inhibition leading to a favorable side effect profile
- absence of MAO-A activity in humans therefore no cheese effect

With all new therapies, drug studies must prove a medication is effective for what it claims to treat. In short time there should be clinical trials seeking patients willing to participate in these research efforts. Those chosen subjects contribute their bodies to furthering the study of pharmacology and are a necessity if we are to move through this period of relatively limited treatment options.⁶

*biospace.com/news_story.cfm?
StoryID=14414020&full=1*

*bioexchange.com/news/news_page.cfm?id=158
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newron.com/safinamide.asp

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LETTERS TO THE EDITOR

"I am having problems reading because of blurred vision. I have been treated for Parkinsons for 7 years with Sinemet and have done OK except that I have wearing off periods about every four hours. So now I take 1 and ? tablets of Sinemet25/100 every 3 to 4 hours. Compared to others, I am still able to walk without help and can do things for myself. But the reading is really bothering me. I didn't have the problem until the last year. My ophthalmologist has examined me and corrected my reading glasses but I still occasionally have blurred or double vision, but not at all times. The eye doctor says that the problem is not with my eyes but my brain. What does he mean by that?"

~~ J.T. Tampa, FL

Dear J.T.

PD patients often complain of problems with vision. For lack of better knowledge, these problems are usually chalked up to age, macular changes or because of non-PD causes. Researchers have demonstrated that visual evoked potentials in PD patients are affected by the course of the disease and are

improved by levodopa. So it is likely that your intermittent visual blurring corresponds to the wearing off of Sinemet effects. It would be important to determine when the blurred vision occurs to see if it is related to wearing off. Then you may be able to adjust your medication schedule with the help of your neurologist.

However, the problem with vision in PD is more complicated and insidious. Studies by several different groups have shown that these visual problems lie not with acuity of vision, but with sensitivity to contrast, difficulty reading or distinguishing shapes with low levels of light. More recent studies has found that deficits in both contrast sensitivity (CS) and color discrimination (CD) are progressive over time and that these visual deficits may lead to worsening of motor impairments in PD. In one report, PD patients were rated at the beginning of the study with the United Parkinson Disease Rating Scale (UPDRS) and Schwab and England test for PD and with the Brief Psychiatric Rating Scale (BPRS) and again at the last examination. The eye examination was conducted while they were in an "on" state and taking their normal course of medications. The exam consisted of two standard

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tests for contrast sensitivity and two for color discrimination. Approximately 20 months later, they were again examined in the same manner, under identical lighting and conditions as the first time. The second exam revealed marked deterioration of both CD and CS. Age alone was not the cause of these deteriorations: contrast sensitivity is most prominent at high frequencies in the aged, but was not found in those frequencies with this group and color discrimination did not follow the typical deterioration encountered with

age. They did find that patients who had worse visual deterioration also had a decline in psychiatric function, although they were not able to determine which came first. The declines of both CS and CD are insidious and patients may not be able to compensate for the changes. Errors in contrast and color perception could also contribute to misjudging distance or depth leading to increased falls, impaired motor functions, visual illusions and also perhaps to hallucinations.

~~ J. S-R.

EDITORS NOTE: We are sorry that significant errors appeared in the last issue of PD UPDATE #143. On page 1020 the title that read "AMIC Nucleus on Health...." should have read "Impact of Deep Brain Stimulation of the Subthalamic Nucleus on Health-Related Quality of Life in Advanced Parkinsonian Patients". On page 1021, the title should have been "Deep Brain Stimulation of the Subthalamic Nucleus for Parkinson's Disease". Finally the title "Impact of deep brain stimulation.." on page 1021 should have read "Long-Term Results of Bilateral Pallidal Stimulation in PD". We think these errors occurred when the document in Word format was imported into the typesetting format. We apologize for the confusion this may have caused in readers.

Sources

1. Eardley, I. et al. "An open-label, randomized, flexible-dose, crossover study to assess the comparative efficacy and safety of sildenafil citrate and apomorphine hydrochloride in men with erectile dysfunction." *BJU Intern.* 93(9): Jun 2004. Hussain, I.F. "Treatment of erectile dysfunction with sildenafil citrate (Viagra) in parkinsonism due to Parkinson's disease or multiple system atrophy with observations on orthostatic hypotension." *J. Neuro. Neurosurg Psych.* 71(3): Sep 2001. Montorsi, F. "Partner responses to sildenafil citrate (Viagra) treatment of erectile dysfunction." *Urol.* 63(4): Apr 2004. O'Sullivan JD. "Apomorphine-induced penile erections in Parkinson's disease." *Mov. Dis.* 13(3): May 1998. Perimenis, P. et al. "A comparative, crossover study of the efficacy and safety of sildenafil and apomorphine in men with evidence of arteriogenic erectile dysfunction." *Intern. J. of Impot Res.* 16(1): Feb 2004. Sadovsky, R. "Side effects included headache in one patient during three sexual encounters. Three-year update of sildenafil citrate (Viagra) efficacy and safety." *Inter. J. of Clin. Prac.* 55 (2): Mar. 2001. www.viagra.com. Zesiewicz, T.A. et al. "Sildenafil citrate (Viagra) for the treatment of erectile dysfunction in men with Parkinson's disease." *Mov. Dis.* 15 (2): Mar. 2000.
2. Di Rosa A.E. et al. "Continuous apomorphine infusion and neuropsychiatric disorders: a controlled study in patients with advanced Parkinson's disease." *Neur. Sci.* 24(3): Oct 2003. Manson A.J. et al. "Apomorphine monotherapy in the treatment of refractory motor complications of Parkinson's disease: long-term follow-up study of 64 patients." *Mov. Dis.* 17(6): Nov. 2002. Priano L. et al. "Nocturnal anomalous movement reduction and sleep microstructure analysis in parkinsonian patients during 1-night transdermal apomorphine treatment." *Neur. Sci.* 24(3) 2003. Priano L. et al. "Transdermal Apomorphine Permeation From Micoremul-sions: A New Treatment in Parkinson's Disease." *Mov. Dis.* 19(8): Aug. 2004.
3. Dogu, O. et al. "A subject with a homozygous exon 4 parkin deletion whose parkinsonism dramatically improves following smoking." *Mov. Dis.* Vol.19, Supp.9., 2004.
4. Ponsen M.M. et al. "Idiopathic Hyposmia as a Pre-clinical Sign of Parkinson's Disease." *Ann. of Neur.* Vol.56 No 2 Aug. 2004.
5. Gill S. S., et al. *Nature Medicine* 9, 2004; Pearson, H. "Parkinson's trial halted." *Nature*; Oct. 2004.
6. Salvati P. et al. "Biochemical and Electrophysiological Studies on the Mechanism of Action of PNU-151774E, A Novel Antiepileptic Comp." *Pharm. and Exper. Ther.* 288 (3) March 1999. Marzo A. et al. "Pharmacokinetics and pharmacodynamics of safinamide, a neuroprotectant with antiparkinsonian and anticonvulsant activity." *Pharm. Res.* 50 (1) Jul. 2004.

*All articles written for PD Update
by Catherine O'Neill.*

Edited by Juan Sanchez-Ramos, PhD, MD