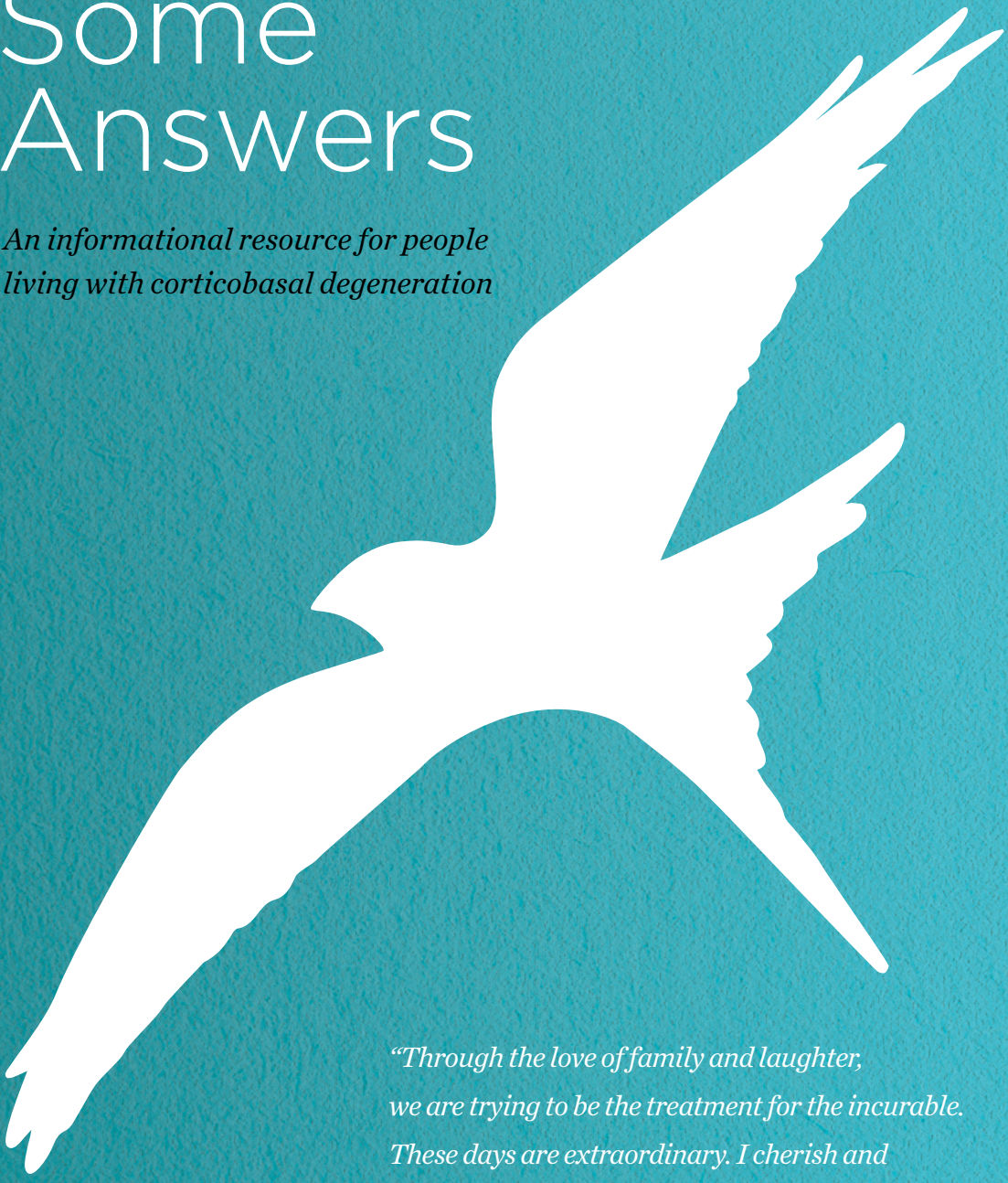
CBD: Some Answers

curePSP
UNLOCKING THE SECRETS OF BRAIN DISEASE®

An informational resource for people living with corticobasal degeneration



"Through the love of family and laughter, we are trying to be the treatment for the incurable. These days are extraordinary. I cherish and approach them all with gratitude."

- Sanjay, grandson of person diagnosed with CBD

What is corticobasal degeneration (CBD)?

Corticobasal degeneration, or CBD, is a rare, adult-onset, neurological disease that impacts movement, thinking, speech and sensory perception.

CBD is commonly referred to as an "atypical parkinsonism disorder," because some of its symptoms are similar to those of Parkinson's disease. CBD varies in the precise areas of the brain affected, which can cause a variety of symptoms, often making the disease difficult to diagnose.

How many people are diagnosed with CBD?

CBD is very rare. The current estimate is 2,000-3,000 people diagnosed with CBD in the United States. This compares with 30,000-40,000 people with progressive supranuclear palsy (PSP), which is a different but related atypical parkinsonism disorder; about 1 million with Parkinson's disease; and 5 million with Alzheimer's disease. However, these numbers for CBD are likely underestimates because many people with CBD are misdiagnosed with another condition, such as PSP or Parkinson's disease.

What are the main symptoms of CBD?

CBD shares with Parkinson's disease its slowness, muscle stiffness, balance problems and sometimes tremor. Most people with CBD also have problems performing complex movements such as cutting food, buttoning or typing. These types of symptoms usually begin by affecting one hand. People with CBD tend to hold part or all of a limb in a fixed posture, called dystonia. An important aspect of CBD is the asymmetry of its symptoms, meaning that it almost always starts on one side of the body. Over time, the other side can become affected, but the first side always remains worse. There can also be very rapid, irregular, small movements of muscles, called myoclonus.

CBD can cause a symptom called apraxia, which is the loss of ability to perform complex, familiar, previously learned movements. Manual tasks or gestures become clumsy, and walking can become frozen for several seconds at a time. An unusual, dramatic type of apraxia seen sometimes with CBD is alien limb phenomenon, where one hand can feel to the person as if it belongs 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. Apraxia can produce a wandering of the limb attempting to find its target that can resemble an involuntary movement. Apraxia in some people with CBD also affects speech, producing pauses and slurring, as well as control of the trunk, causing difficulty sitting down, standing up and maneuvering in bed.

A sensory problem also contributes to the movement problem of CBD. It's not a simple loss of sense of touch but an inability to interpret spatial complexity involving touch. This problem 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. Similar to the other symptoms described above, this sensory problem is also often asymmetric, meaning that it affects one side of the body much more than the other. Sometimes there is also a problem with spatial reasoning in general, causing difficulty in things like dressing or finding one's way around familiar places.

What happens to someone with CBD over time?

Unfortunately, CBD is a progressive neurologic condition. This means that over time, people with CBD will notice increasing severity of their symptoms and/or onset of new symptoms. This can occur over months to years. Not everyone experiences all of the symptoms of CBD, and the appearance and progression of these symptoms vary greatly among individuals.

Often over time, movement symptoms start to affect both sides of the body. New symptoms, such as dystonia, swallowing challenges or unsteadiness with walking, may develop.
Some people develop spasticity, which is an excessive tendency for muscles to contract in response to stretching, such as by a doctor with a reflex hammer or even by normal, voluntary movement. This can produce constant flexion or extension of joints and, in some cases, muscle pain. If the normal range of a dystonic or spastic joint is not maintained by therapy or splints, the muscles and tendons can form contractures, where the abnormal position becomes permanent.

People with CBD can experience changes to cognitive function, especially in more advanced stages of disease. This is usually in the areas of processing speed and organization of thoughts, planning, multitasking and word-finding. Sometimes people with CBD can act impulsively or may lose some behavioral inhibitions.

Most people with CBD live five to ten years after the onset of symptoms but some live much longer. Minimizing complications, such as swallowing problems, infections and falls, can greatly improve life expectancy. Your doctor may recommend regular examinations of your swallowing function to ensure that food is not potentially entering the lungs where it can cause pneumonia. They may also refer to rehabilitation therapists for recommendations for adaptive equipment to improve safety with ambulation, and other preventative measures. Quality of life is enhanced by attentive care, maintaining general health, and perhaps most important, by an optimistic and hopeful attitude on the part of both the patient and family.

We recognize this information can be scary and overwhelming to learn and to think about. It can be helpful to talk this through with your medical team and your family, including planning for the future and your wishes for quality of life. CurePSP and the rest of your support system are here to help.

What is happening in the brain to cause CBD?

In people with CBD, some groups of brain cells break down and die off. This happens because of the abnormal folding and clumping of a protein in the brain cells called tau. Tau is a normal protein found in brain cells. An important part of tau's 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 a toxic effect of the tau protein clumps themselves and not by the reduced availability of tau for its normal function.

Tau misfolds and clumps in about 30 other diseases, including Alzheimer's disease, PSP, chronic traumatic encephalopathy, and about half of all cases of frontotemporal dementia, and the initial cause or causes may be different for each. The specific disease depends on the chemical characteristics of the tau clumps and which sets of brain cells are vulnerable to that specific abnormal form of tau. All of these variable features, as well as the ultimate question of why tau disorders occur in some people and not in others, may come down to genetic differences or exposure to certain chemicals or a combination of these. We do know that the physical shape of the mis-folded tau is the same in everyone with CBD and different from that in PSP, Alzheimer's and the other tau-based disorders. Knowing the misfolding pattern is helping scientists design drugs for CBD's specific form of tau.

For people who are personally impacted by CBD, we recognize that not knowing the cause can be extremely frustrating and confusing. Researchers and doctors are working hard to understand CBD and other related neurodegenerative diagnoses, and we hope this will lead to more answers and treatment options soon.

What are the subtypes of CBD?

The microscopic brain abnormalities of CBD can affect different parts of the brain, producing different symptoms in different people. In all forms of CBD, nearly all patients at some point develop a degree of motor parkinsonism, meaning stiffness, slowness, soft speech, reduction in facial expression, balance difficulty and tremor.

The most common subtype of CBD is called corticobasal syndrome, which affects about half of all people with CBD. About a quarter of people with CBD have symptoms that resemble PSP, which impacts balance, eye movement, speech and swallowing. Another 15% have symptoms of frontotemporal dementia, with inappropriate, uninhibited behavior and difficulty organizing thoughts. Then there are two rare forms, each accounting for about 5% of the total number of cases of CBD. One has a dementia similar to that of Alzheimer's disease, with particular 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.

What is corticobasal syndrome, and how does it differ from corticobasal degeneration?

The classic type of CBD is called corticobasal syndrome (CBS), which starts with difficulty moving one limb, apraxia, dystonia, slowness, stiffness and some degree of sensory problems. The term "syndrome" means a set of abnormalities that appear in the same person at the same time but may or may not be caused by the same underlying disease in every case. It turns out that only about half of all people with CBS actually have the disease corticobasal degeneration. About 20% of those with CBS have the same brain abnormalities that underlie Alzheimer's

disease (but in an anatomical pattern that causes CBS) and another 20% have the same brain abnormalities that underlie PSP. A few are caused by the abnormalities underlying dementia with Lewy bodies or other rare conditions.

Because it is very difficult during life to tell if someone with corticobasal syndrome in fact has corticobasal degeneration as their underlying brain disorder, neurologists are increasingly using the term "CBS" in reference to living patients and "CBD" only in reference to autopsy-proven corticobasal degeneration.

Regardless of the term used or the specific set of neurological signs and symptoms, treatment and care should be tailored to meet the unique needs and preferences of the individual.

How is CBD diagnosed?

Accurately diagnosing CBD can be difficult or sometimes impossible for even the most experienced neurologist. There are no generally accepted blood tests or spinal fluid tests for CBD. To diagnose CBD, a neurologist will gather a person's medical history, including neurological symptoms, and perform a physical examination. Brain scans, such as MRI, CT and PET, can show an asymmetric loss of bulk or function in certain parts of the brain, usually asymmetrically, corresponding to the asymmetry of the outward signs and symptoms. The brain imaging is most useful in ruling out other conditions, such as stroke or multiple sclerosis.

How is CBD treated?

At this time, we have no medication to cure CBD or to slow its progression. Doctors will usually attempt a trial of carbidopa-levodopa, which is the most common medication used to manage Parkinson's disease. Unfortunately, the response to this medication is typically not nearly as dramatic or long-lasting as it is in Parkinson's disease. Still, for some people, it can help to manage slowness and stiffness of CBD. If it is not helpful for someone's symptoms at all, or if the benefit is outweighed by side effects, which can include sleepiness and nausea, the doctor may recommend decreasing the medication over a week or two and then stopping it.

Amantadine is an antiparkinsonian drug that can sometimes help with the freezing of gait in CBD. The dosage of amantadine should not exceed 200-300mg per day because at higher doses, it can cause confusion, constipation and urinary retention. Other drugs often used for Parkinson's disease, such as dopamine agonists, COMT inhibitors and MAO-B inhibitors, do not help CBD and can cause a number of side effects. Additionally, the various extended-release formulations of carbidopa-levodopa do not help more than the regular formulation. However, the orally dissolvable form of carbidopa-levodopa may be easier for people with CBD who have difficulty swallowing pills.

The sometimes-painful muscle spasms that can be experienced by some people with CBD may respond to muscle relaxant drugs, such as cyclobenzaprine, baclofen and tizanidine. A medication for seizures called levitiracetam can also help this symptom and may be better

tolerated than the traditional muscle relaxants. Baclofen and clonazepam, two drugs commonly used for dystonia and spasticity in other disorders, can also help those symptoms in CBD. The most common side effect of these drugs is sleepiness and baclofen can also cause muscle weakness, which could contribute to falls. If it is a bothersome symptom, the myoclonus of CBD, may respond to clonazepam or levitiracetam.

The dystonia of CBD may respond to injections of botulinum toxin (Botox and other brands) into the affected muscles, especially for involuntary eyelid closure ("blepharospasm"). Botulinum toxin may also help limb or neck rigidity in CBD, but higher doses are required than in other disorders because in CBD, spasticity may also be present. While botulinum toxin can improve flexibility and pain in the dystonia of CBD, actual improvement in functional ability is unlikely. Injections into neck muscles must be done with caution, as the fluid can spread into nearby swallowing muscles, which may already be impaired by the disease process.

Generally, the greatest benefit to CBD offered by medication comes from treating specific symptoms in the same way they would be treated if occurring as part of some other disease. Neurologists are familiar with these measures even if they are unfamiliar with CBD. Your doctor will work with you closely to try different medications, timing and dosages to maximize the benefits for your symptoms while also trying to minimize side effects.

What else besides medications can help to manage the symptoms of CBD?

Unfortunately, none of the surgical approaches that can help Parkinson's, such as deep brain stimulation, pallidotomy or focused ultrasound, help CBD. However, cardiovascular exercise can slow the progression of motor decline in most neurodegenerative conditions and exercise is a very important part of disease management for people with CBD. Physical, occupational and speech therapy are also important pillars of treatment to address many of the symptoms and challenges faced by people living with CBD, such as speaking, swallowing, balance and daily activity performance. Home safety evaluations performed by trained physical and occupational therapists are extremely useful to help prevent falls and to recommend adaptive equipment such as grab bars, shower chairs, walkers or wheelchairs.

Devices to support the affected body part are also recommended, as are orthotic devices to slow the progression of dystonic posturing. An exception is dental splints for jaw dystonia, which are generally not tolerated by those with CBD.

Much more on the drug and non-drug treatment of symptoms of CBD can be found in a peer-reviewed journal article, "Best Practices in the Clinical Management of Progressive Supranuclear Palsy and Corticobasal Syndrome: A Consensus Statement of the CurePSP Centers of Care." It is available for free at: *www.frontiersin.org/articles/10.3389/fneur.2021.694872/full*

Is CBD genetic?

CBD almost never runs in families and is not considered a genetic disease. 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. We don't yet know how that version of the tau gene actually affects brain cells. It may increase the amount of tau protein produced or it may change the chemical properties of the protein. Slight variations in six other genes have also been found to be present at greater frequency in those with CBD than in others, and we have only vague ideas about how they may contribute to the cause of CBD. It is important to understand that each of these six gene variants is only very slightly more common in people with CBD than in other people and, even when their effects are totaled, do not explain the cause of CBD. Research being done on these gene variants could pinpoint just what is going wrong in CBD, even in people without any of those mutations. Then drugs could be found or designed to address that specific brain molecule or function.

What research is being done to better understand and treat CBD, and how do I get involved in research?

Due to the rarity of CBD and the difficulty with diagnosing it accurately, drug trials in CBD are not common. To properly test a drug and understand its impact, patients need to be recruited from a number of sites. The fact that only about half of the patients who have the outward corticobasal syndrome actually have corticobasal degeneration, means that the results of a drug trial can be difficult to interpret. Some drug companies and researchers have discovered a new way to get around the problem of recruiting a pure CBD trial patient group. When testing a drug that acts on the tau protein, they recruit patients with any tau-related disease and don't worry about exactly which one they have. To avoid enrolling patients with Alzheimer's disease brain changes as the cause of CBS, such trials screen candidates using a type of brain PET scan that detects the beta-amyloid of Alzheimer's. This approach, where one treatment is tested in a group of diseases sharing that drug's "target" (in this case, tau aggregates), is called a "basket trial" and has been used successfully for years by cancer researchers working with rare conditions.

As far as we can tell at this point, because of the similarities between PSP and CBD, when medications for treating, preventing or curing PSP are created, they will likely be beneficial for people with CBD. So, it's a good idea for those with CBD to keep an eye on new developments in PSP.

When there are opportunities to participate in research for CBD, many people with CBD find that this is a meaningful way to help doctors and scientists understand and treat CBD and related diseases. In the United States, clinical trials are listed on a website maintained by the National Institutes of Health, *www.clinicaltrials.gov*. You can enter "corticobasal degeneration" or "corticobasal syndrome" into the search box. You can also visit

www.curepsp.org for a list of active and pending treatment trials in CBD. Keep in mind that "observational" studies, where information is gathered but no treatment is offered, are important ways for researchers to devise diagnostic tests and to find clues to help develop future drugs. Such studies are listed alongside "interventional" studies in *clinicaltrials.org* and those with CBD and their families should consider participating in one.

Additionally, you can ask your neurologist if they are offering or are aware of studies in CBD at their own center or nearby. The neurologists perhaps most likely to know of research trials in CBD are those in CurePSP's Centers of Care network. For more information, visit *www.psp.org/ineedsupport/centers-of-care/*

While it may be difficult to think or talk about, donating one's brain to science can be a powerful contribution to the understanding of CBD and other neurodegenerative conditions. Each donated brain is also evaluated by a trained neuropathologist to confirm that the diagnosis of CBD was correct. Setting up a brain donation is easiest if done early, ideally months or even years prior to someone's passing, when they can meaningfully participate in the decision. Visit www.psp.org/ineedsupport/braindonation to learn about CurePSP's Brain Donation Assistance Program.

What can I do to support myself and my family with this diagnosis?

Building a support team is foundational to quality of care and life with CBD. Your support team may consist of your partner, family, friends, support group, religious community, healthcare team, professional care and others—people who care about you and show up for you.

When living with a chronic and progressive diagnosis, it is important to find the right medical team to support your needs with CBD over time. CBD needs to be managed by a neurologist. This could be a general neurologist, but, if available in your area, you may also choose to work with a neurologist who has gone through specific training in movement or cognitive disorders. Clinical social workers, nurses and rehabilitation therapists (physical, occupational, pelvic and speech/swallowing therapists) also play important roles in the care of CBD. As symptoms and needs arise, you may also benefit from adding other specialists to your team, such as a urologist, neuro-ophthalmologist or palliative care specialist. Taking care of your emotional health with CBD is also a priority for both the patient and the family. It can be exceptionally beneficial to work with a mental health professional to process the experience, foster coping skills or address other emotional needs. When building your care team, it is important to have providers you like and trust, and to keep in mind that you can change your providers if needed.

Health care advance directives are excellent tools for sharing your wishes regarding care with your support team. Health care advance directives address topics such as how aggressive your medical care should be (for example, whether you would want a feeding tube if the need arose) and how you define quality of life. These directives should be completed with your family and your doctor, and should be reviewed at least annually in case your wishes change.

Many people living with CBD consider professional care services, such as in-home care, adult day care, or long-term care, depending on their care needs and situation. These services can provide an additional layer of support, including companionship or hands-on help for the person with CBD as well as assistance and respite for the family.

It can also be valuable to connect with other people affected by the same diagnosis as you and your family, through support groups or a peer support network. It can feel validating and uplifting to hear others' experiences and insights on how they have adapted to life with CBD. You can exchange helpful tips on ways to cope physically and psychologically with the diagnosis. There are a handful of support groups specifically for CBD and many more for atypical parkinsonism (which can include progressive supranuclear palsy and multiple system atrophy) in the United States and other countries. Visit *www.psp.org/ineedsupport/supportgroups* for a list of regional and virtual support groups facilitated by or in collaboration with CurePSP. Additionally, CurePSP offers educational symposiums and webinars where you can learn about CBD and connect to the community.

We recognize that a diagnosis of CBD can bring up many emotions, changes and considerations. No matter how you find support, please remember that you do not have to navigate the CBD journey alone.

The mission of CurePSP is to raise awareness, build community, improve care and find a cure for PSP, CBD and MSA.

Please contact CurePSP for additional information and resources:
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We also send our appreciation to the individuals and families living with CBD who contributed to the creation of this resource.

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Special note regarding the front cover:

The "swallow tail sign" refers to a unique feature sometimes found on brain imaging that can be used to support a clinical diagnosis of CBD. For some, the bird called a swallow-tailed kite is a symbol of wisdom, adaptability and grace, and it is our hope that this can be a source of hope and strength for our community.