



**The National VA
Parkinson's Disease
Consortium**

**Parkinson's Disease
Research, Education
and Clinical Center
(PADRECC)**

eCommuniqué

Welcome to this research bulletin of the National VA Parkinson's Disease Consortium. The eCommuniqué highlights information about Parkinson's disease (PD) and is provided as a service to members of the national Consortium, other colleagues, and community leaders interested in PD.

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In this Issue:

Risk Factors for Somnolence, Edema, and Hallucinations in Early Parkinson's Disease

Rate of Clinical Progression in Parkinson's Disease (PD): A Prospective Study

Cognitive Changes and Hypofunctioning of the Striatum

Predictors of Freezing in Parkinson's Disease: A Survey of 6,620 Patients

Link Between Parkinson's Disease and Narcolepsy

Chronic Epidural Motor Cortical Stimulation for Movement Disorders

Environmental Risk Factors for Parkinson's Disease and Parkinsonism

Cognitive-Behavior Therapy for Depression in Parkinson's Disease: A Pilot Study

Caregiver Burden in Parkinson's Disease

A New Look at James Parkinson's Essay on the Shaking Palsy

Preventing Neurodegeneration in a Rat Model of Parkinson's disease

A Capsule...of Information

Educational Opportunities

The National VA Parkinson's Disease Consortium

Physicians should be aware of the significance of co-morbid illnesses for the development of somnolence, edema, and hallucinations, and when initiating treatment with pramipexole.

A secondary finding of the CALM-PD (C**omparison of the A**gonist Pramipexole versus **L**evodopa on **M**otor Complications of **P**arkinson's **D**isease) trial was a higher than anticipated development or worsening of somnolence, edema, and the presence of hallucinations as adverse events when evaluating baseline characteristics for these features. A series of Cox proportional hazards models assessed the associations between each of the explanatory variables and the development of these non-motor outcomes. Somnolence was associated with initial pramipexole treatment, male gender, and >5 systems with a comorbid illness. Edema was associated with initial pramipexole treatment, female gender, and comorbid cardiac disease. Hallucinations were associated with age, Mini-Mental State Examination score, and >5 systems with a comorbid illness. Kaplan-Meier curves estimated the cumulative probabilities (at 4 years) of developing somnolence, edema, and hallucinations over time. The authors concluded that physicians need to understand the significance of comorbid illnesses for the development of somnolence, edema, and hallucinations, and when initiating treatment with pramipexole, patients should be assessed for and informed about somnolence and edema. The associations between cognitive functioning, advancing age, and the development of hallucinations should also be assessed.

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17620552&ordinalpos=11&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

Progression of UPDRS scores in PD decreases, but disability continues to deteriorate with advancing disease.

This study investigated the rate of clinical progression of PD in a clinic-based sample of 145 patients over 1 year and a community-based sample of 124 patients over 4 years. Depending on the sample and clinical scale used, mean deterioration of motor and disability scores ranged from 2.4 to 7.4% of the maximum possible score per year and standard deviations indicated marked variability of progression rates between individuals. The two samples differed in their progression rates. The community-based sample showed a slightly faster rate of progression than previous studies of patients on medication with the possibility that medication dosage was inadequate. The progression rate on the UPDRS motor score in the clinic-based sample was similar to that in the 'survivor' group in the Deprenyl and Tocopherol Antioxidative Therapy for Parkinson's Disease (DATATOP study) and other studies where patients received symptomatic treatment. In more advanced disease, motor impairment and increasing rates of disease complications contributed to increased disability. When comparing the two groups, these complications included motor fluctuations, hallucinations, depression, memory problems, and bladder symptoms in the community-based group ($p < 0.01$) whereas dyskinesias, falls, and hallucinations were more common in the clinic-based group. Cognitive and depression scores were also worse in higher disease stages in the clinic-based sample ($p < 0.001$). The authors conclude that progression of PD decreased with advancing disease corresponding with pathological findings of faster progression of neuronal loss in the striatum in early disease. Disability continued to deteriorate with advancing disease due to the development of complications related to additional extrastriatal pathology.

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17415791&ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

Cognitive slowing in PD may be similar to motor slowing due to changes in the corticobasal ganglia circuit.

Researchers in Japan investigated whether cognitive slowing in PD is reflected more by disruption of the corticobasal ganglia circuit or dysfunction of the frontal lobe due to hypofunctioning of the mesocortical dopaminergic system. The study conducted a H₂O PET study with a verbal mental-operation task involving activity in the striatum in 10 mildly impaired patients with PD and 10 matched healthy controls. Patients were asked to stop PD medication for at least 12 hours before the scan. The task required serial updating of mental representations in response to a series of visual stimuli; this process then avoided any influence of abnormal brain activity due to motor deficits. Verbal versions of a mental-operation task and a verbal-fixation task were used for this study; all stimuli were visually presented at the center of a monitor. A trial of the tasks started with a prime stimulus (characters indicating day of the week) followed by a series of instruction stimuli presented at differing speeds that influenced brain activations. Results indicated that healthy controls showed an increase in activities of the anterior striatum and medial prefrontal cortex suggesting the involvement of the corticobasal circuit in normal performance of the task. In contrast, patients with PD lacked an increased in striatal activity whereas the premotor cortex showed a proportional increase. The findings suggest that striatal disruption resulting in abnormal processing in the corticobasal ganglia circuit may contribute to cognitive slowing in PD, similar to motor slowing. More studies are needed for validation.

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17389313&ordinalpos=8&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

Freezing is significantly associated with a longer disease duration and more advanced stage of the illness, and can significantly impair a patient's quality of life and safety.

Over 6,600 members (63% response rate) of the German Parkinson Association were examined for correlation of freezing episodes with age, sex, disease duration, subjective severity of PD, and antiparkinsonism medication. The mean age was 68.5 years and the average disease duration was 9.4 years. Men and women did not differ in age and disease duration. Episodes of freezing were assessed by asking patients whether they already had freezing episodes and if 'yes', how frequently were they experienced. Freezing was defined as "sudden, short, and transient inhibitions of movements while walking or during other movements... triggered by... situations when gait is initiated, under time pressure, or an obstacle is encountered." Forty-seven percent of the patients reported regular episodes of freezing at least twice a month (28% daily, 13% 2-4 times a week, and 6% at least 2-4 times a month). Logistic regression analysis indicated that freezing was significantly associated with a longer disease duration and more advanced stage of the illness (80%). Freezing was more likely to occur in men than in women, and none of the common antiparkinsonian drugs given in combination with levodopa reduced the risk of freezing. Patients taking levodopa and Entacapone, Amantadine, or dopamine agonists experienced slightly increased freezing episodes. Those patients who considered tremor as their main symptom reported less freezing. Almost 3% experienced freezing while driving and 19 patients (out of 361) who had traffic accidents admitted to freezing while behind the wheel. The results suggest that appropriate pharmacotherapeutic and behavioral strategies need to be developed since freezing can significantly impair a patient's quality of life and safety.

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VA-UCLA team discovers link between PD and narcolepsy due to deficiencies of hypocretin.

In a recent issue of *Brain*, a team of researchers at the Greater Los Angeles VA and the University of California Los Angeles reported the similarities of non-motor symptoms of PD with narcolepsy – daytime sleep attacks, nighttime insomnia, and severe fatigue. A deficiency of hypocretin cells was discovered in the brains of 11 deceased patients with PD and those who were in stage 5 of the disease lost a "massive" 62% of hypocretin. This loss of hypocretin may be a cause of the narcolepsy-like symptoms of PD. Earlier research compared findings from deceased patients with narcolepsy with normal brain tissue and found that those with narcolepsy had up to 95% fewer hypocretin neurons. Since no current treatments are available for hypocretin replacement, clinical trials are needed within the next few years.

<http://brain.oxfordjournals.org/cgi/content/abstract/130/6/1577>

Chronic epidural motor cortical stimulation is safe and should be a valuable treatment option for movement disorders.

In this article, the authors discuss the rationale and the physiological mechanisms that are involved in Motor Cortical Stimulation for Movement Disorders. Several factors support the use of chronic cortical stimulation in patients with movement disorders, including the strategic position of the motor cortex, the improvement induced in some motor disorders by cortical lesions, the functional imaging findings that document cortical dysfunction in movement disorders, and the improvement induced in patients with Parkinson's disease and dystonia by repetitive transcranial magnetic stimulation. The most probable mechanism of action of chronic motor stimulation is that of eliciting distant bilateral changes through efferents and afferents that

bilaterally connect the motor cortex with other cortical and subcortical structures. This is in addition to modifications in the motor cortex itself. The authors suggest that the epidural chronic motor cortical stimulation is safe and should be a valuable treatment option for movement disorders.

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A geoparkinson study confirms the negative association between tobacco smoking and PD, the lack of evidence between alcohol and PD, and the increased risk of PD in relation to pesticide exposure and head trauma.

The Geoparkinson study is one of the largest case-control studies to date of genetic, environmental, and occupational risk factors for PD and other parkinsonian syndromes. This case-control study recruited 959 subjects (767 with PD) and 1989 controls from Scotland, Sweden, Italy, Romania, and Malta. Subjects completed an interviewer-administered questionnaire regarding lifetime occupational and hobby exposure to solvents, pesticides, iron, copper, and manganese. Lifetime and average annual exposures were estimated blind to disease status using a job-exposure matrix modified by subjective exposure modeling. Results were analyzed using multiple logistic regression adjusting for age, sex, country, tobacco use, occurrence of unconscious episodes, and family history of PD. Results indicated an increased odds ratio for work with pesticides with a significant exposure response-relationship. Unfortunately, the exact nature of each pesticide and herbicide was not always recalled by the subjects. Thus, the estimates were then generated for tasks associated with agriculture, gardening, and employment. No associations were found with solvent exposure and evidence for metal exposure was lacking. Head injury showed an exposure-response relationship with PD, and use of anti-depressants, anxiolytics or hypnotics also appeared to be associated with PD. However, the incomplete data do not support that these factors predate symptom onset. The study confirms the negative association between tobacco smoking and PD, the lack of evidence of between alcohol and PD, and the increased risk of PD in relation to pesticide exposure.

<http://oem.bmj.com/cgi/content/abstract/oem.2006.027003v2?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&author1=Dick&andorexactfulltext=and&searchid=1&FIRSTINDEX=0&sortspec=relevance&resourcetype=HWCIT>

Individual cognitive behavioral therapy when be a helpful in treating depression for patients with PD.

Fifteen PD patients with PD who had been diagnosed with Major Depressive Disorder received 10-14 sessions of cognitive-behavioral treatment (CBT) that were modified to meet the unique needs of the PD patient. Caregivers attended 2-4 psychoeducational sessions, occurring separately from the patient treatment sessions, which focused on targeted strategies for offering appropriate support and ways to respond to the patients' negative thoughts. Patients experienced a significant reduction in depressive symptoms and negative cognitions, and an increased perception of social support over the course of treatment. Gains were maintained at one-month follow-up. Larger randomized trials are needed to further evaluate the efficacy of this study, but preliminary findings suggest that individual CBT, when modified appropriately, may be a feasible and effective option for PD depression.

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17377926&ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

The main predictors of caregiver burden are the health-related quality of life for patients and caregivers, the clinical aspects of PD, and the caregivers' psychological well-being.

This study examined caregiver burden in relation to sociodemographic variables, emotional factors, and health-related quality of life. The following measures were applied to 80 patients with PD: the Hospital Anxiety and Depression Scale, the EuroQoL (for quality of life), and PD specific measures (Hoehn and Yahr staging and SCOPA-Motor ADL subscale). The caregivers completed the Hospital Anxiety and Depression Scale, the SF-36, the EuroQoL, and Zarit Care Burden Inventory. The Zarit Inventory was found to be a valid and reliable measure in the context of PD. Results indicated a significant association between caregiver burden and health related quality of life. The mental aspects of the caregivers' quality of life and burden were affected by the patient's disability and disease severity. The caregivers' depression had a significant negative effect on both their burden and quality of life. In summary, the main predictors of caregiver burden were the health-related quality of life for patients and caregivers, the clinical aspects of PD, and the caregivers' psychological well-being.

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17238193&ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

A new look at James Parkinson's essay on the Shaking Palsy.

"An Essay on the Shaking Palsy" (1817) was written during a period of transition in medical thinking about diseases and how to define them. Medicine was more concerned about the anatomical and clinical features and less about the cause of diseases, which was difficult to investigate. The authors of this historical review note that Dr. Parkinson's essay had a writing style similar to nonmedical literature and that this more informal style was addressed directly to the readers and followed a narrative prose style. This narrative representation was used by Dr. Parkinson to describe the shaking palsy and its progression over a number of years and to link the early and late forms of the disease. It is believed that the British medical experts acknowledged the essay, but it probably was not widely read overseas or translated into other languages. No other writers influenced Parkinson's description until Trousseau and Charcot. It was Charcot who identified facial motor changes, slowness of movement, and nontremor features. The reviewers suggest that Dr. Parkinson was a self-made clinician who looked for order in the natural and human worlds and who believed in the Enlightenment ideals of observation, recording, classification, and progress.

<http://www.neurology.org/cgi/reprint/69/5/482?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=shaking+palsy&andorexactfulltext=and&searchid=1&FIRSTINDEX=0&sortspec=relevance&resourcetype=HWCIT>

A newly identified protein protects against neurodegeneration in a rat model of Parkinson's disease.

As reported in *Nature*, a newly identified protein, conserved dopamine neurotrophic factor (CDNF), protects and even rescues damaged dopamine-producing neurons in a rat model of PD. A neurotoxin that targets dopamine neurons is injected into the striatum on one's side of the rat's brain resulting in a circling behavior reflecting an imbalance of dopamine activity in the brain's hemispheres. Pretreatment with CDNF six hours before the toxin injection significantly reduced circling and almost completely rescued the dopamine neurons. When CDNF was given 4 weeks after the toxin, dopamine neurons were restored and the circling behavior was reduced.

<http://www.nature.com.ezproxyhost.library.tmc.edu/nature/journal/v448/n7149/full/nature05957.html>

A Capsule...of Information

✓ A study of 272 patients and 226 partners in Germany revealed that **consumption of chocolate** was significantly higher in PD patients compared to controls ($p < 0.0001$). There was no correlation between chocolate consumption and depression symptoms in patients with PD as measured by the Beck Depression Scale. The reasons for the increased consumption are unclear but may be a consequence of high contents of biogenic amines. (Wolz M. et al. Poster Session 2 (605) at Movement Disorders Society, June 6, 2007)

✓ The **Mirror Neuron System** of the premotor and parietal cortices may be used to affect functional changes in hand motor function in persons with ischemic stroke. These motor skills played an important evolutionary role and depended on observation-execution matching. Action observation and imitation may be a new tool in rehabilitation because of its well-regarded neurophysiologic basis. <http://www.cogbehavneurolog.com/pt/re/cbneuro/abstract.00146965-200603000-00007.htm;jsessionid=GDLNL15rJHB41xQ5hTgNnBhKyW9XCLZqRJqGMGlm29XYmc3STmG8!-2603961431181195628!8091!-1?index=1&database=ppvovft&results=1&count=10&searchid=1&nav=search>

✓ A study investigating the **presence of depression** in 413 early, untreated PD subjects found that 27.6% screened positive for depression on the 15-item Geriatric Depression Scale and 40% of these subjects were neither treated with medication nor referred for further evaluation. Depressive symptoms are an important contributor to disability and the decision to start therapy for non-motor symptoms in early PD is needed. http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17646622&ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

Educational Opportunities

- * The American Neurological Association Annual Meeting will be held Oct. 7-10th, 2007 in Washington, DC. <http://www.aneuroa.org/>
- * The Parkinson's Disease Foundation presents its 50th Anniversary Educational Symposium "Frontiers of Science and Clinical Advances in Quality of Life" on Oct. 11-12th, 2007 at the South Street Seaport area in NYC. www.pdf.org/50th .
- * The American Academy of Neurology Annual Meeting will be held April 12-19th, 2008 in Chicago, IL. <http://www.aan.com/>
- * The 12th International Congress of The Movement Disorder Society will be held June 22-26th, 2008 in Chicago, IL. <http://www.movementdisorders.org/congress/congress08/>
- * The "We Move" website has information for patients on movement disorders ranging from Ataxia through Wilson's Disease. Included are brochures on "My Life in Motion" and listings of research sites for patients with movement disorders. The homepage also promotes the Movement Disorders Virtual University for health care professionals. <http://www.wemove.org/par/>
- * The National Parkinson Foundation (NPF) has PDF versions of their newsletters online. They can be accessed at

<http://www.parkinson.org/NETCOMMUNITY/Page.aspx?&pid=246&srcid=201>

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Mission statement: ...to support the provision of optimal care and education for veteran patients diagnosed with Parkinson's disease and related movement disorders through advocacy, scientific inquiry and enhanced clinical expertise.

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