

CBD: Some Answers

Lawrence I. Golbe, MD

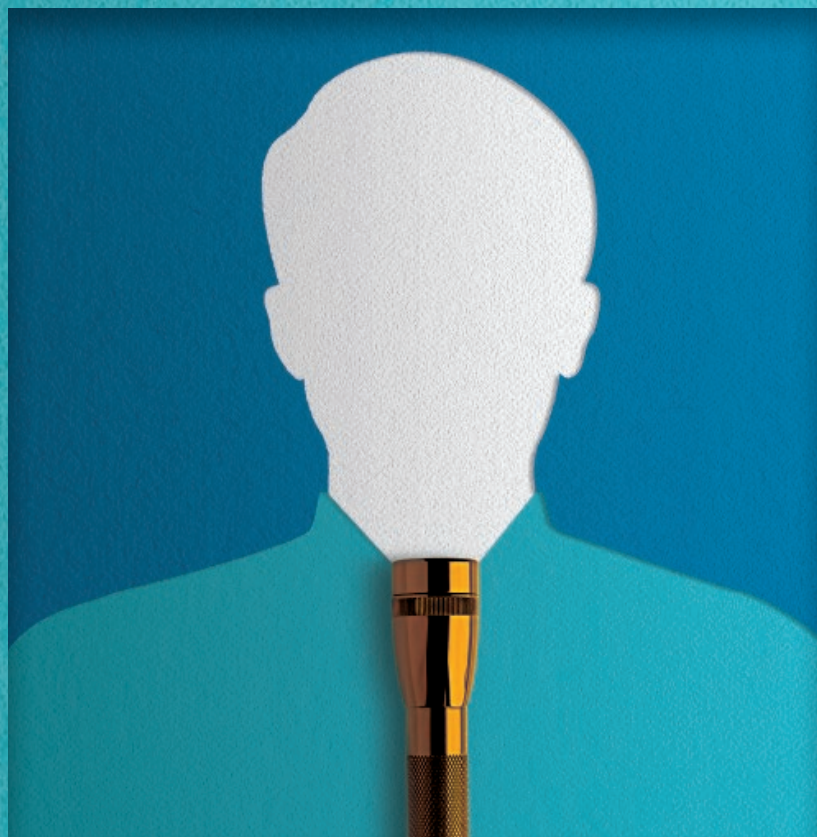
Professor of Neurology,

Rutgers Robert Wood Johnson Medical School

Director of Clinical Affairs and

Scientific Advisory Board Chairman, CurePSP

July 2016



What is corticobasal degeneration (CBD)?

As its name states, corticobasal degeneration is a loss of brain cells emphasizing the cerebral cortex and the basal ganglia. The cortex is the outer layer of the cerebrum, the gray matter where most thinking, speech and sensory perception occur. The basal ganglia are also gray matter, but they're deeper in the cerebrum and coordinate movement. Basal refers to the base of the brain and the ganglia are collections of brain cells in one location devoted to a single purpose.

What are its main signs and symptoms?

CBD is considered one of the “parkinsonian” disorders, or “parkinsonisms.” There are about a dozen such diseases, all of which produce some degree of slowness, muscle stiffness, balance problems and sometimes tremor. Most people with CBD have these things, but in addition they have unusual difficulty performing complex limb movements such as cutting food, buttoning or typing. There is often a tendency to hold part or all of a limb in a fixed posture called *dystonia*. There can also be very rapid, irregular, small movements of muscles called *myoclonus*.

The unusual feature about CBD is that it is almost always very asymmetric, with one side affected much earlier and worse than the other. In half of people with CBD it's the left and in half, it's the right. The side affected has no relationship to the person's handedness.

An important part of CBD that is often difficult for patients and families to understand is *apraxia*. This is the loss of the ability to perform complex movement that required some practice to learn in the first place. Manual tasks or gestures become clumsy and walking can become “frozen” for several seconds at a time. Common examples are loss of ability to use eating utensils or buttons. An unusual but dramatic type of apraxia is *alien limb phenomenon*, where one hand seems to belong to someone else and can perform actions that oppose the person's intentions. Another unusual type of apraxia is *arm levitation*, where one arm tends to move upward involuntarily.

Contributing to the movement problem of CBD is a sensory problem. It's not a simple loss of sense of touch, but an inability to interpret spatial complexity involving touch. This can take the form of an inability to recognize common objects by feel alone, or the inability to know the position of a finger or a limb in space.

How does CBD start?

The first symptom is usually apraxia in one hand, but sometimes it starts as Parkinson's disease does, with general slowing and stiffness, perhaps with a mild tremor and slurred speech. Over the next few months, the symptoms worsen and the dystonia may start. Sometimes CBD starts with *aphasia*, which is difficulty producing or understanding language.

What happens later?

The apraxia and dystonia usually spread to the other arm within two or three years and can affect the legs and feet as well, which can make walking unsteady. There can be troubling slurring of speech and difficulty swallowing liquids, with coughing and even irritation of the lungs by fluids that drip down. Some people develop difficulty multitasking or organizing their thoughts and can lose some behavioral inhibitions.

How common is CBD?

CBD is very rare: about five people per million population, which comes to about 1,600 people in the United States, most of whom have not yet been accurately diagnosed. For Parkinson's, the figure is about 700,000, and for Alzheimer's disease, about 5 million.

How does CBD differ from the more common brain degeneration disorders?

Unlike Parkinson's, CBD usually has little tremor. Unlike progressive supranuclear palsy (PSP), CBD has only mild problems with balance and eye movements. However, CBD does have features that these other diseases usually lack such as apraxia, dystonia and myoclonus. Unlike all of these other diseases, CBD is highly asymmetric in its limb involvement, meaning that either the right or left limbs start to show problems well before the opposite side and remains the worse side throughout. Parkinson's disease is also asymmetric, but not to the same degree.

In CBD, dementia occurs toward the end of the disease or not at all. If it does occur, it does not feature the memory problem that is so apparent in Alzheimer's disease. Rather, the dementia of PSP is characterized by slowed thought, difficulty resisting impulses and difficulty synthesizing several different ideas into a new idea or plan. These mental functions are performed mostly by the front part of the brain (the frontal lobes). In Alzheimer's, on the other hand, the problem is mostly in the part of the brain just above the ears (the temporal lobes), where memory functions are concentrated.

What happens in the brain?

In people with CBD, some groups of brain cells break down and die off. Central to that process is the abnormal folding and clumping of a protein called *tau*, which is a normal component of the brain. Its job is to help maintain the microtubules, which are stiff rods that function as the brain cells' internal transportation and skeletal system. It appears that the cells' death is caused by the tau protein clumps themselves and not by the reduced availability of tau for its normal function. The clumps' technical name is *neurofibrillary tangles*.

We know several reasons why tau might misfold, but we don't know which one(s) are relevant to CBD. Tau forms similar aggregates in about a dozen other diseases, including Alzheimer's disease, PSP, chronic traumatic encephalopathy and about half of all cases of frontotemporal dementia. The specific disease depends on the chemical characteristics of the tau aggregate and which brain cells are involved. We don't yet understand what determines these.

What are the various subtypes of CBD?

The microscopic brain abnormalities of CBD can affect different parts of the brain, producing different sets of outward symptoms in different people. The first variant to be described in the medical literature is called *corticobasal syndrome* and is the most common. It affects about half of all people with CBD and is the archetype of CBD described above.

About a quarter of people with CBD have an outward appearance that resembles the most common form of PSP, which features problems with balance, eye movement, speech and swallowing. Another 15 percent have frontotemporal dementia, with inappropriately uninhibited behavior and difficulty organizing thoughts. Then there are two rare forms, each accounting for about five percent of the total. One has a dementia similar to that of Alzheimer's disease, with important problems with memory or spatial orientation. The other is a form of *aphasia*, which means a problem with language, in this case difficulty finding words and obeying rules of grammar.

All of the forms of CBD at some point include, in almost all patients, a degree of "motor parkinsonism," meaning stiffness, slowness, soft speech and reduction in facial expression, sometimes with balance difficulty and tremor.

Is CBD genetic?

CBD almost never runs in families. However, a variant in the gene on chromosome 17 that encodes the tau protein is a little more common in CBD than in the rest of the population. Called the "H1 haplotype," it occurs in 92 percent of people with CBD and in 77 percent of the rest of the population. So the H1 haplotype is (nearly) necessary but far from sufficient to cause the disease.

We're still not quite sure how the H1 haplotype increases CBD risk. One possibility is that it simply increases the amount of tau produced, which causes that protein to stick together, even if it's not misfolded. Another possibility, discovered only this year, is that it causes too many "methyl groups" to stick to the tau gene, which alters its function. A methyl group is simply a carbon atom with three hydrogens. It can be attached to large molecules including DNA. *Methylation* is a normal way for the cell to regulate the function of DNA, thereby affecting the function of genes without actually changing the content of the genetic code like ordinary mutations do. This is exciting because certain molecules that can be developed into drugs alter DNA methylation.

A detailed analysis of the genetics of CBD was published in 2015 by an international group of researchers. The project was partly sponsored by CurePSP. It found five genetic variants to be associated with CBD in addition to the H1 haplotype in the gene for tau. One of these genes, called MOBP, is also associated with PSP. It is the blueprint for the manufacture of a protein in brain cells' myelin sheath, which serves as a layer of electrical insulation on the wires connecting brain cells together. These findings await confirmation by other research groups using other methods.

If these gene variants are confirmed, the next step will be to figure out how those errors damage the normal function of brain cells. Those insights, in turn, will provide new ideas for drug targets. In other words, once scientists work out which steps in the brain cells' normal function become disordered as a result of these CBD-related gene variations, they will know where new drugs could be directed to prevent the process from proceeding further. Coupled with a test to detect CBD in its earliest stages, before it actually causes any disability, such a drug treatment would amount to a CBD prevention.

How is CBD treated?

Unfortunately, CBD almost never responds to levodopa, the drug that is the mainstay of Parkinson's disease treatment. However, because there are rare exceptions and because the diagnosis of CBD may be wrong, it's usually worth a try in people with apparent CBD who have important muscle rigidity or slowing of movement. A typical approach is to start the carbidopa/levodopa 25/100 size at one tablet once a day on a full stomach and to increase each week by one tablet per day until reaching three per day taken as one tablet three times per day. Then it can be increased at weekly intervals to six tablets per day, then nine, then 12. If that doesn't help, then the drug should be quickly tapered and discontinued. The most common side effects of carbidopa/levodopa in people with CBD are nausea and sleepiness, each occurring in about 10 percent of patients.

There is no evidence that other antiparkinson drugs help, such as the dopamine agonists (pramipexole, ropinirole, rotigotine patch) and they can have more side effects than levodopa. An exception may be amantadine, an old antiparkinson drug with a complex chemical mechanism that can sometimes help the gait freezing of CBD. The dosage of that drug should not exceed 200 mg per day because of its possible side effects of confusion, constipation and urinary retention.

The dystonic muscle spasms that sometimes occur in CBD may respond to muscle relaxant drugs such as cyclobenzaprine, baclofen and tizanidine. A medication for seizures called levetiracetam can also help and may be better tolerated than the traditional muscle relaxants. The most common side effect of these drugs is sleepiness. The myoclonus of CBD, in the unlikely event that it is troublesome, may respond to clonazepam or levetiracetam.

A different sort of drug that can be useful for people whose CBD is complicated by dystonia is botulinum toxin. This substance is produced by certain bacteria that can contaminate food. A dilute solution can be injected into overactive muscles. The effect takes one to two weeks to start and lasts two to three months before having to be repeated.

Unfortunately, deep brain stimulation surgery, which is so useful in Parkinson's, does not help CBD.

Is physical therapy useful?

Formal physical therapy is worth a trial in CBD, especially with the goal of teaching the patient to use gait assistive devices such as a walker. Certain exercises done in the home by oneself on a regular schedule can keep the joints limber. Exercise also has a clear psychological benefit that improves the sense of well-being of anyone with a chronic illness. For people with gait or balance problems, many useful exercises can be performed seated in a chair or lying on a mat. Using a stationary bicycle is usually feasible as long as there is help in mounting and dismounting safely. The best strategy is to have an evaluation and treatment plan from a physical therapist or physiatrist (a physician specializing in rehabilitation of chronic conditions). The same advice applies to the utility of occupational therapy in improving the apraxia and dystonia of the hand(s) that is so common in CBD.

Are there experimental treatments for CBD?

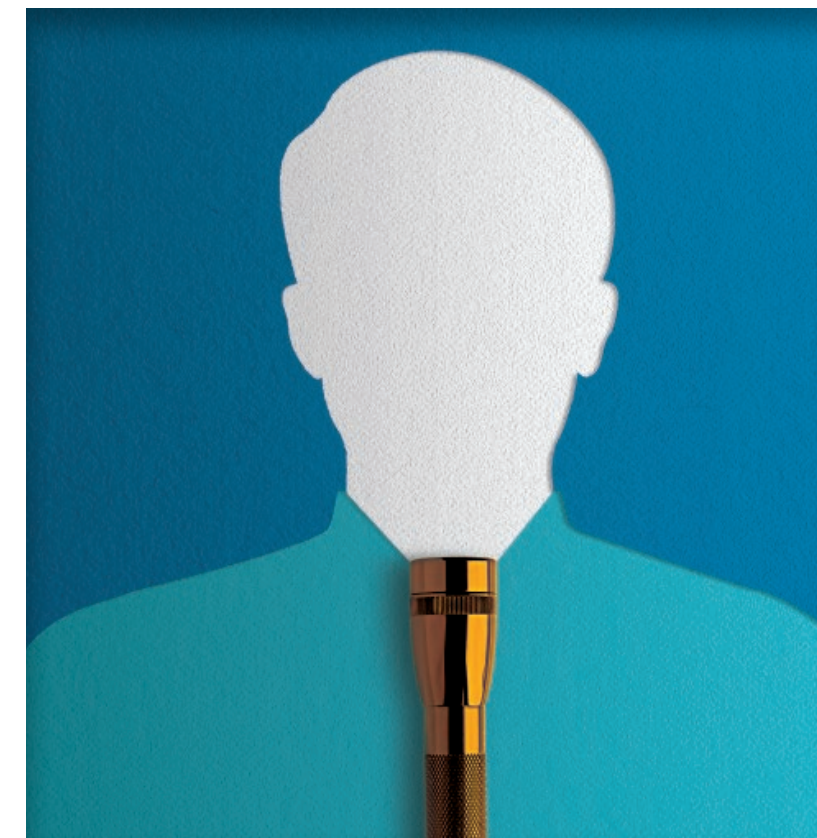
Not so far, but there are experimental trials for PSP, and the two diseases are very similar at the molecular level. As far as we can tell at this point, anything that helps PSP could also help CBD. So it's a good idea to keep an eye on new developments in PSP. One problem in mounting drug trials in CBD is that there are so few patients in any one place that many sites would have to be recruited and coordinated (and paid) in order to have a proper trial. Another problem is that about half of the patients who have the outward *corticobasal syndrome* actually have corticobasal degeneration, so any benefit of a drug could be diluted by the non-CBD patients in the trial, creating a false-negative result. Furthermore, any positive result in such a trial could be explained by an effect in some of the non-CBD patients, a messy result that would not satisfy most researchers, drug companies or the FDA.

How long do people with CBD live?

Most people with CBD encounter life-threatening complications between five and ten years after the first symptoms appear. However, some live much longer. Survival is enhanced by dedicated caregiver support, professional nursing care as needed in the more advanced stages, maintaining general health, and perhaps most important, by an optimistic and hopeful attitude of the patient and family.

Should I make arrangements to donate my brain after death?

An important way to help research to benefit future generations is to make arrangements to donate your brain after death. CurePSP sponsors the Eloise H. Troxel Memorial Brain Bank located at the Mayo Clinic in Jacksonville, FL. Brains donated there are stored and used only for research in PSP and CBD by legitimate researchers who request it. Donating to a brain bank does not interfere with funeral arrangements and costs a few hundred dollars for expenses of brain removal and transportation, which may be reimbursed by CurePSP. The family will receive at no charge a full diagnostic report from the Mayo Clinic pathologist, Dennis W. Dickson, MD, who is one of the world's foremost authorities on PSP, CBD and related disorders. Further information is available from CurePSP or by calling the Brain Bank directly at 904-953-2439. There are several other brain banks throughout the country, generally located at major university hospitals.



More information on research is available from CurePSP (www.curepsp.org or 1-800-457-4777), which includes CBD among the disorders for which it provides education and support for patients and their families.

CurePSP[®]

UNLOCKING THE SECRETS OF BRAIN DISEASE[®]

404 5th Avenue
3rd Floor
New York, NY 10018
347-294-2873 (CURE)
Canada: 844-287-3777
www.curepsp.org
[Facebook.com/curepsp.foundation](https://www.facebook.com/curepsp.foundation)

©2016 CurePSP, Inc.

CurePSP and Unlocking the Secrets of Brain Disease are registered trademarks of CurePSP, Inc.