

DEPARTMENT OF VETERAN AFFAIRS AND AMERICAN PARKINSON DISEASE ASSOCIATION, INC.

Summer 2015

PARKINSON PRESS NEWSLETTER

Consider the environment. Print newsletter as necessary.

INTERPLAY OF MARIJUANA, ENDOCANNABINOIDS, AND LEVODOPA IN PARKINSON'S DISEASE

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Introduction. Medical marijuana (cannabis) is a hotly-debated and actively discussed topic. In my experience, individuals with Parkinson's disease broach the subject tentatively compared to those with seizures, multiple sclerosis, and pain who may have even taken action and purchased cannabis and/or cannabis products. This "well-advised caution" of the Parkinson group may stem from the conservative and law-abiding personality make-up of those with Parkinson's disease (1). Why well-advised? Please read on while keeping in mind that new data and new methods for acquiring and evaluating data are ongoing. Also keep in mind that the effects of marijuana use can be measured in terms of both function and of form.

Effects on Executive Function. One major study (2) found effects of chronic marijuana use on six aspects of executive function. This study is accessible on-line and worth your review. These aspects of executive function included attention and concentration, decision-making and risk-taking, inhibition and impulsivity, working memory, and verbal

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fluency. Consider the hypothetical case of a CEO who had mild impairment of executive function and the consequences that would follow for his company's mission, short and long-term goal planning, budgeting, unanticipated problems, self-evaluation, etcetera and etcetera.

Effects on Biochemical Function and on Neuroanatomy. A recent report examined the effect of cannabis addiction on dopamine release. Kate Johnson, a writer for Medscape Medical News, called attention to an abstract presented at the 2015 annual meeting of the Society of Nuclear Medicine and Molecular Imaging (3). This set of experiments measured the release of dopamine, in particular to dopamine that binds to D3 receptors (4).

This work under discussion compared eleven heavy cannabis users with 12 control subjects who did not use cannabis. The average age was 28 years. Cannabis usage began about age 16 and continued daily for most of the group. Cannabis users had no other medical or psychiatric conditions and were addicted only to cannabis. There was no history of alcohol or other drug use including nicotine in their profiles.

The study was conducted as follows. To prepare subjects for the experiment, there was abstinence from cannabis for 5-7 days with the intent of resetting the brain level of cannabis to zero. Next, a baseline PET scan to localize the baseline or non-stimulated D3-dopamine release was conducted. Finally the experiment could start. Subjects were given an oral challenge of amphetamine medication which is known to trigger dopamine release from substantia nigra neurons.

The results were statistically significant. Compared to the baseline level of the probe there was 24.9% release in controls and 18.4% release in cannabis users. This difference of 6.5% may not seem large, but it correlated with an impairment of working memory and learning in the cannabis users.

A report a year earlier showed that even casual marijuana use changed the brain. This study from Northwestern University and Massachusetts General Hospital in Boston reported in the *Journal of Neuroscience* (5) that recreational use of marijuana altered the brain. In forty young adults who smoked marijuana once a week, MRIs of their brains showed that the *nucleus accumbens* had increased in size and altered its shape. The *nucleus accumbens* is a brain region involved in reward processing and additionally has a role in memory and motivation.

However, to be fair and balanced, a third report (6) found that daily marijuana use was not associated with brain changes in measurements from adolescents and adults. This work compared brain structures in 29 chronic marijuana users and 29 non-users using a detailed voxel-based morphometric analysis (7). Additionally, these individuals were matched according to alcohol use in order to minimize the role of alcohol on brain structures of marijuana users.

Prior Review of Marijuana for Parkinson Patients. Dr. Michael Okun is the Medical Director for the National Parkinson Foundation. He wrote a detailed review on this subject for the National Parkinson Foundation (8). This report is available on line, and is worthwhile to read. Dr. Okun's statement about the position of the AAN is quoted here. "A recent report from the guideline development subcommittee of the American Academy of

Neurology (AAN) tackled the evidence-base supporting the use of marijuana for neurological disorders. Spasticity, central pain syndromes and bladder dysfunction (disorders not including Parkinson's disease) seemed to be improved with marijuana use. The few available studies revealed that marijuana was not helpful in Parkinson's disease related tremor or levodopa-induced dyskinesias. The report was careful to outline the risks and the benefits of medical marijuana, and it recommended education and counseling for anyone considering this option. The risk of serious psychopathologic effects (hallucinations, etc.) was cited to be about 1%."

Endocannabinoids, Anandamide, and Endocannabinoid Receptors. The brain is able to respond to cannabis because there are receptor molecules for tetrahydrocannabinol (THC) on nerve cells. Tetrahydrocannabinol is the principal psychoactive component of cannabis. If the brain has already synthesized receptors for THC, it is not surprising to learn that the brain also synthesizes an internal form of THC called anandamide. The first part of the word means "joy, bliss, delight" in Sanskrit (Wikipedia). Paired together, anandamide and anandamide receptors comprise the endocannabinoid system.

Why discuss endocannabinoids? The brain structures important in Parkinson's disease (substantia nigra and its neighbors) are densely supplied with endocannabinoid receptors. Activation of these receptors in the putamen nucleus, a first target of substantia nigra neurons, may counteract the slowness of Parkinson's disease. In a sense the putamen is analogous to a "muscle car" that is waiting to be driven and Pharmaceutical companies are looking for the driver. The use of cannabis itself has potentially serious consequences as discussed above and is not a candidate to be the driver. However, as some of you already know, the endocannabinoid system is ramped up by exercise in a similar way to the endorphins—internal opiate system. Thus it is reasonable to speculate that the neuroprotective effect of exercise for Parkinson's disease may relate to the boost in both endogenous opiates and endogenous cannabinoids.

REFERENCES

1. Paulson GW and Dadmehr N. Is there a premorbid personality typical for Parkinson's disease? *Neurology* 199;41(suppl 2):7376.
2. Crean RD, Crane NA, Mason BJ. An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. *J Addict Med.* 2011 March 1; 5(1):1-8.
3. Abi-Dargham and Weinstein, J. Cannabis harms brain structures. Society of Nuclear Medicine and Molecular Imaging 2015 Annual Meeting.
4. For review, remember that tablets with levodopa are ingested and absorbed into the bloodstream and then moved to the brain. The levodopa is converted to dopamine for uptake into nerve cells, particularly the *substantia nigra*. Nigral neurons are able to release dopamine when stimulated and that release affects the next nerve cell in the circuit. The way that dopamine carries out this action is by interaction with a receptor molecule like a "doorknob". There are at least three doorknobs called the D1, D2, and D3 receptors on target neurons.

5. Gilman JM, Kuster JK, Lee S, Lee MJ, Kim BW, Makris N, et al. Cannabis use is quantitatively associated with nucleus accumbens and amygdala abnormalities in young adult recreational users. *J Neurosci*. 2014 Apr 34(16):5529-38.
6. Weiland BJ, Thayer RE, Depue BE, Sabbineni A, Bryan, AD, and Hutchison, KE. Daily marijuana use is not associated with brain morphometric measures in adolescents or adults. *Neurosci*. 2015 Jan 35(4): 1505-1512.
7. Voxel-based morphometry is a technique used for accurate comparison of images of the same brain region in different brains.
8. Okun MS, Everything you need to know about medical marijuana and Parkinson's disease. Archives National Parkinson Foundation.

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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 Expands Benefits:

The Department of Veterans Affairs (VA) has published a new regulation that expands eligibility for some benefits for a select group of Air Force and Air Force Reserve veterans who were exposed to the herbicide Agent Orange through regular and repeated contact with contaminated C-123 aircraft that had been used in Vietnam as part of Operation Ranch Hand. This regulation is an interim final rule so VA can immediately begin providing benefits to eligible Airmen who submit a disability compensation claim for any of the 14 medical conditions that have been determined by officials to be related to exposure to Agent Orange. The decision to expand benefits was made following publication of a 2015 report, "[Post-Vietnam Dioxin Exposure in Agent Orange-Contaminated C-123 Aircraft](#)," by the National Academy of Sciences Institute of Medicine. The interim final rule can be found on the [Federal Register](#). Individuals with specific benefit questions related to herbicide exposure on C-123s may call VA's special C-123 hotline at 800-749-8387 (available 8 a.m. - 9 p.m. EST) or e-mail VSCC123.VAVBASPL@va.gov.

State Veterans Benefits, from Military.com:

Everyone knows about the federal benefits available to veterans, but did you know many states also offer great benefits to their veterans? State benefits range from free college and employment resources to free hunting and fishing licenses. Most states also offer tax breaks for their veterans and specialized license plates, some states even provide their veterans with cash bonuses just for serving in the military. [Select your state to view a list of Veteran Benefits.](#)

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

Clinical Trials www.ClinicalTrials.gov

Center Watch www.centerwatch.com

What's New???

American Parkinson Disease Association and Davis Phinney Foundation Join Parkinson's Action Network Unified Partners Program:

PAN's Unified Partners Program allows Parkinson's-related organizations to formally support PAN's work and strengthen the unified voice for better treatments and a cure for Parkinson's disease. "APDA is truly excited as we join forces with PAN to affect policy changes that will directly impact and improve the quality of life for those coping with Parkinson's disease," said Leslie A. Chambers, APDA President & CEO. "We are proud of our vast nationwide grassroots network and confident that our collective resources now as a PAN Unified Partner will play an important role in the legislative process while continuing to live out our mission to *Ease the Burden – Find the Cure* for millions of people impacted each day."

Inhaled Levodopa Convenient for Parkinson 'Off' Episodes: A novel inhaled form of levodopa provides relief of "off" episodes for patients with Parkinson's disease (PD) and does not increase the amount of "on" time with dyskinesia, a recent study shows.

The drug, CVT-301 (Acorda Therapeutics) addresses the problem of "delayed 'on' or unreliable onset of levodopa effects", lead author Peter LeWitt, MD, MMed Sc, director of the Parkinson's Disease and Movement Disorders Program at Henry Ford Hospital in West Bloomfield, Michigan, and professor of neurology at Wayne State University School of Medicine in Detroit, Michigan, told Medscape Medical News.

"The route of administration by inhalation is rapid, less than 10 minutes in some of the reported data, and also the reliability is quite good," he said. Oral medications can take up to 45 minutes before having an effect.

The phase 2 trial was reported at the International Parkinson and Movement Disorder Society (MDS) 19th International Congress. Dr. Maurizio Facheris, senior associate director for research programs at the Michael J. Fox Foundation for Parkinson's Research, reiterated De Witt's caution that the drug is only levodopa, so it is for people already taking levodopa/carbidopa. "Otherwise, it will be inefficacious because without carbidopa the drug will be destroyed in the periphery without reaching the brain." To read the full article: http://www.medscape.com/viewarticle/846740_print
Citation: "Inhaled Levopda Convenient for Parkinson 'Off' Episodes. Medscape, Jun 19, 2015

Upcoming Educational Events

XXII World Congress of Neurology, October 31-November 5, 2015, Santiago, Chile. For further information, please contact Kenes International-WCN, World_Congress_of_Neurology@mail.vresp.com

Northern Nevada Support Group

Contact information: 775-328-1715 or 888-838-6256 ext. 1715

Website: www.reno.va.gov/parkinsons/parkinsons.asp

Spanish Springs	July 1	August 5	September 2
First Wednesday	Mary Brock	Group Members	Lori Waldorf
10:00 am	What is Respite?	Group Discussion	Caregiver Support Group
Cascades of the Sierra, 275 Neighborhood Way, 2 nd floor Great Room			

Carson City	July 14	August 11	September 8
Second Tuesday	Rachel Carr	Paula Gessler PT	Cindy Chorjel OTR
2:00 pm	Medication Therapy Management	Exercise in PD	Equipment Needs in PD
Carson City Senior Center, 911 Beverly Drive, lower level Tahoe Room			

Reno	July 10	August 14	September 11
Second Friday	Group Members	Sandy Wilson PT	Mary Brock
2:00 pm	Group Discussion	LSVT "BIG"	What is Respite?
Atria at Summit Ridge, 4880 Summit Ridge Drive, Main Dining Room			

Reno	July 21	August 18	September 15
Third Tuesday	Group Members	Valerie & Ericka	Nancy Ryman
5:00pm	Group Discussion	Cognitive Decline in PD	Speech & PD
Veterans Administration Medical Center, 975 Kirman Ave, Meet in Kirman Lobby			

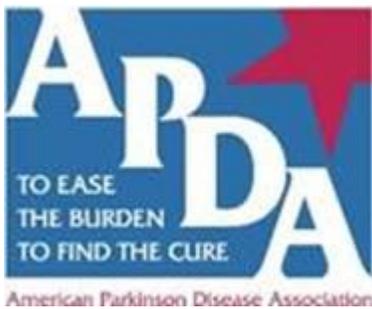
Sparks	July 23	August 27	September 24
Fourth Thursday	Byron Parks SW	Group Discussion	Jessica & Dani Pharmacy Residents
2:30 pm	Caregiver Support Program	Group Members	Medications in PD
Morning Star Senior Living, 2360 Wingfield Hills Drive, Sparks, NV, 2 nd floor			

Reno	July 16	August 20	September 17
Third Thursday	Group Members	Group Members	Group Members
2:00pm	Group Discussion	Group Discussion	Group Discussion
Five Star Premier Residences of Reno, 3201 Plumas Street, Reno, NV			

Elko-Las Vegas-Reno	July 3	August 7	September 4
First Friday	Cancelled	Kim Mason RD	Hope Williams, Librarian
1:00 pm	July 4 th Holiday	Nutrition & PD	NV Talking Books
University of Nevada Cooperative Extension, 4955 Energy Way. Reno, NV University of Nevada Elko, 701 Walnut Street, Elko, NV			

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.



Parkinson’s Day at the Aces Ball Park is August 30, 2015. Meet outside the Ball Park at the American Parkinson Disease Association table to exchange your voucher for a ticket. The game starts a 1:05pm and the Aces are playing Memphis. Gates will open at 12:05pm. Make sure you arrive by 11:15 to exchange your voucher for a ticket.

Please contact Susan Gulas at 775-328-1715 for a \$12.00 voucher for the game. Proceeds from our ticket sales will benefit Parkinson’s disease. We have reserved handicap seating in right field.

I’ll see you at the Ballpark!