Giving The Villain The Slip: Removal Of Alphasynuclein

John H. Peacock, M.D., Ph.D.

GIVING THE VILLAIN THE SLIP: REMOVAL OF ALPHASYNUCLEIN

Many of you are weary of reading about the protein, Alphasynuclein, and at the mention of the word are thinking, "oh boy here we go again". The fact is that there is too much Alphasynuclein in a key nerve cell center in the brain, the substantia nigra. When this nucleus doesn’t work correctly, our mobility is impaired.

Ultimately the malfunction of substantia nigra neurons is accompanied by their death and the result is insufficient dopamine to allow normal movement. Hence the development of medication based on dopamine replenishment/augmentation, long the mainstay in treatment of Parkinson's disease. However, a new era may be dawning in medication management in Parkinson’s disease, i.e. treatment based on either limiting the production of alphasynuclein or hastening its removal.
Two drugs have been identified as potential candidates for removing *alphasynuclein*, nilotinib and phenylbutyrate. Both medications are FDA approved but for different diseases than Parkinson’s disease. Nilotinib is used in the treatment of chronic myeloid leukemia and phenylbutyrate in urea cycle disorders. Each drug was studied extensively in the laboratory prior to the introduction of its use in clinical trials. First the work of Dr. Charbel Moussa and his colleagues (1, 2) at Georgetown University Medical School will be discussed and then that of Dr.’s. Freed and Zhou (4, 5) from the University of Colorado School of Medicine.

These laboratories have focused on studies about clearance of accumulated intracellular proteins impairing normal cellular function of those cells. Sound familiar. *Alphasynuclein* is a normal protein that has accumulated to excess in substantia nigra neurons. The normal process to eliminate abnormal proteins is called “autophagy” meaning self-digestion. Dr. Moussa knew that some anti-cancer drugs such as nilotinib induced autophagy. Nilotinib also possessed an essential property for a Parkinson medication i.e. the capability for crossing the blood brain barrier and entering the central nervous system in order to be able to penetrate cells in the substantia nigra. He and his group carried out a detailed series of basic science studies to pave the way for a human clinical trial. The plan for the clinical trial was to investigate the effects of an escalating dose of nilotinib in triggering simultaneously an escalated release of *alphasynuclein* from the brain into blood.

The result of a small pilot trial was reported in October 2015 at the Society for Neuroscience Annual Meeting. This was an open label trial wherein patients knew what drug that they were receiving. The dosage of nilotinib was 150mg to 300mg daily compared to the dosage in chronic myeloid leukemia of 800mg to 1200mg daily. Of the 12 patients, 10 had significant improvement in motor and cognitive function. One wheelchair-bound patient was able to walk and 4 patients regained the ability to talk.

Next is the work of Curt Freed MD and Wenbo Zhou PhD. Their group reported at the same 2015 Annual Meeting of the Society for Neuroscience that phenylbutyrate also mobilized the transfer of *alphasynuclein* from the brain to the bloodstream where that protein could be eliminated. Their clinical trial was also based on extensive laboratory studies. Those studies had determined that phenylbutyrate activated a neuroprotective gene, DJ-1. The action of DJ-1 was to promote the clearance of waste proteins in the cell. In experimental work, phenylbutyrate increased *alphasynuclein* in the blood by 100% compared to controls.

In order to see if phenylbutyrate had a similar clinical effect, a trial was designed to give the drug for three weeks to 20 people with newly diagnosed Parkinson’s disease and to 20 age-matched subjects without the disease. The result was an increase in the level of *alphasynuclein* in the blood of all 40 subjects ranging from 50 to 150 per cent of baseline values. The authors concluded that phenylbutyrate had a neuroprotective effect by its action of removal of *alphasynuclein* from brain into the blood.

Both groups emphasized that a double-blind, placebo-controlled trial in newly diagnosed Parkinson patients was essential to prove if phenylbutyrate or nilotinib can stop the progression of Parkinson’s disease.
Bibliography


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Fax:  775-784-7951(new number)
Internet Site:  www.reno.va.gov/parkinsons/parkinsons.asp
Intranet Site:  www.va.reno.va.gov/parkinsons/parkinsons.asp
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Website:  www.apdaparkinson.org

Disclaimer:
The material in this newsletter is presented solely for the information of the reader. It is not intended for treatment purposes, but rather for discussion with the patient’s physician.
Veteran Update

VA makes changes to Veterans Choice Program

Changes remove barriers and expand access to care

Posted on Tuesday, December 1, 2015 11:27 am
VA today announced a number of changes to make participation in the Veterans Choice Program easier and more convenient for Veterans who need to use it. The move, which streamlines eligibility requirements, follows feedback from Veterans along with organizations working on their behalf.

“As we implement the Veterans Choice Program, we are learning from our stakeholders what works and what needs to be refined,” said VA Secretary Bob McDonald. “It is our goal to do all that we can to remove barriers that separate Veterans from the care they deserve.” To date, more than 400,000 medical appointments have been scheduled since the Veterans Choice Program went into effect on November 5, 2014.

Under the old policy, a Veteran was eligible for the Veterans Choice Program if he or she met the following criteria:

- Enrolled in VA health care by 8/1/14 or able to enroll as a combat Veteran to be eligible for the Veterans Choice Program;
- Experienced unusual or excessive burden eligibility determined by geographical challenges, environmental factors or a medical condition impacting the Veteran’s ability to travel;
- Determined eligible based on the Veteran’s current residence being more than 40 miles driving distance from the closest VA medical facility.

Under the updated eligibility requirements, a Veteran is eligible for the Veterans Choice Program if he or she is enrolled in the VA health care system and meets at least one of the following criteria:

- Told by his or her local VA medical facility that they will not be able to schedule an appointment for care within 30 days of the date the Veteran’s physician determines he/she needs to be seen or within 30 days of the date the Veteran wishes to be seen if there is no specific date from his or her physician;
- Lives more than 40 miles driving distance from the closest VA medical facility with a full-time primary care physician;
- Needs to travel by air, boat or ferry to the VA medical facility closest to his/her home;
- Faces an unusual or excessive burden in traveling to the closest VA medical facility based on geographic challenges, environmental factors, a medical condition, the nature or simplicity or frequency of the care needed and whether an attendant is needed. Staff at the Veteran’s local VA medical facility will work with him or her to determine if the Veteran is eligible for any of these reasons; or
- Lives in a State or Territory without a full-service VA medical facility which includes: Alaska, Hawaii, New Hampshire (Note: this excludes New Hampshire Veterans who live within 20 miles of the White River Junction VAMC) and the United States Territories (excluding Puerto Rico, which has a full service VA medical facility).

Veterans seeking to use the Veterans Choice Program or wanting to know more about it, can call 1-866-606-8198 to confirm their eligibility and to schedule an appointment. For more details about the Veterans Choice Program and VA’s progress, visit: www.va.gov/opa/choiceact.

VA to Launch Vets.gov

According to Military.com, the Department of Veterans Affairs (VA) will launch a new website, Vets.gov on Veterans Day, November 11. The new website will consolidate the approximately 1,000 websites the department now manages. The portal is designed to help veterans find and apply for benefits and services on one website rather than go through the maze of VA-managed websites that exist now. The new website will have content but not the single, secure sign-on function that veterans will need to provide access to all other departmental sites. That capability is expected to
take another year. A Request for Information for technical support for the new Vets.gov website is available on the FedBizOpps.gov website.

RESEARCH OPPORTUNITIES

If you are interested in current research regarding Parkinson’s disease, please visit one or all of the sites listed below.

Fox Trial Finder [www.foxtrialfinder.org](http://www.foxtrialfinder.org)

Clinical Trials [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov)

Center Watch [www.centerwatch.com](http://www.centerwatch.com)

What's New??

A Breakdown Product of Aspirin: A new study finds that a component of aspirin binds to an enzyme called GAPDH, which is believed to play a major role in neurodegenerative diseases, including Alzheimer’s, Parkinson’s and Huntington’s diseases.

Researchers at the Boyce Thompson Institute and John Hopkins University discovered that salicylic acid, the primary breakdown product of aspirin, binds to GAPDH, thereby stopping it from moving into a cell’s nucleus, where it can trigger the cell’s death. The study, which appears in the journal PLoS ONE, also suggests that derivatives of salicylic acid may hold promise for treating multiple neurodegenerative diseases. Journal reference PLoS ONE (http://medicalxpress.com/journal/plos-one/).
### January 26 2016: Spotlight on Treatment Advances Webinar

Join the American Parkinson Disease Association for a phone and online event to hear expert perspectives on the latest treatment advances for Parkinson's. This program is designed to help people with Parkinson's, family members and care partners. Register online.

**Email addresses:** Please call or email me with your current email address. Did you know that you can receive the newsletter via email and save APDA the fee for postage? Susan.gulas@va.gov or 775-328-1715

### Northern Nevada Support Group

Contact information: 775-328-1715 or 888-838-6256 ext. 1715  
Website: [www.reno.va.gov/parkinsons/parkinsons.asp](http://www.reno.va.gov/parkinsons/parkinsons.asp)

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<th>Spanish Springs</th>
<th>January 6</th>
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<tr>
<td>First Wednesday</td>
<td>Cori Eden Hospice</td>
<td>Sherilyn Elliott Gentiva</td>
<td>Caregiver Support Group</td>
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<td>10:00 am</td>
<td>Pain Management</td>
<td>LSVT BIG</td>
<td>Susan Gulas/Jessica Helgren</td>
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<td></td>
<td>Cascades of the Sierra, 275 Neighborhood Way, 2nd floor Great Room</td>
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<tr>
<td>Second Tuesday</td>
<td>Caregivers Only support group</td>
<td>Group Members</td>
<td>Byron Parks LCSW</td>
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<tr>
<td>2:00 pm</td>
<td>Susan Gulas</td>
<td>Group Discussion</td>
<td>Caregiver Support Program</td>
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<td>Carson City Senior Center, 911 Beverly Drive, lower level Tahoe Room</td>
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<td>Second Friday</td>
<td>Group Members</td>
<td>Nancy Ryman</td>
<td>Kim Mason RD</td>
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<td>Group Discussion</td>
<td>Speak Loud</td>
<td>Nutrition &amp; PD</td>
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<td>Atria at Summit Ridge, 4880 Summit Ridge Drive, Main Dining Room</td>
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<td>Reno</td>
<td>January 19</td>
<td>February 16</td>
<td>March 15</td>
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<td>Third Tuesday</td>
<td>Bonnie Deach ST</td>
<td>Valerie Williams PhD</td>
<td>Group Members</td>
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<td>5:00pm</td>
<td>LSVT?</td>
<td>Memory &amp; PD</td>
<td>Group Discussion</td>
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<td>Veterans Administration Medical Center, 975 Kirman Ave, Meet in Kirman Lobby</td>
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<td>TBA</td>
<td>Group Members</td>
<td>Jeffrey Johnson</td>
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<td>2:30 pm</td>
<td>Group Discussion</td>
<td>Equipment &amp; PD</td>
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<tr>
<td>Morning Star Senior Living, 2360 Wingfield Hills Drive, Sparks, NV, 2nd floor</td>
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<td>Medication in PD</td>
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<td>New Year's Day</td>
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<td>Dr. Peacock</td>
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<td>Group Discussion</td>
<td>Update on PD</td>
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**Bowling Group:**
Join the Parkinson’s disease bowling group each Thursday @11:30am at High Sierra Lanes on South Virginia & Moana Street. Please call the APDA I&R Center @775-328-1715 for further information.

**VAMC Los Angeles PADRECC Veterans Telephonic Support Group**
Join us ~2 min. prior to the hour on the 2nd Tuesday of each month
1-800-767-1750, Access code 54321#
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Veterans Affairs-Greater Los Angeles Healthcare System
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