



The VA Parkinson Report



*A Newsletter for the Parkinson's Disease Research, Education and Clinical Centers
and The National VA Parkinson's Disease Consortium*

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Update on Management of Psychiatric and Cognitive Symptoms in Parkinson's Disease

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(PADRECC and MIRECC)

Although Parkinson's disease (PD) is traditionally considered a movement disorder, the high prevalence of cognitive impairment and psychiatric complications suggests that it is more accurately conceptualized as a neuropsychiatric disease. The non-motor symptoms of PD have become an area of intense research focus. This article provides a summary of recent developments in the management of several common disorders.

Cognitive Impairment and Dementia

Only one large controlled cholinesterase inhibitor (ChEI) study on dementia in Parkinson's disease (PDD) has been published.¹ Statistically significant effects for rivastigmine on a range of primary and secondary outcome measures were observed.² ChEI treatment was well tolerated in this study, although tremor was more commonly reported as an adverse event with active treatment.

In a recent controlled study that included both PDD and dementia with Lewy body (DLB) patients, memantine (an NMDA receptor antagonist) was found to be beneficial on a measure of clinical impression and on a test of speed/attention. A subgroup analysis found that improvement was observed in PDD patients only.³ In contrast, another placebo-controlled randomized trial of PDD and DLB patients did not demonstrate any benefit for memantine in patients with PDD (in contrast to a small observed treatment effect in DLB patients).⁴

There have been several small studies of cognitive enhancing medications for the treatment of non-demented PD patients. No benefit for galantamine (a ChEI) was demonstrated in a controlled trial,⁵ but in open-label studies donepezil and atomoxetine (a selective norepinephrine reuptake inhibitor [NRI]) were associated with improvement in executive dysfunction^{6,7} or global cognition.⁸ There is also preliminary evidence that cognitive training

or rehabilitation can improve executive abilities in non-demented patients.^{9,10}

Depression

Approximately 20%-25% of PD patients in specialty care take an antidepressant at any given time, most commonly a selective serotonin reuptake inhibitor (SSRI). Numerous open-label trials using SSRIs and other newer antidepressants in PD suggest a positive effect and good tolerability. While concern has been raised via case reporting and physician surveys about SSRIs worsening parkinsonism, clinical experience and open-label studies suggest good tolerability.

Relatively few controlled antidepressant studies for d(depression)PD have been published. Tricyclic antidepressants (TCAs; nortriptyline or desipramine) were found to be superior to placebo in three studies,¹¹⁻¹³ but TCAs can be difficult for PD patients to tolerate due to aggravation of orthostatic hypotension, constipation, and cognitive problems. Two controlled SSRI studies were underpowered and reported negative findings.^{14,15} Another small study reported positive findings.¹² In a recent controlled study, atomoxetine treatment was not efficacious for depression but was associated with improvement in global cognition and daytime sleepiness.⁸

Preliminary studies suggested that dopamine agonists (DAs) have antidepressant properties, and a recent large controlled study found pramipexole to be efficacious for the treatment of depressive symptoms in PD.¹⁶ Selegiline, a selective monoamine oxidase B (MAO-B) inhibitor, has also been reported to have antidepressant properties in PD.¹⁷ Concern that the combination of MAO-Bs and SSRIs might lead to serotonin syndrome has been somewhat allayed by clinical experience.¹⁸

Electroconvulsive therapy (ECT) can be effective for severe dPD and also improves parkinsonism, though the

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motor benefits wear off once treatment is discontinued.¹⁹ A recent controlled treatment study with left PFC repetitive transcranial magnetic stimulation (TMS) in PD reported improvement in depressive symptoms.²⁰ Psychotherapy, including cognitive behavioral therapy (CBT), is increasingly being explored as a treatment of dPD.²¹

Psychosis

In managing psychosis in PD, a thorough medical evaluation for delirium should be performed, any non-essential non-PD medications that might contribute to mental impairment should be discontinued, and the risk-benefit ratio of each antiparkinsonian medication should be reviewed. This initial management strategy can be sufficient for a significant percentage of patients.²²

Antipsychotic (AP) treatment is initiated for persistent and problematic psychosis. High potency typical APs are not recommended, as they can significantly worsen parkinsonism.^{2,3} Clozapine is efficacious for PD psychosis at much lower dosages than typically used in psychiatric populations,^{24,25} but it is usually reserved for treatment-refractory patients. Quetiapine has become the most commonly-used AP in PD patients, but all controlled clinical trials of quetiapine for PD psychosis with reasonable sample sizes have been negative or uninterpretable.²⁶⁻²⁸ Regarding safety, there is a "black box warning" for use of both typical and atypical APs in elderly dementia patients, but the morbidity and mortality risks associated with AP use in PD have not been established.

Several small open-label studies found donepezil and rivastigmine to be beneficial for PD psychosis in the context of dementia. A recent controlled clinical trial of pimavanserin, a serotonin_{2A} receptor inverse agonist, for PD-P was negative.²⁹

Impulse control disorders

Impulse control disorders (ICDs), including compulsive gambling, buying, sexual behavior, and eating, often resolve after discontinuing or reducing DA treatment, typically offset by an increase in levodopa dosage to compensate.³⁰ However, many patients do not want or tolerate DA discontinuation, and a DA withdrawal syndrome (DAWS) was recently described, characterized by anxiety, dysphoria, autonomic changes, and medication craving.³¹

The relationship between DBS and ICDs is complex. Subthalamic nucleus (STN) DBS was associated with improvement in ICD symptoms in a case series,

likely due to significant reductions in dopaminergic therapy that occurred post-surgery.³² However, there is also anecdotal evidence that ICDs may begin or worsen after STN DBS.³³

Psychiatric treatments, most commonly SSRIs and atypical APs, have been used clinically to treat ICDs in PD.³⁴⁻³⁶ A placebo-controlled study reported benefit for amantadine as a treatment for pathological gambling in PD,³⁷ although amantadine use was associated with ICDs in a large epidemiological study.³⁸

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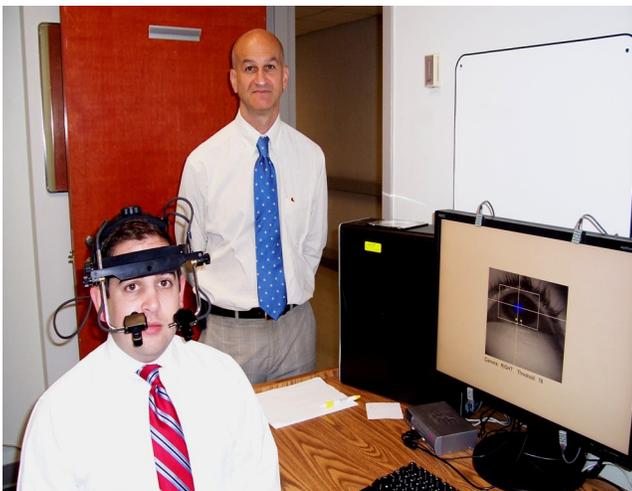
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Mark Baron, MD, Director, Southeast/Richmond PADRECC (R) and George Gitchel, PhD (L) candidate in biomedical engineering, in collaboration with Dr. **Paul Wetzel**, Associate Professor, Biomedical Engineering, Virginia Commonwealth University, are investigating the eye movements of patients with movement disorders. They have enrolled over 350 patients and control subjects in multi-faceted investigations of eye movements using sophisticated eye tracking equipment. Based on extensive testing, eye movement tracking provides a sensitive and specific means to differentiate Parkinson's disease (PD) from essential tremor and other movement disorders with close to 100% accuracy. Additional pursuits include assessing the utility of eye movement testing for detecting preclinical PD.

2010 National VA Parkinson's Disease Consortium Conference

Rebecca Martine, MSN, RN, PMHCNS, Chairperson
Dawn McHale, Program Specialist, National Coordinator
Philadelphia PADRECC, National VA PD Consortium

The success of the National VA PD Consortium centers around education, collaboration, and advocacy. We deem it critical that members are given the opportunity to meet face to face to interact and foster alliances and professional development. On September 8-10, 2010, the Consortium held its fourth national conference in San Francisco, California. Parkinson's Disease Research, Education and Clinical Center (PADRECC) staff and Directors from 32 Consortium Centers gathered for didactic lectures, case presentations, a poster session, and in-depth discussions on clinical roadblocks and methods to improve care. Representatives from the Parkinson non-profit community also attended, including the American Parkinson's Disease Foundation, the Parkinson Alliance, the Parkinson Action Network, and the Davis Phinney Foundation for Parkinson's. The VA Employee Education System served as co-sponsor, providing conference management and continuing medical education credits.

The meeting commenced with a welcome by the National Chief of Neurology, Dr. Robert Ruff. Dr. William Langston, guest keynote speaker from the Parkinson's Institute in Sunnyvale, California, followed with an informative update on the etiologies of Parkinson's disease. The remainder of the day consisted of presentations by PA-

DRECC and Consortium Center Directors. Topics included Agent Orange exposure, scientific advancements in neuroprotection, discussion of emerging therapies, and a briefing on Deep Brain Stimulation Cooperative Study #468. Conference planners dedicated the second day to logistical and clinical approaches for revolutionized care. The meeting concluded with a review of educational resources and final remarks by the Consortium Co-Chair, Dr. Jeff Bronstein, Director of the Southwest PADRECC.

Participants hailed the conference a success as it strengthened the mission of the Consortium Center Network. PADRECC and Consortium leaders continue to advocate for centralized support of this expanding program, which will allow for standardized care for Veterans with PD across the VA Healthcare System.

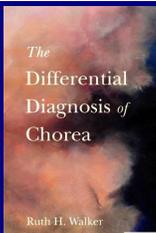


L to R: **Eugene Lai, MD, PhD**, Director and **Brenda Wade, AO**, of the Houston PADRECC, attended the San Francisco Consortium Conference along with **Catherine Gallagher, MD**, Consortium Director at the William S. Middleton Memorial VAMC, Madison, WI.

Featured Book

Ruth H. Walker, MD, PhD (Editor) Hardcover: 480 pages
Publisher: Oxford University Press, USA; 1 edition (October 4, 2010)

This book describes the latest clinical and etiological information regarding the causes of chorea. Experts working at the forefront of research address psychopathology, management, and pathophysiology of chorea. It is vital to make correct diagnoses and, with advances in molecular medicine, it is easier to identify new genetic causes of chorea and expand the phenotype of disorders. Contributors also discuss non-genetic etiologies, psychopathology, medication management, and pathophysiology of chorea. Ruth H. Walker, MD, PhD, obtained her medical degree from the University of Edinburgh, Scotland and went on to obtain a PhD in basal ganglia neuroanatomy at the University of Edinburgh and Massachusetts Institute of Technology. Following a neurology residency at New York University School of Medicine, Dr. Walker completed a fellowship in Movement Disorders at Mount Sinai School of Medicine. She is currently the Director of the Movement Disorders Clinic at the James J. Peters Veterans' Affairs Medical Center and is a member of the Department of Neurology at Mount Sinai School of Medicine. Dr. Walker's research focuses on the functional neuroanatomy of the basal ganglia and clinicopathologic correlations of neurogenetic disorders. Her particular clinical interests are the hyperkinetic disorders, especially the rarer inherited causes of chorea.



National VA Consortium Centers At a Glance: Updates

Bronx, NY

James J. Peters VAMC PADRECC Consortium Center

Director: Ruth H. Walker, MD, PhD

The James J. Peters VAMC PADRECC Consortium site in the Bronx, is planning the 8th Parkinson's Disease Awareness Day for May 2011. The Movement Disorders Clinic continues to provide specialized care to a large number of Veterans with PD and other movement disorders, including a recent referral for a service member still on active duty. Dr. Walker published her third paper regarding basic mechanisms of brain surgery for PD, seven papers from other collaborative projects, and edited a book (see Featured Book). In addition to contributing chapters on chorea to a number of texts, she served as guest editor for the Movement Disorder Society's Aug/Sept 2010 website entitled "A 2010 Update on the 'Other' Choric Disorders".

Las Vegas, NV

Las Vegas VAMC PADRECC Consortium Center

Director: Selina Parveen, MD,

The Las Vegas VAMC PADRECC Consortium Center provides clinical and pharmacological care for Veteran patients with Parkinson's disease and other movement disorders. Selecting patients appropriate for DBS, post surgical management, and providing Botulinum toxin injections are included in the range of services. The Center covers a wide area of Southern Nevada, Utah, and Arizona. Dr. Parveen, a former movement disorder fellow at the Philadelphia PADRECC, works closely with the Southwest PADRECC and was a member of the Task Force for the pilot study, "Improving Quality of Care in Parkinson's Disease: A Randomized Controlled Trial."

West Haven, CT

West Haven, CT VAMC PADRECC Consortium Center

Director: Diana Richardson, MD

The West Haven Parkinson's Disease (PD) Consortium promotes health and well being for Veteran PD patients. Currently, they offer an Annual PD Fair, an annual lecture series, and bimonthly noon hour classes. Topics include PD updates, medication management, nonmotor symptoms, and information on navigating the VA system. Class sessions alternate with a program using the Wii video game system. Participants work on motor skills, cognitive speed, and social interaction. An annual, multidisciplinary PD Symposium gathers experts from neurology, neuroscience, and other health care disciplines to educate patients, caregivers, and professionals. Clinical activities include weekly PD and Movement Disorder Clinics, Botox Clinic, DBS programming, and surgical referrals. Staff also participate in the Parkinson's Unity Walk in Central Park, New York City. The hospital affiliates with Yale School of Medicine/Yale New Haven Hospital and hosts training for residents and medical students. Within the Consortium, a special PD clinical rotation provides training for Geriatric Psychiatry Fellows who work closely with Dr. Diana Richardson.



West Haven, CT Parkinson Disease Consortium Center staff participate in the annual Parkinson's Unity Walk, Central Park, New York City.

Deep Brain Stimulation for Parkinson's Disease: Comparison of Two Targets – Globus Palladium and Subthalamic Nucleus

Frances M. Weaver, PhD on behalf of the CSP #468 Study Team

Earlier we reported on Phase I of a multi-site randomized trial in which persons with advanced Parkinson's disease were randomized to either best medical therapy (BMT) or deep brain stimulation (DBS) (The VA Parkinson Report, Vol 7, No 1, Fall 2009). Results found DBS superior to BMT in improving motor function and quality of life (QOL). However, the DBS group had many more serious adverse events (Weaver et al. JAMA 2009).

Phase II involved randomizing patients to one of two targets for DBS, the globus pallidum or the subthalamic nucleus. Patients initially randomized to BMT were offered the opportunity to continue on to DBS and were randomized to surgical target. We evaluated patients at baseline and 6 months, 12 months, 18 months, and 24 months following surgery. A subset of patients who enrolled early completed an additional assessment at 36 months. We conducted evaluations, including blinded assessments of motor function using the Unified Parkinson's Disease Rating Scale part III, at baseline, 6 and 24 and 36 months. Assessments included the entire UPDRS, the Parkinson's Disease Quality of Life (PDQ-39) scale, a motor diary, and a neurocognitive test battery. We closely monitored adverse events. This report includes the results of the 24-month assessment. (We are still examining 36-month data.)

We randomized 299 patients to surgical target (152 to pallidal stimulation and 147 to subthalamic stimulation). Thirteen patients died and 25 patients withdrew before completing the 24-month assessment. We based analyses on the intention-to-treat principle. At baseline, patients were similar on most characteristics. The mean age was 61.8 years, most were white, and the majority were men diagnosed with PD for over 11 years. Patients were moderately impaired on motor function with a UPDRS III score off medication of 42 (range 0-108, higher is worse).

The GPi and STN patients experienced similar improvements in motor function (off medication/on stimulation) over baseline at 24 months (improvement of 11.7 points for GPi and 10.8 points for STN; difference -1.1 points; 95% confidence interval, -4.2 to 2.1; $p=0.50$). Approximately 2/3rds of patients in both groups experienced at least a 5-point improvement in motor score over baseline (considered a minimal measurement of clinically im-

portant change in function) when on stimulation/off medication. Data from patients' self-reported motor diaries supported motor findings. Good motor function increased from 6.5 to 11.4 hours in the GPi group and from 7.0 to 11.0 hours in the STN group. Following DBS, Levodopa equivalents decreased significantly more in the STN than the GPi group. Quality of life, measured with the PDQ-39, improved on six of the subscales but worsened for the communication subscale 24 months following DBS in both groups. Neurocognitive function assessments showed slight worsening on all measures of function except processing speed, where the amount of decline was greater in the STN than the GPi group. Scores on the Beck Depression Inventory improved slightly for the GPi group and worsened slightly for the STN group over 24 months ($p=0.02$). Patients experienced a large number of serious adverse events ($n=335$), but there were no between group differences in the types of events experienced. Both groups had implant-site infections (12 in GPi, 11 in STN), and there were more injurious falls in the STN group (13) than the GPi group (5; $p=0.05$). There were 13 deaths over the 24-month follow-up period: 5 GPi and 8 STN patients. One STN death, an intracranial hemorrhage, occurred within 24 hours of surgery. One GPi patient committed suicide. As expected, voltage and average pulse widths were higher for the GPi than the STN group (3.95 vs. 3.16 $p<0.001$; 95.7 μsec vs. 75.9 μsec ; $p=0.001$). Frequencies were similar for both targets (168 Hz and 165 Hz).

This is the first large trial to compare bilateral DBS of the GPi and STN over time. Motor function improved similarly following DBS of the STN and GPi and was stable over 24 months. Quality of life improved following DBS on several domains, but patients experienced slight declines in neurocognitive function over time. Findings suggest that neurologists consider how DBS target affects other aspects of PD beyond motor function when considering the surgery site. For example, the difference in medication needs following DBS could be an important consideration for target choice. For those patients who experience side effects of medication, its reduction may positively influence QOL. However, reduction may not be desirable for those whom medication helps with other non-motor aspects of the disease. (cont bottom pg 7)

VA Benefits for Vietnam Veterans with Parkinson's Disease and Agent Orange Exposure

Lynn Klancher, MS, RN, Southeast (Richmond) PADRECC, Associate Director of Education

Vietnam-era veterans exposed to Agent Orange (AO) or other herbicides no longer have to prove a connection between their Parkinson's disease (PD) and military service to receive Department of Veteran Affairs (VA) benefits. The VA published final regulations recognizing the association of PD with Vietnam herbicide exposure www.publichealth.va.gov/exposures/agentorange/ on August 10, 2010 in the Federal Register. This regulation took effect on October 31, and the VA began paying disability benefits to qualifying Vietnam Veterans on November 1, 2010.

For Veterans diagnosed with PD who served in-country or inland waterways of Vietnam between January 9, 1962 and May 7, 1975, the VA now presumes that they were exposed to herbicides. Presumptive service-connection means that VA acknowledges a condition is service-connected even without direct evidence that it was incurred during military service, speeding up the benefits application process. However, Veterans must file claims to be considered for disability compensation. In addition to PD, ischemic heart disease and b-cell (or hairy-cell) leukemia were added to the list of recognized illnesses under VA's "presumption" rule.

Secretary of Veterans Affairs Eric K. Shinseki's decision to add PD as presumptive is based on the latest evidence provided in an independent study by the Institute of Medicine (IOM). *Veterans and Agent Orange: Update 2008* (released July 24, 2009) concluded that there is "suggestive but limited evidence that exposure to Agent Orange and other herbicides used during the Vietnam War is associated with an increased chance of developing PD." This is the 8th report in this series since Congress passed the Agent Orange Act of 1991. It acknowledged "the preponderance of epidemiologic evidence supports an association between herbicide exposure and PD." However, IOM expressed concerns about the lack of data relating PD incidence to exposure in Vietnam Veterans and recommended more studies.

The VA's final regulation does not include Parkinsonism and similar diseases. According to Update 2008, "PD must be distinguished from a variety of parkinsonian syndromes, including drug-induced parkinsonism and neurodegenerative diseases, such as multiple system atrophy.

Deep Brain Stimulation for Parkinson's Disease (cont from page 6)

Study investigators plan other analyses including examining the long term effect of DBS on outcomes using data from patients who completed the 36-month assessment and closer examination of neurocognitive data and non-motor outcomes. A longitudinal study to follow patients for up to 7 years post-DBS implant has just started (W. Marks, PI; CSP 468F) and will provide important data on the much longer effects of DBS.

which have parkinsonian features combined with other abnormalities." VA will reconsider this ruling if the IOM provides additional guidance in future reports.

With the anticipated rise in Agent Orange claims and to improve the benefits application process, VA introduced two new initiatives:

Fast Track Claims Processing System is an accelerated claims process dedicated to Vietnam Veterans diagnosed with PD, ischemic heart disease, and b-cell leukemia. To apply for disability compensation, Veterans should go to www.fasttrack.va.gov or call the Special Health Issues Helpline at 1-800-749-8387. Veterans who have already filed a claim for one of the three new conditions should contact VA Benefits at 1-800-827-1000.

Parkinson's Disease Disability Benefits Questionnaire (DBQ) – VA Form 21-0960C-1 (May 2010) is an online form about the Veteran's medical condition to be completed by the physician. Its purpose is to expedite the Fast Track Claims Process so Veterans can apply for disability benefits. The questionnaire can be found on the Agent Orange website:

www.publichealth.va.gov/exposures/agentorange/conditions/parkinsonsdisease.asp or at www.vba.va.gov/disabilityexams.

A variety of VA benefits are available for Vietnam Veterans with PD who were exposed to Agent Orange. Each type has a separate application process.

Disability Compensation Benefit is a monthly payment. Vietnam Veterans seeking disability compensation for PD should apply using VA's online Fast Track Claims Processing System.

Agent Orange Registry Health Examination is a free examination. Most VA medical facilities have an Agent Orange Desk or a Compensation and Pension (C&P) Office that can help Veterans sign up for the Registry and arrange an evaluation—or, ask the facility's Environmental Health Coordinator or Patient Care Advocate for guidance.

Health Care Benefits is medical treatment. Veterans who served in Vietnam or where Agent Orange was sprayed do not have to prove they were exposed to get VA health care benefits for exposure-related diseases. (cont bottom pg 8)

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Visit our Website: www.parkinsons.va.gov

Our special guest contributor, **Daniel Weintraub, MD**, is an Associate Professor of Psychiatry at the Hospital of the University of Pennsylvania and consults with both the PADRECC and MIRECC (Mental Illness Research, Education and Clinical Center) at Philadelphia Veterans Affairs Medical Center. His clinical research focuses on depression, impulse control disorders, cognition, and psychosis in PD, and he has published over 40 journal articles, reviews, and book chapters. He lectures extensively.

VA Benefits for Vietnam Veterans

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www.visn20.med.va.gov/Portland/PADRECC/Index.asp**Newsletter Editor**

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Survivors Benefits for surviving spouses, children, and dependent parents of AO exposed Veterans who died from a presumptive illness may be eligible for benefits.

Other Benefits offered by the VA, including education and training, vocational rehabilitation, home loan guaranties, life insurance, pension, burial benefits and more.

Many Veterans Service Organizations (VSOs) and Advocacy groups such Parkinson's Action Network and US Military Veterans with Parkinson's worked to get PD added to the presumptive Agent Orange list. These groups advocate for Veteran access to health care and benefits. Vietnam Veterans of America publishes a "*Self-Help Guide to Service-Connected Disability Compensation for Exposure to Agent Orange*." VSOs (some have offices at VA facilities) have representatives who can assist Veterans prepare and pursue claims. Examples of VSOs are: Disabled America Veterans (DAV), Veterans of Foreign Wars (VFW), and Military Order of the Purple Heart.

References

Veterans and Agent Orange: Update 2008, Institute of Medicine of the National Academies, The National Academies Press (Washington, DC, 2009), pp.515-516; pp. 526-527. Available online at www.iom.edu/Reports/2009/Veterans-and-Agent-Orange-Update-2008.aspx

Federal Register, The Daily Journal of the United States Government Website: www.federalregister.gov

VA News Releases (Office of Public Affairs Media Relations) available online at: www.va.gov. Click on "Media Room".

Resources

Agent Orange: Parkinson's Disease Website (Veterans Affairs, Office of Public Health & environmental Hazards)

www.publichealth.va.gov/exposures/agentorange/conditions/parkinsonsdisease.asp

Special Health Issues Toll-free Helpline: 1-800-749-8387

VA Benefits: 1-800-837-1000 or www.va.gov

VA Health Care Benefits: 1-877-222-8387

Fast Track Claims Processing System: www.fasttrack.va.gov

Survivors Benefits: www.vba.va.gov/survivors

Veteran Service Organizations (VSO) listing: www.va.gov/vso

US Military Veterans with Parkinson's (USMVP) Go to Yahoo groups at www.yahoo.com, and search "vets_parkinsons_agentorange"

Vietnam Veterans of America (VVA): www.vva.org

Parkinson's Action Network (PAN): www.parkinsonsaction.org