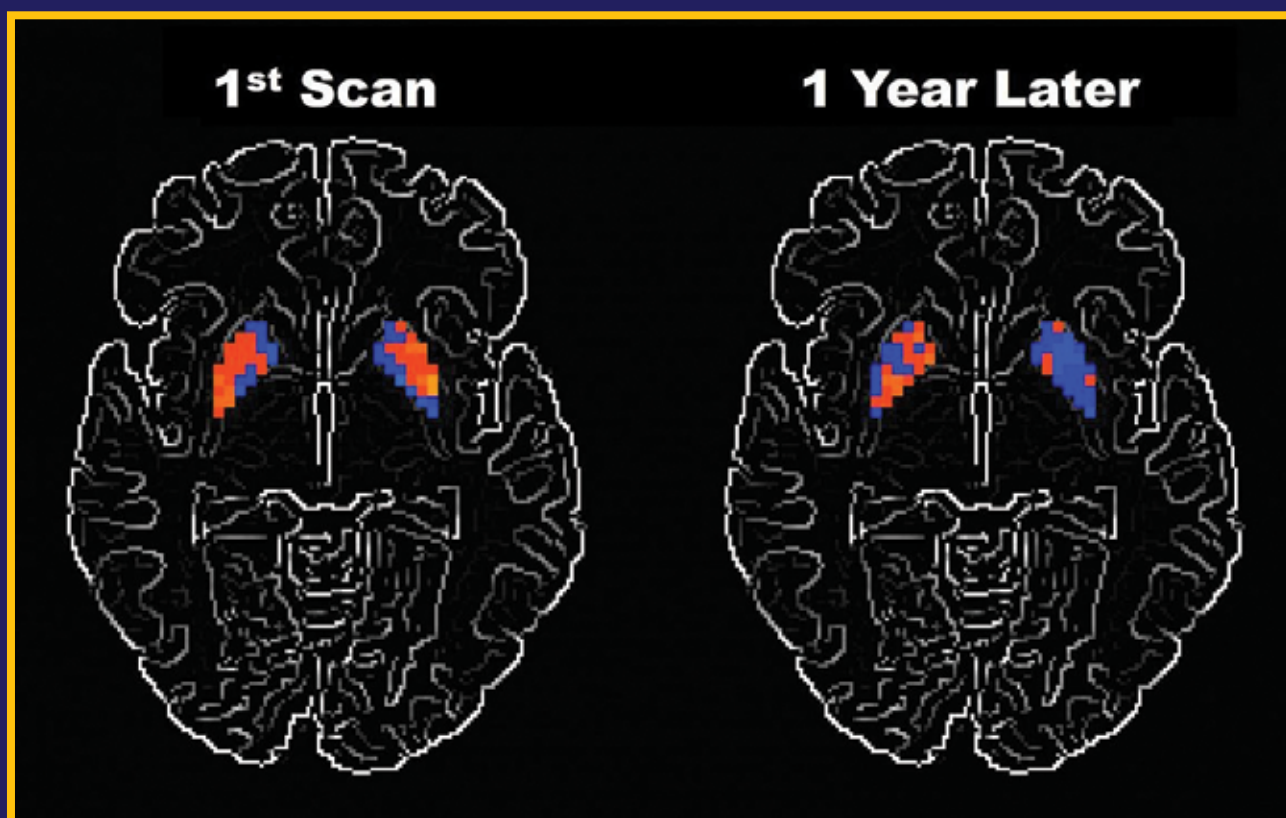


MEETING THE CHALLENGES OF PARKINSON'S DISEASE IN THE DEPARTMENT OF VETERANS AFFAIRS



Available to VA* and DOD/TRICARE

Orally inhaled levodopa

A BRIDGE BETWEEN DOSESSM

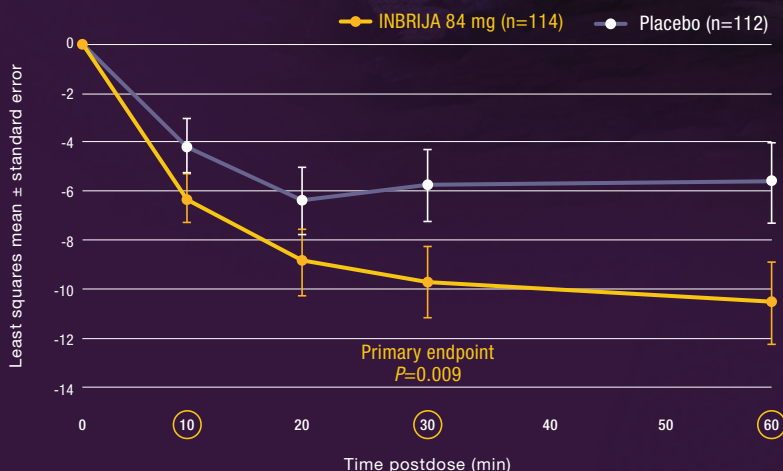
of carbidopa/levodopa



INBRIJATM is indicated for intermittent treatment of OFF episodes in patients with Parkinson's disease (PD) treated with carbidopa/levodopa (CD/LD).

SPANSM-PD — Study Results at Week 12

Unified Parkinson's Disease Rating Scale (UPDRS) Part III motor score change from 0-60 minutes postdose



Returned to ON and sustained ON through 60 minutes:
58% for INBRIJA vs 36% for placebo ($P=0.003$)

*Available in VA pursuant to an approved non-formulary request.

See following pages for additional Clinical Trial Information.

SELECTED IMPORTANT SAFETY INFORMATION

- INBRIJA is contraindicated in patients taking or who have recently taken (within 2 weeks) nonselective monoamine oxidase (MAO) inhibitors (e.g., phenelzine and tranylcypromine) due to risk of hypertension. Discontinue use of nonselective MAO inhibitors at least 2 weeks prior to initiating INBRIJA.
- INBRIJA is not recommended in patients with asthma, COPD, or other chronic underlying lung disease because of the risk of bronchospasm.
- The most common adverse reactions ($\geq 5\%$ and $>$ placebo) were cough (15% vs 2%), upper respiratory tract infection (6% vs 3%), nausea (5% vs 3%), and sputum discolored (5% vs 0%).
- Additional respiratory-related adverse reactions ($\geq 2\%$ and $>$ placebo): nasopharyngitis (3% vs 2%) and nasal discharge discoloration, oropharyngeal pain, and bronchitis/pneumonia (each 2% vs 0%).

Please see additional Important
Safety Information on next page.

Inbrija™

(levodopa inhalation powder)
42 mg capsules

FOR PATIENTS WITH PARKINSON'S ON CD/LD

The only orally inhaled levodopa for on-demand use to treat OFF periods



Onset of action
as early as
10 minutes postdose



Significant improvement
in motor function at
30 minutes postdose



Continuation of effect
at 60 minutes postdose

99.8%

of 629 patients in 2 clinical trials demonstrated the ability to self-administer INBRIJA while in an OFF period after instruction¹

SELECTED IMPORTANT SAFETY INFORMATION

- Patients treated with levodopa, the active ingredient in INBRIJA, have reported falling asleep during activities of daily living, including operation of motor vehicles, which sometimes resulted in accidents. Many patients reported somnolence but some reported no warning signs (sleep attack). This may occur more than a year after initiating treatment. Reassess patients for drowsiness/sleepiness including occurrence during specific activities. Advise patients of potential for drowsiness and ask about factors that may increase this risk (e.g., sedating medications, sleep disorders).
- Consider discontinuing INBRIJA in patients who report significant daytime sleepiness or falling asleep during activities that require active participation. If continuing INBRIJA, advise patients not to drive and to avoid activities that may result in harm. There is insufficient information that dose reduction will eliminate episodes of falling asleep during activities of daily living.
- Neuroleptic malignant syndrome-like symptoms (e.g., elevated temperature, muscular rigidity, altered consciousness, autonomic instability) have been reported with rapid dose reduction, withdrawal of, or changes in dopaminergic therapy.
- Hallucinations (with or without confusion, insomnia, and excessive dreaming) may occur and may respond to reducing levodopa therapy. Abnormal thinking and behavior may present with paranoid ideation, delusions, hallucinations, confusion, psychotic-like behavior, disorientation, aggressive behavior, agitation, and delirium.
- INBRIJA should ordinarily not be used in patients with major psychotic disorder due to risk of exacerbating psychosis. Dopamine antagonists used to treat psychosis may exacerbate symptoms of PD and may decrease INBRIJA efficacy.

Please see additional Important Safety Information on next page.



**Breathe in,
move ONSM**

Capsules to be kept in blisters until ready to use.

For more information, visit
www.inbrija-hcp.com

ADDITIONAL CLINICAL TRIAL INFORMATION

SPANSM-PD: a 12-week randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of INBRIJA.

Patients were 38-82 years of age (mean, 63.0 yr), predominantly male (75%) and white (95%).¹

At baseline, patients had:

- ≥2 hours per day of OFF time
- CD/LD regimen not exceeding 1600 mg of levodopa per day
- Mean UPDRS Part III motor scores in ON state at screening: 14.9 for INBRIJA and 16.1 for placebo

DOSING

- One dose (84 mg) = two 42-mg capsules
 - For oral inhalation only; capsules must not be swallowed as the intended effect will not be obtained
- No more than 1 dose per OFF period
- May be taken as needed up to a maximum of 5x per day when symptoms start to return
 - Average number of doses in SPAN-PD: ~2 per day
- Effective only in combination with CD/LD
- INBRIJA capsules are only for use with the INBRIJA inhaler



LEARN MORE AT

www.inbrija-hcp.com

ADDITIONAL IMPORTANT SAFETY INFORMATION

- Patients on medications that increase central dopaminergic tone such as INBRIJA can experience intense urges to gamble or spend money, increased sexual urges, binge eating, and/or other intense urges, and inability to control them. In some cases, these urges stopped with dose reduction or medication discontinuation. Since some patients may not recognize these behaviors as abnormal, ask patients or their caregivers about development of new or increased urges and consider stopping INBRIJA if this occurs.
- INBRIJA may cause or exacerbate dyskinesias. If troublesome dyskinesias occur, consider stopping INBRIJA or adjusting other PD medications.
- Monitor patients with glaucoma for increased intraocular pressure.
- Abnormalities in laboratory tests may include elevations of liver function tests (e.g., alkaline phosphatase, AST, ALT, lactic dehydrogenase, bilirubin), blood urea nitrogen, hemolytic anemia, and positive direct antibody test. Increased levels of catecholamines and their metabolites in plasma and urine may result in false-positive results suggesting pheochromocytoma.
- Use of selective MAO-B inhibitors with INBRIJA may be associated with orthostatic hypotension.
- Monitor patients taking these drugs concurrently.
- Dopamine D2 receptor antagonists (e.g., phenothiazines, butyrophenones, risperidone, metoclopramide) and isoniazid may reduce levodopa efficacy; monitor for worsening symptoms.
- Iron salts or multivitamins with iron salts may reduce levodopa bioavailability.
- INBRIJA should be used during pregnancy/nursing only if potential benefit justifies potential risk. There are no adequate data on INBRIJA in pregnant women or breastfed infants. Animal data shows carbidopa/levodopa is developmentally toxic (including teratogenicity). Levodopa may affect milk production, interfering with lactation. Levodopa has been detected in human milk.
- Safety and effectiveness in pediatric patients have not been established.
- Geriatric patients (n=56) experienced more of the following adverse reactions than patients <65 (n=58): cough (25% vs 5%), upper respiratory tract infection (11% vs 2%), nausea (7% vs 3%), vomiting (4% vs 2%), pain in extremities (4% vs 0%), and discolored nasal discharge (4% vs 0%).

Please see adjacent Brief Summary of Full Prescribing Information.

Reference: 1. Data on file. Acorda Therapeutics.

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ACORDA
THERAPEUTICS

INBRIJATM (levodopa inhalation powder)

Brief Summary of Full Prescribing Information

4. CONTRAINDICATIONS

INBRIJA is contraindicated in patients currently taking a nonselective monoamine oxidase (MAO) inhibitor (e.g., phenelzine and tranylcypromine) or who have recently (within 2 weeks) taken a nonselective MAO inhibitor. Hypertension can occur if these drugs are used concurrently [see *Drug Interactions* (7.1)].

5. WARNINGS AND PRECAUTIONS

5.1. Falling Asleep During Activities of Daily Living and Somnolence

Patients treated with levodopa, the active ingredient in INBRIJA, have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes resulted in accidents. Although many of these patients reported somnolence, some reported no warning signs (sleep attack) and believed that they were alert immediately prior to the event. Some of these events have been reported more than 1 year after the initiation of treatment.

Prescribers should reassess patients for drowsiness or sleepiness. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities.

Before initiating treatment with INBRIJA, advise patients about the potential to develop drowsiness and ask about factors that may increase the risk for somnolence with INBRIJA such as the concomitant use of sedating medications and the presence of sleep disorders. Consider discontinuing INBRIJA in patients who report significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.).

If treatment with INBRIJA continues, patients should be advised not to drive and to avoid other activities that might result in harm if the patients become somnolent. There is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

5.2. Withdrawal-Emergent Hyperpyrexia and Confusion

A symptom complex that resembles neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in dopaminergic therapy.

5.3. Hallucinations/Psychosis

In placebo-controlled trials, hallucinations were reported in less than 2% of patients treated with INBRIJA. Hallucinations may be responsive to reducing levodopa therapy. Hallucinations may be accompanied by confusion, insomnia, and excessive dreaming. Abnormal thinking and behavior may present with one or more symptoms, including paranoid ideation, delusions, hallucinations, confusion, psychotic-like behavior, disorientation, aggressive behavior, agitation, and delirium.

Because of the risk of exacerbating psychosis, patients with a major psychotic disorder should ordinarily not be treated with INBRIJA. In addition, medications that antagonize the effects of dopamine used to treat psychosis may exacerbate the symptoms of Parkinson's disease and may decrease the effectiveness of INBRIJA [see *Drug Interactions* (7.2)].

5.4. Impulse Control/Compulsive Behaviors

Patients treated with INBRIJA can experience intense urges to gamble, increased sexual urges, intense urges to

spend money, binge eating, and/or other intense urges, and the inability to control these urges while taking one or more of the medications that increase central dopaminergic tone. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued.

Because patients may not recognize these behaviors as abnormal, it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with INBRIJA. Consider stopping the medication if a patient develops such urges while taking INBRIJA.

5.5. Dyskinesia

INBRIJA may cause or exacerbate dyskinesias. If troublesome dyskinesias occur, prescribers may need to consider stopping treatment with INBRIJA and/or adjusting the patient's daily medications for the treatment of Parkinson's disease. In Study 1, 4% of patients treated with INBRIJA 84 mg reported dyskinesia, compared with 1% for patients on placebo [see Adverse Reactions (6.1)].

5.6. Bronchospasm in Patients with Lung Disease

Because of the risk of bronchospasm, use of INBRIJA in patients with asthma, COPD, or other chronic underlying lung disease is not recommended.

In a double-blind, placebo-controlled, crossover clinical study, 25 otherwise healthy subjects with mild or moderate asthma on a stable regimen of asthma medication received placebo or INBRIJA 84 mg every 4 hours for a total of three doses. Cough was the most frequent adverse reaction, reported by 60% of subjects following administration of INBRIJA and 0% following administration of placebo. Following administration of INBRIJA, 10 subjects (40%) had temporary reductions from baseline (between 15% and 59%) for FEV₁; 4 of these subjects also had a reduction in FEV₁ following administration of placebo. Subjects with a reduction in FEV₁ remained asymptomatic and did not require rescue treatment.

5.7. Glaucoma

INBRIJA may cause increased intraocular pressure in patients with glaucoma. Monitor patients for increased intraocular pressure during therapy with INBRIJA.

5.8. Laboratory Test Abnormalities

Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, AST, ALT, lactic dehydrogenase (LDH), and bilirubin. Abnormalities in blood urea nitrogen (BUN), hemolytic anemia and positive direct antibody test have also been reported.

Patients taking levodopa or carbidopa-levodopa may have increased levels of catecholamines and their metabolites in plasma and urine giving false positive results suggesting the diagnosis of pheochromocytoma in patients on levodopa and carbidopa-levodopa.

6. ADVERSE REACTIONS

The following serious adverse reactions are discussed below and elsewhere in the labeling:

- Falling Asleep During Activities of Daily Living and Somnolence [see Warnings and Precautions (5.1)]
- Withdrawal-Emergent Hyperpyrexia and Confusion [see Warnings and Precautions (5.2)]
- Hallucinations/Psychosis [see Warnings and Precautions (5.3)]
- Impulse Control/Compulsive Behaviors [see Warnings and Precautions (5.4)]
- Dyskinesia [see Warnings and Precautions (5.5)]
- Bronchospasm in Patients with Lung Disease [see Warnings and Precautions (5.6)]
- Glaucoma [see Warnings and Precautions (5.7)]

6.1. Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse Reactions in Study 1

Study 1 was a double-blind, placebo-controlled study, in which 114 patients received INBRIJA 84 mg (two 42 mg capsules) for an average of 2 doses per day, to a maximum of 5 times a day, and 112 patients received placebo. INBRIJA-treated patients were 45-82 years of age (mean 63.5 years of age) and were predominantly male (72%) and white (94%). All patients were also treated with oral carbidopa/levodopa. The most common adverse reactions ($\geq 5\%$ and higher than placebo) in Study 1 were cough, nausea, upper respiratory tract infection, and sputum discolored.

Study 1 adverse reactions ($\geq 2\%$ and $>$ placebo): cough (15% vs 2%); upper respiratory tract infection (6% vs 3%); sputum discolored (5% vs 0%); nausea (5% vs 3%); dyskinesia (4% vs 1%); vomiting (3% vs 0%); nasopharyngitis and fall (each 3% vs 2%); nasal discharge discoloration, oropharyngeal pain, bronchitis/pneumonia, headache, laceration, skin abrasion, chest discomfort, blood bilirubin increased, red blood cell count decreased, orthostatic hypotension/blood pressure decreased (each 2% vs 0%); pain in extremity and insomnia (each 2% vs 1%).

Adverse Reactions Leading to Discontinuation in Study 1: In Study 1, 6 of 114 patients (5%) in the INBRIJA 84 mg group and 3 of 112 patients (3%) in the placebo group discontinued because of adverse reactions. The most common of these adverse reactions was cough, which led to discontinuation in 2% of patients in the INBRIJA 84 mg group and none in the placebo group.

7. DRUG INTERACTIONS

7.1. Monoamine Oxidase (MAO) Inhibitors

The use of nonselective MAO inhibitors with INBRIJA is contraindicated [see Contraindications (4)]. Discontinue use of any nonselective MAO inhibitors at least two weeks prior to initiating INBRIJA.

The use of selective MAO-B inhibitors with INBRIJA may be associated with orthostatic hypotension. Monitor patients who are taking these drugs concurrently.

7.2. Dopamine D2 Receptor Antagonists and Isoniazid

Dopamine D2 receptor antagonists (e.g., phenothiazines, butyrophenones, risperidone, metoclopramide) and isoniazid may reduce the effectiveness of levodopa. Monitor patients for worsening Parkinson's symptoms.

7.3. Iron Salts

Iron salts or multivitamins containing iron salts can form chelates with levodopa and consequently reduce the bioavailability of levodopa.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary: There are no adequate data on the developmental risk associated with the use of INBRIJA in pregnant women. In animal studies, carbidopa/levodopa has been shown to be developmentally toxic (including teratogenic effects) [see Data]. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data: When administered to pregnant rabbits throughout organogenesis, carbidopa/levodopa caused

both visceral and skeletal malformations in rabbits. No teratogenic effects were observed when carbidopa/levodopa was administered to pregnant mice throughout organogenesis.

There was a decrease in the number of live pups delivered by rats receiving carbidopa/levodopa during organogenesis.

8.2. Lactation

Risk Summary: The prolactin-lowering action of dopamine suggests that levodopa may interfere with lactation, although there are limited data on the effects of levodopa on milk production in lactating women.

Levodopa has been detected in human milk. There are no adequate data on the effects of levodopa on the breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for INBRIJA and any potential adverse effects on the breastfed infant from INBRIJA or from the underlying maternal condition.

8.4. Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5. Geriatric Use

Of the Parkinson's disease patients in Study 1 who took INBRIJA 84 mg, 49% (n=56) were 65 years of age and older and 51% (n=58) were under 65 years of age. Of these patients, the following age-related differences in adverse reactions were reported in patients 65 years of age and older vs. in patients under 65 years of age, respectively: cough 25% vs. 5%; upper respiratory tract infection 11% vs. 2%; nausea 7% vs. 3%; vomiting 4% vs. 2%; pain in the extremities 4% vs. 0%; and discolored nasal discharge 4% vs. 0%.

10. OVERDOSAGE

Based on the limited available information, the acute symptoms of carbidopa/levodopa overdose can be expected to arise from dopaminergic overstimulation. Using more than one dose (84 mg) to treat the same OFF period may result in CNS disturbances, with an increasing risk for cardiovascular disturbance (e.g., hypotension, tachycardia) and increased risk for new or worsening psychiatric problems at higher doses.

Reports of rhabdomyolysis and transient renal insufficiency suggest that levodopa overdose may give rise to systemic complications.

Monitor patients and provide supportive care. Patients should receive electrocardiographic monitoring for the development of arrhythmias; if needed, appropriate antiarrhythmic therapy should be given. The possibility that the patient may have taken other drugs, increasing the risk of drug interactions (especially catechol-structured drugs) should be taken into consideration.

13. NONCLINICAL TOXICOLOGY

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: In rats, oral administration of carbidopa/levodopa for two years resulted in no evidence of carcinogenicity.

Mutagenesis: Studies to assess the potential mutagenic or clastogenic effects of levodopa have not been conducted.

Impairment of Fertility: In reproduction studies in rats, oral administration of carbidopa/levodopa resulted in no effects on fertility.

Manufactured by:

Acorda Therapeutics, Inc.
420 Saw Mill River Road
Ardsley, NY 10502 USA

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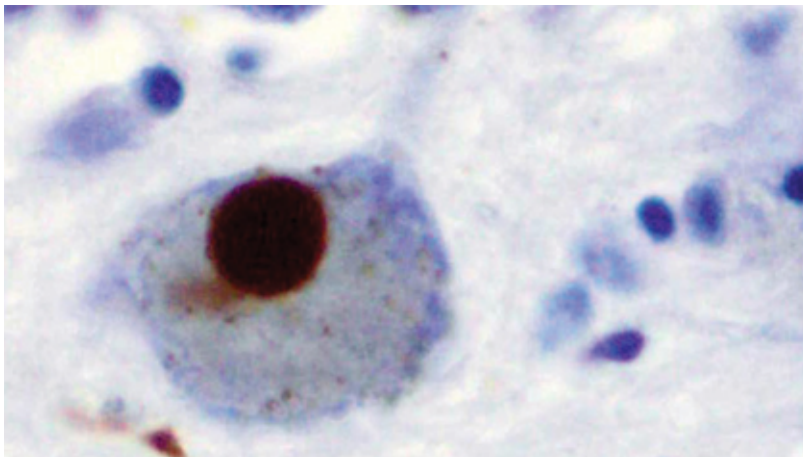
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A Lewy body (stained brown) in a brain cell of the substantia nigra in Parkinson's disease. The brown colour is positive immunohistochemistry staining for alpha-synuclein. —Wikipedia

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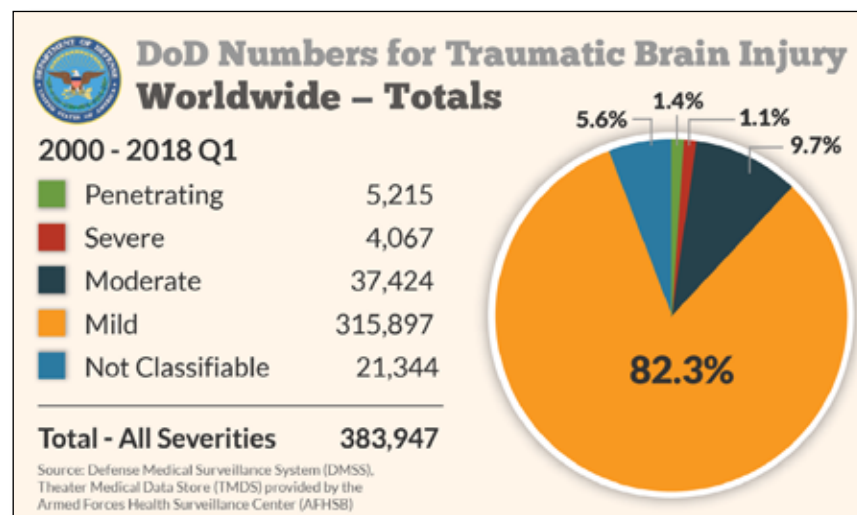
Cover image: Tracking brain changes in people with Parkinson's: A new study has found that neural activity in certain brain areas declines over time in individuals with Parkinson's disease and two related syndromes. —David Vaillancourt, Ph.D., University of Florida

MONITOR VETERANS WITH ANY LEVEL OF TBI FOR DEVELOPMENT OF PARKINSON'S DISEASE

SAN FRANCISCO—Traumatic brain injury has been called the “signature injury” of recent conflicts, with the DoD reporting nearly 384,000 TBIs sustained between 2000 and the first quarter of 2018. More than 4 out of 5 of those TBIs were considered mild, the kind from which most people recover rapidly. But recent research urges continued caution for veterans with any TBI—even mild—as they face an increased risk of Parkinson’s disease.

In a study published in *Neurology*, researchers at the San Francisco VAMC found that traumatic brain injury of any severity was associated with a 71% increase in risk of Parkinson’s disease. Even mild TBI increased the risk 56%. Veterans with the mildest of TBIs, those that occurred without loss of consciousness, had a 33% increase in risk, though the small number of individuals in this group prevented determination of a significant association.¹

While blast-related TBIs affected many military servicemembers who served in Iraq and Afghanistan, most TBIs among servicemembers and veterans occur in connection with more ordinary events. Rigorous operational and training activities, motor vehicle accidents, recreational activities and demanding physical fitness programs all



Source: Defense Medical Surveillance System and Theater Medical Data Store (TMDS) provided by the Armed Forces Health Surveillance Branch

increase the risk of TBI in young people. Veterans in their 70s and 80s have seen the largest increase in TBIs, generally as a result of falls, according to the Defense and Veterans Brain Injury Center.

PROTEIN AGGREGATION

How does TBI increase the risk of PD? A protein seems to be the culprit.

“Sometimes people who die right after sustaining a very severe TBI have the hallmark protein of Parkinson’s disease, and sometimes people develop Parkinson’s disease or Parkinsonism immediately after a TBI,” noted study lead author Raquel Gardner, a staff neurologist at the San Francisco

VAMC and assistant professor of neurology at the University of California-San Francisco.

Parkinsonism includes the symptoms of Parkinson’s disease, such as slowed movements, rigidity, tremor and poor balance, which may occur in other conditions besides PD.

On autopsy, the brains of people with and without Parkinson’s disease have very different levels of the alpha-synuclein protein. In individuals with the disease, faulty versions of the protein accumulate inside neurons, forming clumps.

“One of the really, extremely exciting things we’ve figured out in the last 10 years is that a lot of age-related disorders—Parkinson’s

disease, Alzheimer's, amyotrophic lateral sclerosis—all have abnormal accumulation of proteins in the brain. That's led to a fundamental shift in our understanding of the brain," added study co-author Kristine Yaffe, MD, chief of neuropsychiatry at the San Francisco VAMC and vice chair of the UCSF department of psychiatry, neurology and epidemiology.

Alzheimer's disease is characterized by aggregation of misfolded tau proteins, while ALS is characterized by accumulation of multiple proteins. In a fourth disease, Huntington's, mutant huntingtin proteins form clumps in the neurons of patients.

In all these diseases, the protein massing leads to rupturing of the neurons' vesicles, which impairs neuronal functioning. The proteins also resist cells' usual cleansing mechanisms, instead continuing to build up in the brain.²

Previous research indicated that TBI might increase the risk of Alzheimer's, but other researchers at the San Francisco VAMC did not find a link between TBI and increased levels of tau protein, calling that conclusion into question. Instead, they discovered that "people with a history of TBI had much higher levels of alpha-synuclein protein in their brains, even though the injury occurred much earlier in life," Gardner told *U.S. Medicine*.³

"That research set the stage," Yaffe said. "We're seeing now that TBI may be an important risk exposure for accelerating these proteins developing in Parkinson's disease. If it takes years before the accumulation has a negative impact on

neurons, maybe we have a window of opportunity to intervene."

TBI IMPLICATIONS

An association between mild TBI and PD could have broad public health implications.

"A handful of studies have tried to estimate lifetime prevalence of TBI in the population," Gardner said. "About 40% have had some level of TBI in their lifetime, though current studies probably underestimate the lifetime burden in the general and veteran population."

"All of us had had some sort of fall, sports injury or bump on the head. Even if you don't lose consciousness, you may actually have had symptoms of TBI, if you didn't feel well or generally felt out of it," Yaffe told *U.S. Medicine*. Other signs of TBI without loss of consciousness include confusion, memory and speech issues, prolonged headache, sensory disturbance, tinnitus and loss of balance or coordination.

While genetics may play a bigger role than TBI in Parkinson's disease, it appears to be about as significant as pesticide exposure and other environmental factors, Gardner and Yaffe noted.


To reduce the risk of PD in individuals who have experienced TBI as well as those who have not, Gardner recommended a "brain healthy lifestyle—stay physically, cognitively and socially active and make sure any chronic medical conditions are well managed."

Individuals who have suffered a TBI need to take an additional step to protect their brains and reduce the risk of PD. "In people who have

had TBI, it is extremely important to prevent subsequent brain injury as their risk for having another TBI is higher," Gardner advised.

Research among athletes indicates that individuals who have had one concussion or mild TBI have three to six times the risk of having a second compared to those who have not had any concussions, according to the American Association of Neurological Surgeons.

For older people, ground level falls are the most common cause of TBI, so it's important to take steps to reduce the risk of those by eliminating tripping hazards, installing grab bars in the home, using stair railings, increasing lighting, keeping eyeglass prescriptions current and talking to a healthcare provider about any medications that increase dizziness.

For younger veterans, TBI prevention relies on well-known strategies, Gardner noted: "Drive safely. Wear a seat belt. Use a helmet." 

¹ Gardner RC, Byers AL, Barnes DE, Li Y, Boscardin J, Yaffe K. Mild TBI and risk of Parkinson disease: A Chronic Effects of Neurotrauma Consortium Study. *Neurology*. 2018 May 15;90(20):e1771-e1779. Epub 2018 Apr 18.

² Flavin WP, Bousset L, Green ZC, Chu Y, Skarpathiotis S, Chaney MJ, Kordower JH, Melki R, Campbell EM. Endocytic vesicle rupture is a conserved mechanism of cellular invasion by amyloid proteins. *Acta Neuropathol*. 2017 Oct;134(4):629-653. Epub 2017 May 19.

³ Weiner MW, Crane PK, Montine TJ, Bennett DA, Veitch DP. Traumatic brain injury may not increase the risk of Alzheimer's disease. *Neurology*. 2017;89(18):1923-1925.

VA EXPANDS PARKINSON'S DISEASE SERVICES TO IMPROVE PATIENT CARE NATIONWIDE

PHILADELPHIA—Building on the success of the Parkinson's Disease Research, Education and Clinical Centers, established in 2001, the VA has expanded care for the nearly 100,000 veterans affected by the neurodegenerative disease through the creation of the National VA Parkinson's Disease Consortium.

"Our biggest accomplishment has been the establishment of the PADRECCs and now the consortium, which brings together experts interested in advancing understanding of veterans with Parkinson's disease in a hub and spoke system that today includes 54 facilities," said John E. Duda, MD, national director of the PADRECC programs, director of the Philadelphia PADRECC and co-director of the Center for Neurotrauma, Neurodegeneration and Restoration, both based at the Michael J. Crescenz VAMC in Philadelphia. Duda also is an associate professor of neurology at the Perelman School of Medicine at the University of Pennsylvania.

"As one of the clinicians with the program since the inception of PADRECCs 18 years ago, I've seen a dramatic change in how veterans with Parkinson's disease are taken care of," he told *U.S. Medicine*. "Patients were cared for by general neurologists, but a whole slew of new Parkinson's

disease drugs came on board, making that hard to do."

To keep up with the advancements in the disease and improve care, the PADRECCs were set up to offer expert, multidisciplinary care that included specialists in neurology as well as psychology, psychiatry, speech, pharmacology, physical therapy and other areas.

In addition to PD, the centers focus on other movement disorders including dyskinesia, dystonia, essential tremor and restless leg syndrome as well as atypical Parkinsonian disorders, such as progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration and Lewy body disease, the second-most-common type of dementia after Alzheimer's.

The six centers in Houston, Philadelphia, Portland/Seattle, San Francisco, West Los Angeles and Richmond, VA, provided geographic coverage across the U.S., "but many veterans were still not able to get to a PADRECC," Duda said.

Creation of the consortium improved access to expertise for patients and education and collaboration opportunities for clinicians. Each of the 21 VISNs now has at least one consortium center, allowing veterans to receive specialty care closer to home. Biannual consortium meetings review movement disorder care, current research initiatives and

provide educational programming for clinicians.

Bringing the experts together in a structured way also allowed for better communication with the VA's pharmacy benefits management team. That led to changes in the national formulary to better serve patients with PD, Duda noted.

TELEHEALTH ACCESS

Recent expansion of telehealth has further expanded the program's reach.

"Access to care is a big challenge in the VA and everywhere. There are simply not enough movement disorder neurologists to cover everybody with Parkinson's disease," Duda explained. Telehealth provides one option for better leveraging neurologists with the expertise to help patients in more distant locations.

Research results indicate telehealth is a win for both veterans and the VA.

"Jayne Wilkinson completed the largest study to date comparing in-person care and telehealth care. It shows that, by all measures, telehealth is just as valid, and it's preferred by a lot of patients because they don't have to travel," Duda said. Wilkinson, MD, MSCE, is the associate clinical director of the Philadelphia PADRECC and an associate professor of neurology at the Perelman School of Medicine at the University of Pennsylvania.

Recommended Service Areas for PADRECCs



Veterans Health Administration

Source: VA Establishes Six Parkinson's Disease Centers; Parkinson's Disease Research, Education and Clinical Centers & VA PD Consortium; U.S. Department of Veterans Affairs; www.parkinsons.va.gov/New_Front_Page.asp

Her randomized controlled trial compared in-person visits to video telehealth sessions at home or a satellite clinic near the patient for follow-up care over a 12-month period. The trial enrolled 86 men with an average age of 73 years.¹

The study found that all patients were satisfied with their care, with no significant difference between the locations or modes of delivery. The veterans reported greater satisfaction with telehealth, however, in terms of convenience, accessibility and distance. Clinical outcomes and healthcare utilization were similar across groups.

The study supports results seen in other research reporting high levels of satisfaction with telehealth by both patients and providers. In one study done by the University of Rochester Medical Center in New York, 97% of patients said they were satisfied with virtual visits, and 55% preferred them to in-person visits. Notably, 85% of the neurologists also expressed

satisfaction.²


Reaching more patients means better care and better outcomes.

“Over 40% of people with Parkinson's disease never receive care from a neurologist, yet studies have shown that people who see a neurologist are less likely to be hospitalized with illnesses related to Parkinson's disease, have greater independence and are less likely to die prematurely,” said URM study co-author Ray Dorsey, MD, professor of neurology and director of the Center for Health + Technology at URM.

Telehealth also makes mental health services available to veterans with Parkinson's disease. Many patients with PD experience depression, which can further reduce their motor skills, cognitive ability, relationships and overall quality of life.

Relatively few clinicians have the training in both PD and depression that allows them to understand the interaction of the two conditions.

A study that started in 2016 at the VA New Jersey Health Care System hopes to expand access to the clinicians with experience in PD and depression via a video-to-home platform that offers a 10-session cognitive behavioral therapy program for veterans and a three-session skills training program for caregivers.

Other telehealth initiatives include initial assessment of veterans for deep brain stimulation. Across the board, Duda noted, “all the PADRECCs are active in increasing access via telehealth.” 

¹ Wilkinson JR, Spindler M, Wood SM, Marcus SC, Weintraub D, Morley JF, Stineman MG, Duda JE. High patient satisfaction with telehealth in Parkinson's disease: A randomized controlled study. *Neurol Clin Pract.* 2016 Jun;6(3):241-251.

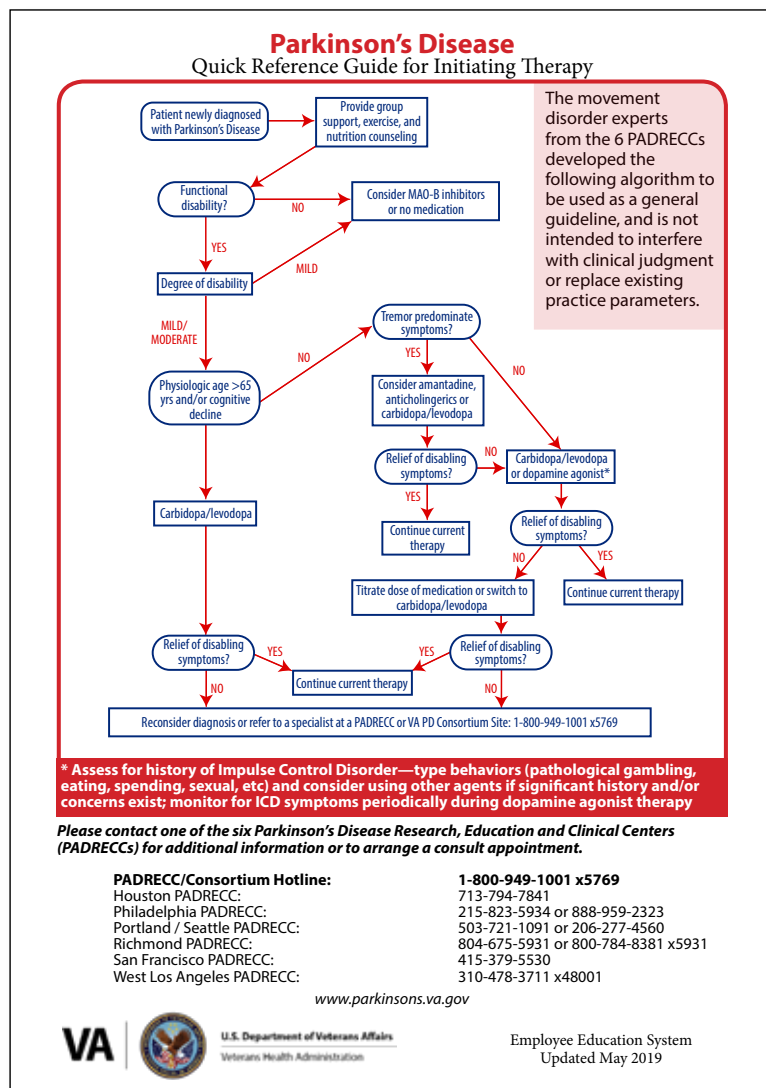
² Beck CA, Beran DB, Biglan KM, Boyd CM, and the Connect Parkinson Investigators. National randomized controlled trial of virtual house calls for Parkinson's disease. *Neurology.* 2017 Sep 12;89(11):1152-1161.

THERAPY ADVANCES HELP VETERANS MANAGE COMMON PARKINSON'S DISEASE 'OFF EPISODES'

PHILADELPHIA—For five decades, physicians have used carbidopa/levodopa to treat the rigidity, tremors and slowed movement associated with Parkinson's disease. For just as long, they've struggled to manage the disruptive and often painful "off episodes" that occur when the combination wears off or fails to work, but recent therapeutic advances have dramatically increased the options available to more consistently control troubling symptoms.

"There are a number of pharmacological agents that have come out over recent years considered adjunctive to carbidopa/levodopa to smooth out off-episodes," said John E. Duda, MD, national director of the VA's Parkinson's Disease Research, Education and Clinical Centers; director of the Philadelphia PADRECC and co-director of the Center for Neurotrauma, Neurodegeneration and Restoration, both based at the Michael J. Crescenz VAMC in Philadelphia; and an associate professor of neurology at the Perelman School of Medicine at the University of Pennsylvania.

In Parkinson's disease, misfolded alpha-synuclein proteins aggregate in the dopamine-producing neurons involved in the motor pathways and trigger neuronal death. As the neurons die, dopamine levels in the brain drop, and



issues with movement and tremors develop.

Carbidopa/levodopa transforms into dopamine in the brain, reducing the symptoms of PD. Over time, however, response to the drug declines, and patients experience

more and longer periods when the medication isn't working and symptoms recur.

"We used to believe that starting carbidopa-levodopa later and using other agents initially might be more beneficial, but now we're

starting to use it earlier on to treat disabling and bothersome symptoms," Duda told *U.S. Medicine*.

"None of the treatments available change the progression of the illness," Duda added. "You need the neurons for levodopa to work, but patients continue to lose those neurons over time."

Increasing the dosage or frequency can help, but high levels of carbidopa-levodopa cause dyskinesia, uncontrolled or abnormal movements.

SMOOTHING OUT DELIVERY

Several new formulations and delivery methods for carbidopa-levodopa minimize off episodes.

Rytary combines immediate and extended release formulations of carbidopa/levodopa in a capsule to maintain plasma concentrations of the drug for a longer period. Concentrations peak after about 60 minutes, then stay fairly level for four to five hours before dropping.

The combination received approval from the U.S. Food and Drug Administration in 2015. Several clinical trial results showed more than an hour reduction in off time per day in patients taking Rytary compared to those taking immediate release carbidopa-levodopa or immediate release carbidopa-levodopa plus entacapone (Stalevo). Entacapone is another drug that reduces the breakdown of levodopa, increasing and smoothing the levels of dopamine in the brain.

"Using extended release/regular release combination is a reasonable option for off episodes," Duda noted.

"We also use Inbrija, an orally inhaled levodopa formulation," he added. "It just came out last year and is starting to be used to minimize off episodes when motor fluctuations are difficult to manage."

Inbrija received FDA approval last December. It acts as the equivalent of a rescue inhaler for asthmatics but for patients with Parkinson's. When symptoms begin to reemerge between carbidopa-levodopa doses, a patient can inhale a powdered form of levodopa that delivers a dose deep into the lungs. By bypassing the gut, the dose enters the bloodstream more quickly and at a more reliable level.

A Phase 3 clinical trial showed symptom reduction within 10 minutes and a daily reduction of 1.32 to 1.42 hours in off time. Parkinson's symptoms improved throughout the 52-week trial. Notably, sucking action activates the inhaler, so patients with motor issues do not have to struggle to press or manipulate it while inhaling.¹

An intestinal infusion pump for a gel formulation of carbidopa-levodopa (Duopa) is also available. The pump delivers 16 hours of the drugs directly to the small intestine. Duopa is specifically recommended for people with advanced PD who experience motor fluctuations. In advanced disease, emptying of the stomach becomes more erratic and slower, affecting the absorption into the bloodstream. Delivery to the small intestine avoids that issue, but requires a percutaneous gastrojejunostomy.

"Duopa frankly has a limited number of good candidates," Duda noted. "It can be useful for certain

patients, but a lot of people don't like having a bag they have to fill every night."

"For patients experiencing a sudden off episode, apomorphine, an injection of a dopamine agonist, can be helpful," he added. Apomorphine has been used for 15 years in the U.S. Because the drug is associated with a very high incidence of nausea and vomiting, patients are required to pretreat with the antiemetic trimethoprim. Patients may also experience pain and nodules at injection sites. The FDA rejected an application for a sublingual formulation of apomorphine in January.

Safinamide is another adjunctive medication for Parkinson's disease, designed to be taken once daily by patients on a stable dose of carbidopa-levodopa. It received FDA approval in 2017.

OTHER OPTIONS

In addition to offering a full range of pharmacologic agents for treatment of PD, the VA has undertaken "a lot of research that has affected care," Duda said.

A large study of deep brain stimulation for Parkinson's disease with a five-year follow-up has just concluded at the San Francisco PADRECC. "The initial report will be likely be out before the end of the year. It's given us more insight into which type of surgery is best utilized for particular outcomes," Duda added.

Deep brain stimulation is an option for veterans who fail to respond to medication. The procedure implants a device in the chest that send electrical signals to stimulation electrodes in a targeted

region(s) of the patient's brain. DBS can significantly reduce tremors, involuntary movement and off episodes.

The procedure is typically done on awake patients, but Paul Larson, MD, PhD, chief of neurosurgery and director for the Center for Advanced Neurosurgical Operative Procedures at the San Francisco VA Health Care System, "has been developing MRI [magnetic resonance imaging]-guided DBS, in which the patient is asleep through the whole procedure," Duda said. "It's weird to have someone poking around in your brain when you're awake, and we can get as good results with interoperative MRI."

As a bonus, the DBS "studies serendipitously show huge progress in tinnitus, which is a big issue for veterans," he added. A recent study at the VA also showed DBS confers a modest survival advantage.²

Still, "not everyone wants a hole in their head," Duda said, and the VA has continued to explore other options.

"A new advance becoming available is focused ultrasound therapy in which a large machine shoots ultrasounds to cause a small lesion in the brain. Kind of like ablation therapy, this burns part of the brain without cutting any skin," he explained.

"It's been used in essential tremor and now in Parkinson's disease as well. It's particularly good for veterans we're worried about who live a long way away from a center, as it's a once and done process and for those who have treatment resistant tremor on one of the body," Duda noted.




In an example of nonpharmacological treatment, Army veteran Gary Pauley, a Parkinson's disease patient at the VA, is now a certified Level 1 weightlifting coach helping others in his community—Savannah, GA—with movement disorders.

Integrative therapy plays a role in improving PD symptoms, too. At the West Los Angeles VAMC, veterans with PD are encouraged to take yoga and tai chi classes, and the program uses acupuncture and other aspects of integrative care. The San Francisco VAMC has developed an integrative care model for end of life care.

"At the Philadelphia PADRECC, we got tired of waiting for breakthrough medications and started a brain wellness clinic that focuses on social connection, fitness, nutrition, stress reduction and sleep. That model has since been expanded to three or four other PADRECCs," Duda said.

"While we can't prove it slows down progression, it changes the mindset from a victim to someone fighting back against the disorder,

and that's very empowering," he noted. "And the side effects—reduced cardiovascular risk, weight loss, improved fitness—they're all good." 

¹ LeWitt PA, Hauser RA, Pahwa R, Isaacson SH, Fernandez HH, Lew M, Saint-Hilaire M, Pourcher E, Lopez-Manzanares L, Waters C, Rudzinska M, Sedkov A, Batycky R, Oh C; SPAN-PD Study Investigators. Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Neurol*. 2019 Feb;18(2):145-154.

² Weaver FM, Stroupe KT, Smith B, Gonzalez B, Huo Z, Cao L, Ippolito D, Follett KA. Survival in patients with Parkinson's disease after deep brain stimulation or medical management. *Mov Disord*. 2017 Dec;32(12):1756-1763.

COURT RULING, NEW LAW SUPPORT ‘BLUE WATER VETERANS’ WITH PARKINSON’S DISEASE

WASHINGTON—A recent political development, more than 50 years in the coming, has the potential to significantly change who receives benefits for Parkinson’s disease through the VA.

About 2.6 million veterans who served during the Vietnam War were potentially exposed to the herbicide Agent Orange (2,4,5-trichlorophenoxyacetic acid and 2,4-dechlorophenoxyacetic acid), according to the VA.

The Institute of Medicine, now the Health and Medicine Division of the National Academies of Sciences, Engineering and Medicine, determined in its report *Veterans and Agent Orange: Update 2008* that “suggestive but limited evidence [indicates] that exposure to Agent Orange and other herbicides used during the Vietnam War is associated with an increased chance of developing Parkinson’s disease.”

More evidence linking the two has emerged since that report. A study of Korean veterans exposed to the defoliant during the Vietnam War recently found a number of significant differences between Parkinson’s patients with Agent Orange exposure and those without it. Agent Orange-exposed veterans had less facial expression, worse motor symptoms and notably different brain imaging, researchers found, suggesting “the possibility of different pathophysiology of PD in patients exposed to Agent Orange from idiopathic PD.”¹



Blue Water veterans lobby in Washington for VA benefits related to Agent Orange exposure.
—Photo from website of U.S. Rep. Vern Buchanan (R-FL)

The VA recognized PD as a presumptive illness arising from Agent Orange exposure in 2010. That meant veterans filing disability claims for PD who were exposed to the chemical did not have to prove an association between their disease and military service.

But, based on a restrictive reading of the law providing benefits for servicemembers exposed to Agent Orange, the VA limited disability compensation to veterans who could demonstrate “boots on the ground” in Vietnam or its inland waterways. As a result, servicemembers who served in the waters off of Vietnam, often called the “Blue Water Navy,” did not qualify for presumptive coverage, if they developed PD.

That changed in January when a federal court ruled in *Procopio v. Wilkie* that veterans who served

in the ships offshore of Vietnam are entitled to a presumption of service connection for illnesses linked to Agent Orange exposure in disability claims.

Five months later, President Donald Trump signed into law H.R. 299, the Blue Water Navy Vietnam Veterans Act of 2019. The new law codified coverage for veterans who served in the 12 nautical mile territorial sea of the Republic of Vietnam and expanded presumptive benefits to also include veterans who served in the Korean Demilitarized Zone. In addition, the law included a stay allowing the VA to wait until January 2020 to begin processing claims.

“Tonight, we can finally tell the tens of thousands of veterans who were exposed to Agent Orange during the Vietnam War but wrongly denied benefits that justice is

finally coming. By passing the Blue Water Navy Vietnam Veterans Act, Congress has proven to the nation, to our veterans and their families, and the surviving loved ones of those we lost to toxic exposure, that we have righted a terrible injustice," said Rep. Mark Takano (D-Calif.), who introduced the bill, after the Senate unanimously passed it.

Many veterans groups shared his view. "The VFW is proud of the 116th Congress for ending this benefits inequity, and we salute President Trump for quickly signing H.R. 299 into law," said Veterans of Foreign Wars National Commander B.J. Lawrence.

Other veterans' advocates were less pleased, notably John Wells, executive director of Military-Veteran Advocacy and one of the attorneys who represented Alfred Procopio Jr.

in his suit against the VA.

"The *Procopio* [ruling] gives us a chance to move into the waters offshore which extends past the territorial sea. That could result in another 55,000" veterans qualifying for coverage beyond those specified by the new law, he told *U.S. Medicine*.


The VA estimated that the number of Blue Water veterans is as high as 420,000 to 560,000.

Wells put the number closer to 90,000, based on "the Congressional Research Service and the Navy Historical and Heritage Command. We also did an analysis based on the 713 ships that deployed and their manning levels as well as factoring in crew rotations."

VA Secretary Robert Wilkie cited the larger number in explaining the

need to wait until January to begin processing claims, as provided under the law.

"If that law was not passed, the VA would have had to continue to process the claims under *Procopio*. It was a harmful action by the chairman of the House veterans committee that actually hurt veterans," Wells said.

For those who served in the territorial waters of Vietnam and who have illnesses such as Parkinson's disease that will be presumptively associated with their service, however, both the court ruling and the new law represent a light at the end of a decadeslong tunnel. 

¹ Yang Y, Cheon M, Kwak YT. Is Parkinson's Disease with History of Agent Orange Exposure Different from Idiopathic Parkinson's Disease? *Dement Neurocogn Disord*. 2016;15(3):75-81.

TREATMENT FOR HEPATITIS C MIGHT LOWER THE RISK OF PARKINSON'S DISEASE

WASHINGTON—In a case of welcome unintended consequences, the VA might be lowering the risk of Parkinson's disease by treating another common condition: hepatitis C virus.

An unresolved question is whether the treatment, which is no longer in widespread use, or the elimination of HCV possibly provided protection against Parkinson's.

A large study of patients infected with HCV published in *JAMA Neurology* found that treating the infection reduced the risk of developing Parkinson's disease.¹ If that's borne out in subsequent studies, it could indicate an additional benefit to the VA's successful program to eliminate hepatitis C in veterans.

The retrospective cohort study of 188,152 patients with HCV compared those treated with interferon therapy

between Jan. 1, 2003 and Dec. 31, 2013, to a propensity score-matched group who did not receive treatment. The untreated group was 40% more likely to develop Parkinson's disease.

"The advantage of antiviral therapy reached statistical significance at the five-year follow-up (HR, 0.75; 95% CI, 0.59-0.96), and this advantage continued to increase until the end of follow-up (HR, 0.71; 95% CI, 0.58-0.87)," the researchers reported.

While the results are encouraging, Jane Battles, PhD, scientific program manager in the VA's Office of Research and Development urged caution in extrapolating the results to the VA because of demographic and treatment differences.

"The treatment used in this cohort was interferon-based, which is a general

regimen used to stimulate immune and anti-inflammatory responses and not well-tolerated by most patients," she told *U.S. Medicine*. "It is no longer the treatment of choice for hepatitis C infections in the U.S. veteran population."

The VA has cured hepatitis C in more than 100,000 veterans, nearly all of them since the development of oral direct-acting antivirals in 2014. The newer generation of HCV medications are much better tolerated and far more effective than interferon, raising the cure rate from 36% to more than 90%.

¹ Lin W, Lin M, Weng Y, et al. Association of Antiviral Therapy With Risk of Parkinson Disease in Patients With Chronic Hepatitis C Virus Infection. *JAMA Neurol*. Published online June 05, 2019.

