Transcript

Welcome and Introductions

Rebecca Gilbert, MD, PhD

[Slide 1] Welcome everyone and thank you so much for joining us today.

[Slide 2] My name is Rebecca Gilbert, and I am APDA's Vice President and Chief Scientific Officer.

I'm pleased to welcome you to this Web/teleconference education program designed for people with Parkinson's disease, care partners, family members, and healthcare providers. I would like to thank Acadia Pharmaceuticals for funding this important program and acknowledge their appreciation of the critical need to provide educational programs like this one to people impacted by Parkinson's disease. During this time of uncertainty, we know that you still have concerns regarding your Parkinson's treatment and identifying ways to continue to live your best life with PD.

American Parkinson Disease Association, or APDA for short, is the largest grassroots network dedicated to fighting Parkinson's disease and works tirelessly to assist the more than 1 million Americans with Parkinson's disease. APDA distinguishes itself as the national organization working one-on-one with the Parkinson's community to make each day better. And now to our program.

[Slide 3] Our presenter today is Dr. Daniel Weintraub, Professor of Psychiatry at the University of Pennsylvania School of Medicine and Psychiatrist at the Parkinson's Disease Research, Education and Clinical Center at Philadelphia VA Medical Center in Philadelphia, PA.

Today we are delighted to have Dr. Weintraub share with us the latest information about brain health in Parkinson's disease. After the presentation, we will open the program for questions from both telephone and Web participants. We encourage everyone on the line to complete the evaluation after the program because your feedback is instrumental in helping us plan for future educational offerings, including teleconferences like this one and other programs.

It is now my pleasure to turn the presentation over to Dr. Weintraub.

Presentation

Daniel Weintraub, MD

Thank you, Rebecca, and for the invitation to present today and to the American Parkinson's Disease Association, and good morning and good afternoon to everyone on the line. It's my pleasure to be with you today, particularly in this difficult environment and climate that we're all living in.

As you can see from the slide, I'm a psychiatrist; and for the past approximately 20 years, I've been seeing patients with Parkinson's disease almost exclusively, first involved in clinical care, now involved in clinical research. And as a psychiatrist, formerly a geriatric psychiatrist by training, I treat the psychiatric and cognitive aspects of Parkinson's disease. I work in collaboration with movement disorders neurologists and don't manage the motor symptoms of the illness but collaborate and work closely with a movement disorders specialist at the University of Pennsylvania and the Philadelphia Department of Veterans Affairs. I just wanted to provide that little bit of background.

[Slide 4] Here are my financial disclosures in terms of research funding or support, honoraria, and licensee payments for research that I've been involved in.

[Slide 5] These are the goals of the presentation for today. In a relatively brief period of time, approximately 30 minutes, it's only possible to cover so many disorders and to go into so much depth; and we'll have a chance at the end for any specific questions or comments that people have. But I want to provide an overview of the neuropsychiatric symptoms and cognitive changes that can occur in the course of Parkinson's disease, both how they present, potential risk factors, how to assess them from a clinical standpoint, and how to best manage them.

We recognize that nonmotor symptoms currently may have the greatest impact on the quality of life, function, and caregiver burden in Parkinson's disease. It may not have always been this way, but the recent advances over the past decade to two in the management of the motor symptoms of Parkinson's disease have really brought to the fore the importance of these nonmotor symptoms, including the psychiatric and cognitive ones that I'll be discussing today.

[Slide 6] What are some of the potential neuropsychiatric symptoms in Parkinson's disease? So, the ones that are highlighted here in blue are the ones that I'll focus on today, partly because they're among the most common and well-studied, but also because time only allows to cover so much. So, depression and anxiety, which are sometimes together called affective disorders, psychosis, impulse control disorders, and cognitive changes. And I'll touch briefly on disorders of sleep and wakefulness, fatigue, and apathy.

[Slide 7] First, I'd like to start with some caveats, particularly when I'm speaking to an audience primarily of patients and loved ones. So, first, many Parkinson's patients have no or few psychiatric or cognitive complications. So, it's not that these changes are inevitable or happen even to the majority of the patients. Psychiatric and cognitive complications are not the fault of and do not represent weakness in the patient, and I think that's true for mental illness in general, and I think it's particularly true for patients with Parkinson's disease, given the strong connection between the biological

changes that happen with Parkinson's disease itself and these psychiatric and cognitive complications I'm talking about.

PD patients, Parkinson's disease patients, in general, cope extremely well given that they have a chronic, progressive, and sometimes disabling disease. That has been brought home to me time and time again over the past 20 years that I've been working with Parkinson's patients.

And, finally, the family members and caregivers of Parkinson's disease patients, who I often meet – it's much more common I see a patient with a family member than I see a patient by him or herself. These family members and caregivers are, in general, remarkably supportive and understanding and helpful. So, those are some important caveats I wanted to make to what is to follow.

[Slide 8] Having the illness or its treatments may have unrecognized or underrecognized beneficial effects. Potential mood or cognition benefits for a particular class of medication, dopamine agonists or monoamine oxidase inhibitors, there's some evidence for that. There may be enhanced creativity for patients that are treated with dopamine agonists, that's been reported. And then, finally, we had done some, what's called qualitative research with Parkinson's disease patients and their loved ones, primarily spouses, some time ago and found that there seemed to be a greater understanding and appreciation of life and relationships that comes out of having an illness such as Parkinson's disease. Things such as personal growth, greater marital equality for both members of the marital dyad. So, I think these are important points to make also about the illness.

[Slide 9] Let's go ahead and jump into the first one of the disorders that I wanted to cover, which is depression.

[Slide 10] I sometimes refer to Robin Williams when discussing this topic of whether Parkinson's disease depression or depression in the context of Parkinson's disease is due to some psychological effect of having the illness or to the biology of the illness. And, really, the two are intricately linked and can't be separated. And the reason I mentioned Robin Williams was because it was noted that when he first was diagnosed with Parkinson's disease, eventually his diagnosis changed to dementia with Lewy bodies, but it's that it was an extremely life-altering event for him; and that's true for anybody with Parkinson's disease. To be diagnosed with a chronic, progressive, neurodegenerative disease is, without a doubt, a life-altering event. And there are challenges every step of the way in having an illness such as this because there's no doubt that there's a psychological impact to having the illness.

In addition to that, we know very well now that there are biological reasons that somebody may become depressed with Parkinson's disease, that the brain regions and chemicals that are affected by Parkinson's disease are also those that are responsible for mood regulation. And we know from studies that there's increased rates of depression prior to the onset of motor symptoms, which we now call prodromal Parkinson's disease. So, these are patients who don't even know they have Parkinson's disease but yet are at increased risk for mood disturbances. And that's because some of the earliest brain regions that are affected, prior to the regions that are affected that control motor symptoms, are those that are responsible for mood regulation.

[Slide 11] What are some of the risk factors or symptoms accompanying depression? Well, we know that there's a higher frequency in females, female Parkinson's patients compared with males, and

those with cognitive impairment. However, that's also true for depression in the general population. About 10% to 15% of patients with Parkinson's disease now receive deep brain stimulation at some point during the illness, and the question often arises, "What about its effect on mood?" Well, in general, depressive symptoms or depression rating scales improve on average after DBS surgery, deep brain stimulation surgery; and there's some question about whether one of the lead placements commonly used, the GPi, or globus pallidus interna, may have better mood outcomes than the STN, or subthalamic nucleus placement, although that's still somewhat controversial.

When researchers have looked at risk factors to predict depression, some of the same risk factors in the general population seem to explain most of the risk in Parkinson's patients as well: higher age, female sex, a prior depression history personally, a family history of depression, and other medical conditions. There are relatively few Parkinson's variables themselves that predict depression other than perhaps more advanced disease.

[Slide 12] Depression in Parkinson's disease can be complex to diagnose because when we look at our diagnostic and statistical manual, what's called DSM currently in its 5th iteration, so DSM-5, we have nine symptoms that we can use to diagnose depression; and five of those nine are common in Parkinson's disease, regardless of the presence of depression: so changes in sleep; changes in appetite and weight; psychomotor slowing, so mental, physical slowness; fatigue; changes in concentration and thinking. We know that all of these can occur in Parkinson's, regardless of depression. The best that we can do is say that we try, and unless there's some compelling reason not to, if somebody has one or more of these symptoms or has a combination of them, we tend to recommend counting them toward a diagnosis of depression so that we're not underrecognizing and undertreating somebody who may have a treatable condition, depression.

One thing we do though is emphasize mood as opposed to loss of interest because loss of interest can also be found to be the defining characteristic of apathy, a lack of motivation. So that's one way to try to distinguish depression from apathy is by emphasizing the mood changes and also to focus on cognitive symptoms of depression that would not be confounded or overlap with the illness itself. The cognitive symptoms would include helplessness, hopelessness, even thoughts of death, feelings of guilt. So, we may try to emphasize those symptoms to see if somebody has those to support a diagnosis of depression.

[Slide 13] What about the management/treatment of depression in Parkinson's disease? Well there's been a lot of progress over the past decade or so with multiple, what we call randomized, controlled trials. So those are the highest level of scientific evidence for a medication for a treatment. We have evidence that an older antidepressant, a tricyclic antidepressant called nortriptyline; a selective serotonin reuptake inhibitor or SSRI, paroxetine in this case; a serotonin norepinephrine reuptake inhibitor or an SNRI called venlafaxine in this case; and, finally, even one of the Parkinson's disease medications, a dopamine agonist called pramipexole have all been shown to be beneficial for depression in Parkinson's disease. There's also been a relatively recent positive study for one specific type of psychotherapy called cognitive behavioral therapy.

[Slide 14] In terms of medication tolerability, because any time somebody with Parkinson's disease is exposed to a medication, a psychiatric medication, you want to know it, not only does it work but how

is it tolerated. The SSRIs, there is some case literature in psychiatry, not in Parkinson's, but psychiatry of them causing tremor, so more of an essential tremor. That's the tremor when your hands are extended as opposed to a resting tremor that's characteristic of Parkinson's disease. But the best evidence comes from randomized, controlled trials; and in that randomized, controlled trial that included both venlafaxine and paroxetine, two of the medications I mentioned before, both were found to be very well-tolerated from a motor standpoint, from a parkinsonism standpoint.

The other question about antidepressant treatments in Parkinson's disease is the co-prescribing of MAO-B inhibitors (monoamine oxidase-B), the most commonly, that would be selegiline and now rasagiline and any antidepressant. Where it will bring up a red flag, particularly from a pharmacy, for something called serotonin syndrome, which is acute change in mental and neurological state. But anecdotal experience is that this is extremely rare, probably less than 1% based on data from a recent randomized, controlled trial. So, patients should be warned if they are going to be co-prescribed a MAO-B inhibitor and an antidepressant. But I will say that it's commonly done, both by neurologists and by psychiatrists including myself.

[Slide 15] Anxiety is often covered in conjunction with depression, and the reason for that is that most patients with an anxiety disorder also have depression and vice versa, at least within Parkinson's disease. My clinical experience is that anxiety is often more disabling than depression, both from a psychological standpoint, the distress that it brings on patients, and also physically distressing, particularly for people with severe anxiety or anxiety attacks where your heart can beat very fast, you can become short of breath, your stomach becomes upset. It can be a very physically upsetting experience.

The presentation of anxiety can either be generalized anxiety disorder, so that's anxiety symptoms day in and day out the majority of the time. It can be social anxiety symptoms where patients may be reluctant to be in public over embarrassment over their Parkinson's symptoms, or may even become agoraphobic and reluctant to leave the house. And then, finally, anxiety attacks or panic attacks. These may be particularly associated with fluctuations in motor symptoms or one-off periods, and we now call these symptoms nonmotor fluctuations. So as a patient's wearing off their Parkinson's medications, if they experience psychological or psychiatric distress, those are called nonmotor fluctuations.

[Slide 16] In terms of treatment, we really lag compared with depression in the management of anxiety and Parkinson's disease. There's been no published treatment studies that are adequate. We use newer antidepressants because all antidepressants not only have FDA approval for depression but also for anxiety symptoms as well. And we use them over antianxiety agents or benzodiazepines first because they tend to be better tolerated.

Sometimes we do need to use benzodiazepines, and the three that are used the most commonly, at least in my practice, are lorazepam, alprazolam, and clonazepam. But we have to be cautious because they can have cognitive side effects, they can have sedation as a side effect, and they can also lead to changes in balance and gait. And all three of those would be very problematic side effects in a Parkinson's disease patient. So, we tend to start at a low dosage, and they can be used

on an as-needed basis, what we call PRN or on a scheduled basis, depending on the nature of the symptoms and the tolerability.

There are some patients who experience anxiety when they develop some mild cognitive changes because they find cognitive tasks more challenging and more frustrating and become anxious. Some of those patients may respond to a cognitive-enhancing medication in terms of also improving their anxiety.

[Slide 17] A third major psychiatric syndrome that can occur in Parkinson's disease is called psychosis.

[Slide 18] To a psychiatrist, psychosis means two primary symptoms. They can occur independently of each other or together. Visual hallucinations are what were first reported most prominently in Parkinson's disease, but we now recognize that people can have hallucinations in any sensory domain, including auditory, olfactory, and tactile. So, really, we have to ask about hallucinations across the board, not just visual changes. Related to hallucinations are illusions, which are a misidentification of an actual stimulus where hallucination is where there is no stimulus at all.

There's also something called passage and presence phenomena. Parkinson's patients sometimes report feeling something in the periphery or noticing something in the periphery of their vision that's moving, and that would be a passage phenomenon or they may actually feel the presence of something, including a human being in the periphery of their vision, and that would be presence phenomena.

Delusions are fixed, false beliefs, so a subset of patients with psychosis also experience delusions. They tend to be less common than hallucinations and typically occurring in those with more severe cognitive impairment. The description of the delusions most typically fits what we call paranoia, which are persecutory ideations, the feeling that somebody is trying to do something to the patient in some way. It could be spousal infidelity, it could be intruders in the house, so that's the general flavor of the symptoms.

Unfortunately, psychosis, if it becomes severe enough, can lead to institutionalization. It's one of the more common reasons for institutionalization or hospitalization in Parkinson's disease because it can be accompanied by agitation, it can impair sleep; and when those things start to happen, it leads to significant caregiver burden.

[Slide 19] There's a complex etiology for psychosis in Parkinson's disease, and some of the factors associated with it include a range of Parkinson's disease medications; and the more that you're on and the higher the dosages, the worse that it can be in terms of its risk for psychosis, increasing severity of Parkinson's disease, and more advanced disease, and cognitive impairment. So those patients with significant cognitive changes, significant memory changes, for instance, compared with those who have intact cognition are more vulnerable to developing psychosis. Increasing age is also a risk factor. Visual impairments that can occur in Parkinson's disease, comorbid psychiatric disorders including REM (rapid eye movement) sleep behavior disorder, also known as RBD. But likely there's a complex interaction between all of these variables and also involving three key brain chemicals or neurotransmitters. Dopamine, which is most closely linked with the motor symptoms of

Parkinson's disease, serotonin, which I've already mentioned in terms of depression, and acetylcholine which is most closely linked with cognition or thinking ability. But all three of these neurochemicals also potentially play a role in psychosis in Parkinson's disease.

[Slide 20] In terms of the clinical management of Parkinson's disease, there's expert consensus about how to best manage the Parkinson's medications, so they tend to get discontinued in the order that I have listed on this slide, top to bottom. Anticholinergic medications first, then one called amantadine, then dopamine agonists, then monoamine oxidase-B inhibitors; and then finally at the end of the day, the Parkinson's disease clinician, the neurologist, is typically using levodopa primarily to manage the motor symptoms of Parkinson's disease.

[Slide 21] In terms of antipsychotic treatment, sometimes if these steps mentioned above don't work, if an acute medical condition and infection that might also be causing hallucinations is ruled out and treated, we do have to resort to antipsychotic treatment. So, there it becomes balancing the potential benefits, the antipsychotic benefits versus risk, including worsening parkinsonism.

The two most commonly prescribed antipsychotics over the years have been one of the atypical antipsychotics, a newer one called quetiapine, which has been really the antipsychotic of choice for most neurologists for a long time now in dosages ranging from 25 to 200 milligrams per day. However, one important point to make about quetiapine is that all the clinical trials have been negative or inconclusive to date, so we don't really have a good sense, other than clinicians' personal anecdotal clinical experience about whether that medication [or] this medication is effective for psychosis in Parkinson's disease.

One medication that has been shown to be effective, but is rarely used, is one called clozapine at lower dosages. It's an older atypical antipsychotic and in a couple of studies was shown to be beneficial. However, since patients have to have routine blood monitoring to monitor for a low white blood cell count, it's not commonly used by clinicians.

And then, finally, there's a third compound that was approved a couple of years ago now, FDA approved specifically for the treatment of Parkinson's disease psychosis called pimavanserin; and it affects the serotonin system but not the dopamine system at all. So that puts it in contrast with other antipsychotics; so, therefore, there's less concern about worsening motor symptoms if you're not blocking the dopamine system.

There was, after its release, some stories that arose out of the popular press expressing some concern about whether there might be an elevated death risk with pimavanserin; and I will say this caused complications for both patients and clinicians. We've had a chance to be involved in research going back a while now looking at the risks of antipsychotics and both death and medical worsening in patients with Parkinson's disease, and this comes out of the literature of general dementia patients such as Alzheimer's disease having an increased risk with antipsychotic exposure for death and morbidity or medical complications.

We did show in previous research before pimavanserin came out that that risk may be there for Parkinson's disease patients as well, and that's important to note, a slightly increased risk. I'd say

there hasn't been enough data to really weigh in on pimavanserin one way or the other at this point and that additional research is needed to determine where pimavanserin fits into this picture.

[Slide 22] One of the last two conditions I wanted to cover was impulse control disorders.

[Slide 23] So impulse control disorders are a DSM-5 category that used to include compulsive behavior such as compulsive gambling, sex, buying, and eating behaviors. Those are the four major impulse control disorders that have been reported to occur in Parkinson's disease.

And I give some examples of how that can actually present. For gambling, it can be going to casinos or frequent low stakes such as slot machines, scratch cards. Sexual behaviors could be demands on the spouse for sexual activity, use of pornography sites on the Internet, prostitution, and even changes in sexual orientation can occur. Buying can be purchasing the same items repeatedly, leading even to hoarding behaviors, and these are in excess of what's needed. And, finally, eating can be craving for certain foods, overnight eating when there is craving, it's typically for sweets.

And there's some related behaviors, one called dopamine dysregulation syndrome, which is more like a psychiatric addiction disorder where patients are misusing and escalating the dose of their Parkinson's medications. Most commonly it's levodopa. And hobbyism which is just any task that a person takes to the extreme, so repeating a task over and over without any real clear reason or purpose.

[Slide 24] The frequency of these behaviors could be as high as 15% to 20% of patients, particularly those treated with a dopamine agonist, which is the medication most closely associated with it. If you add in related behaviors, it could be up to a quarter of Parkinson's patients could experience some symptoms along these lines over the course of the illness. And it's, again, highest in people treated with a dopamine agonist relative to other Parkinson's medications like levodopa.

If a person has one impulse control disorder, there's about a one-in-four chance that they have two or more. So, when I ask patients about these symptoms, I don't ask about just one disorder but all of them. And the other point to make about this is that the symptoms may not present until many years after initiating dopamine agonist treatment. One study that we had data for showed that it was about four to five years after initiation was really the average time of onset. So just because somebody doesn't have symptoms after a year or two years of treatment doesn't mean that you don't need to keep asking about these symptoms.

[Slide 25] Some of the associated factors. Dopamine agonist treatment, at any dose apparently, even lower dosages. Higher-dose levodopa, so maybe not lower doses as much. There's also been shown an association even with amantadine and rasagiline. So, to me, really any Parkinson's disease treatment potentially can cause this. Younger age or younger age of onset seems to be associated with impulse control disorders. There may be sex differences for particular behaviors, which also reflect how these behaviors present in society at large, and male sex for sexual behaviors and female sex for buying and eating behaviors. And, interestingly, a personal or family history of similar behaviors is also associated with this.

[Slide 26] In terms of the management of these symptoms when they occur, we'll typically look first at modifying the Parkinson's disease medications. So, one way would be to decrease the dopamine agonist dose and to offset that by increasing the levodopa dosage. But we now recognize that some people experience a syndrome called DAWS, or dopamine agonist withdrawal syndrome, which has physical and mental symptoms of substance abuse withdrawal that can be very problematic for patients, makes them very uncomfortable, and sometimes causes them to go back on the dopamine agonist, at least at a lower dosage.

There's some very preliminary evidence that perhaps longer-acting oral or alternative delivery patch dopamine agonists may be associated with less impulse control disorder symptoms than the shorter-acting dopamine agonists.

Deep brain stimulation tends to help with these symptoms, particularly when it's accompanied by a Parkinson's disease medication decrease post-surgery. Some psychiatric medications are used off-label but with little evidence, I would say. We did conduct one study with what's called an opioid antagonist, called naltrexone. Naltrexone is actually FDA approved for the treatment of alcoholism, and in that study, we did show benefit on an impulse-control disorder rating scale for naltrexone treatment, and there's also been psychotherapy study that's been shown to be beneficial for these symptoms. And I will say psychotherapy or at least counseling is often crucial, given the problems that can arise with these symptoms when they occur.

[Slide 27] Then, finally, cognitive changes.

[Slide 28] So when we talk about cognitive changes in general, we talk about somebody either having normal cognition or mild cognitive impairment or a more severe level of cognitive impairment called dementia. So mild cognitive impairment is where there's been some change compared with your pre-Parkinson state in this case, some impairment when we do cognitive testing, but not so severe that there's functional impairment for the patient. Dementia is when there's greater impairment on the testing that we do and also some clear significant functional impairment that then meets the criteria for what we call dementia.

Sometimes the question comes up about what's the difference between Parkinson's disease and dementia with Lewy bodies, and at this point it's very complicated to explain. But typically, once somebody has an established diagnosis of Parkinson's disease and then develops dementia at some point down the road, we say that person has Parkinson's disease dementia. If the dementia comes very early or precedes the onset of the parkinsonism, then they're more likely to meet criteria for dementia with Lewy bodies, and they shouldn't be diagnosed with both. They also shouldn't be diagnosed, the person with both Alzheimer's disease and Parkinson's disease. You can have Alzheimer's disease and then develop some secondary parkinsonism, or you could have Parkinson's disease and develop cognitive changes, but we then call that Parkinson's disease with cognitive impairment. But, really, somebody should not meet clinical criteria for both Alzheimer's disease and Parkinson's disease.

[Slide 29] In terms of risk factors for cognitive changes, increasing age, increasing severity of the Parkinson's symptoms, and male sex are all what are most strongly associated with cognitive impairment in Parkinson's disease.

Atypical Parkinson's disease features, so lack of a tremor but more of what's called the akinetic-rigid syndrome where people have more problems with balance or gait might be more associated with this. There's also some evidence that patients that undergo deep brain stimulation, on average, have a mild decrease in cognitive abilities over time. So if they're tested six months later or one year or two years later, they may do a little bit worse on their cognitive testing than somebody who did not go through deep brain stimulation, and that could be a mix of both the surgical effects of the surgery itself or the stimulation effects, the stimulator.

[Slide 30] The cognitive profile in Parkinson's disease we now recognize can affect any of the five commonly examined domains, so that's why we test all five of these if possible. Executive abilities are those that require planning, sequencing, adapting, problem-solving. Attention is one's ability to pay attention, sustain attention. Visual-spatial abilities are the ability to navigate objects and space or to work in three dimensions, such as might be required for driving abilities.

Memory is the ability to register, remember, and discriminate in terms of memory, and changes in that regard can happen in Parkinson's disease. And then language, particularly ability to express or understand language, and one common language issue that Parkinson's patients describe are word-finding problems.

[Slide 31] In terms of treatment, we have two major classes of medications. Unfortunately, they both come from the Alzheimer's disease world. They weren't developed for Parkinson's disease. One is called cholinesterase inhibitors of which there's three. And one, rivastigmine, one of the three, is FDA approved for Parkinson's disease dementia. But I will say the benefits are modest overall. Still, they probably are underutilized in Parkinson's disease patients. They tend to be well-tolerated, but there can be some nausea and vomiting and tremor with this class of medication.

And the other major class approved for Alzheimer's disease but also tested in Parkinson's is called memantine, and there have been a couple of studies in patients with Parkinson's disease dementia. I would say the data is inconclusive regarding this, about whether it actually improves cognition or not.

[Slide 32] Well, what else can be done while we're waiting for newer treatments to be developed, tested, approved? Well, in terms of general good cognitive fitness tips or cognitive health tips, cardiovascular exercise and maintaining a good Body Mass Index as is possible; cognitive exercise, so challenging oneself as often as possible through whatever games or exercises one finds challenging and entertaining; managing vascular risk factors, so things such as high cholesterol levels, high blood pressure, diabetes if applicable. That can all help minimize cognitive decline.

Thinking of what particular medication classes, anticholinergic medications, benzodiazepines, and pain medications such as opioids. Treating psychiatric symptoms, many of which are linked with cognitive changes in Parkinson's disease. Getting a good night's sleep. We know that patients with obstructive sleep apnea and REM sleep behavior disorder or RBD tend to do worse on cognitive testing than those without these comorbid conditions. And, finally, treating orthostatic hypotension or getting lightheaded upon going from a sitting to a standing position. Those patients that have those symptoms, that orthostatic hypotension, tend to do worse on cognitive testing because they're not getting enough blood to their brain.

[Slide 33] And then, finally, other disorders just to wrap up.

[Slide 34] Apathy I mentioned early on is a decreased initiation or engagement in activities, speech, and emotion. It appears to be associated with cognitive impairment to the front part of the brain, and it's relatively common in Parkinson's disease. It's often confused with depression, but they seem to be really distinct disorders. There are no antipathy treatments, but clinically stimulants and stimulating antidepressants such as bupropion, that's one antidepressant, can be used.

[Slide 35] Daytime sleepiness and fatigue are thought to be distinct disorders, although they again overlap some. Fatigue can be either physical or mental and is a sense of exhaustion. Few treatment studies have been done to date, but again stimulants or stimulating antidepressants such as bupropion are used clinically.

[Slide 36] REM sleep behavior disorder, you could have a whole talk just on sleep disturbances in Parkinson's disease. But the physical and verbal acting out of dreams during rapid eye movement phase of sleep is what RBD is. It tends to be recognized by the spouse, not the patient. It can be disruptive and associated with daytime fatigue and sleepiness and can be a particular burden to the spouse.

It's not to be confused with hallucinations. Hallucinations occur while awake, fully awake. REM behavior disorder, RBD occurs while someone is asleep. This is often treated with clonazepam or now maybe melatonin at bedtime, although again the clinical trial evidence to support this has been very limited at this point.

[Slide 37] Pseudobulbar affect or repeated spontaneous brief episodes of emotionality, typically crying, but it can be laughing, it can occur in Parkinson's disease; and it's not meant to be confused with depression because it's not usually connected with an underlying depressed mood. Treatment is typically with antidepressants, but there actually is a specific FDA-approved treatment for what's called pseudobulbar affect; and it's a combination of two drugs, dextromethorphan and quinidine.

[Slide 38] And this is my concluding slide, so I'd like to highlight, and this has really been the story, I think, of what I've learned in my career, that Parkinson's disease is a motor disease in which neuropsychiatric symptoms are increasingly recognized as common and important. Comorbidity of these neuropsychiatric symptoms is common, which means that if one occurs, they typically occur with another one. In isolation is less common. Neuropsychiatric symptoms are associated with disease-related brain changes for many of them, so we do think of them as related to the illness itself.

The Parkinson's medications and treatments themselves appear to have mixed effects, so Parkinson's medications may help for some of these symptoms but actually may cause other ones. Under-recognition and undertreatment of most disorders do persist, and I think it's very understandable that that occurs. Movement disorders neurologists have a lot to manage with a Parkinson's disease patient, and it's close to impossible to manage all of the motor aspects of the illness and the nonmotor aspects as well; and there's just not so many psychiatrists or other people who specialize in this area that are available to treat all the Parkinson's disease patients.

And there's still a need for new treatments for most of these disorders. As I already mentioned, a lot of the treatments are borrowed from other disease states, such as Alzheimer's disease or depression in the general population. And very few have been developed specifically for Parkinson's disease disorders; the one exception being the recent pimavanserin approval.

So that is the end of the formal presentation.

Question & Answer

Rebecca Gilbert, MD, PhD

[Slide 39] Thank you so much, Dr. Weintraub, for your very detailed and informative presentation. It is now time for the Question & Answer session.

We will take our first question from our Web audience, and the question is, "Is cognitive decline or slight dementia a result of dopamine deficiency?"

Daniel Weintraub, MD

I would say that if you had to give a yes/no answer, that it would be no. Early on in Parkinson's disease, before patients are treated, there can even be some mild cognitive changes. And when patients first start dopamine treatment, there may be some slight improvement in certain cognitive abilities. But over time everybody with Parkinson's disease ends up on dopamine replacement, typically enough to improve their motor symptoms. But in spite of that, you can still see cognitive changes, cognitive worsening.

So, I think, in general, it's not just a dopamine deficit. There may be some role for that, but it probably involves more likely other neurotransmitters or chemicals as well, and probably it represents to some extent the spread or evolution of the illness throughout the brain from just the motor part of the brain early on.

Rebecca Gilbert, MD, PhD

Okay, fantastic. Let's take one of our questions from the phone.

Operator

Our next call is from James from Florida. Please state your question. Your line is now live.

James from Orlando

Hello, Dr. Weintraub. This is James from Orlando. I wanted to ask you something. In general, I've got a little bit of all of these things; and I was wondering if there's one specialist who can handle it or you should have certain specialists on your team, and who would they be?

Daniel Weintraub, MD

Right, so that gets to an important question about what constitutes a good team for a Parkinson's patient, and it's hard to make the team just the right size because you don't want to have too many providers.

So, to me, an ideal team starts with a movement disorders neurologist at the center of the team who can manage the motor symptoms and many of the other symptoms as well – ideally, a movement disorders neurologist. Complementary pieces, depending on the symptoms that the patient has, could

include a psychiatrist such as myself focused on psychiatric and cognitive issues. It could involve a psychologist, so somebody who could provide some nonpharmacologic mental health treatment. It's nice to have a neuropsychologist available if you just want to have detailed cognitive testing done at some point, so that could just be a single referral. Having a social worker available to help address the important psychosocial issues that come up in the context of Parkinson's disease. At times you may need a physical therapist or an occupational therapist, depending on the needs of the patient. And I'd also say a speech and a swallowing therapist can be very important for people that have trouble with swallowing. There may be other specific referrals that are done from time to time, like to a speech specialist, but those are, I think, the key elements. I probably missed something for a Parkinson's disease patient.

Rebecca Gilbert, MD, PhD

Fantastic. So, let's take our next Web question. This is a really common question. You mentioned that there are cognitive exercises that may be helpful to help people who have cognitive impairment. Are there particular cognitive exercises that you have found people find success with?

Daniel Weintraub, MD

I think not, and the reason I'm also saying that is because I don't want people to think that there's something that they've seen that's advertised or online that involves spending money necessarily because sometimes people make claims or pitches for a for-profit company.

I think, in general, it really depends on the age of the patient, because we have younger patients that are still working, and working is probably the most cognitively stimulating activity that somebody can go through. But many patients are older and retired.

Even conversations, stimulating conversation is a cognitive exercise. Some people like board games, puzzles, crossword puzzles particularly. They can be done with paper and pencil. They can be done on computers. There are many computer-stimulating games that are out there. I think playing the game of Jeopardy is stimulating. So, I think it's just the general idea that you are stimulating your thinking, testing your memory, trying to pay attention. That's more important than perhaps just any formal program that somebody might go through.

Rebecca Gilbert, MD, PhD

Thank you very much. Let's take our next phone question.

Operator

Our next call is from Cathy from Minnesota. Please state your question. Your line is now live.

Cathy from Minnesota

Yes, hello. In reference to Slide 31 where you're talking about inhibitors for or help with cognitive issues, are those drugs different than memory drugs?

Daniel Weintraub, MD

So, the medications that are used again only fall into two classes, the cholinesterase inhibitors and memantine. That is all that's approved really for any memory condition, including Alzheimer's disease. So, this is a huge unmet need.

So, when these medications are approved, even though Alzheimer's disease may be thought to be primarily a memory problem, they're approved for all the cognitive issues that potentially can arise in that condition. And those include things related to planning abilities, what we call executive abilities, attention; and other studies have shown that those domains or cognitive domains can improve. So, I think of them as not just memory drugs but as cognitive-enhancing medications.

Rebecca Gilbert, MD, PhD

Okay, very good. Let's take our next question from our Web audience. You mentioned that physical exercise is good for Parkinson's disease, cognitive issues. The question is are there specific nutritional recommendations for brain health that you can inform the audience about?

Daniel Weintraub, MD

There are many studies ongoing and many interesting lines of research about the importance of diet and exercise but diet in Parkinson's disease. I would say both in Parkinson's disease and for other conditions such as Alzheimer's disease, there is no clear evidence at this point that dietary modifications have long-term benefits. It doesn't mean that you shouldn't do it, that you shouldn't eat healthy for probably many reasons – physical and other health reasons included. But to say that there's clearly known that dietary modifications may have some impact on the progression of Parkinson's disease or the nonmotor symptoms of Parkinson's disease, we're just not in the position to say that at this time.

Rebecca Gilbert, MD, PhD

Okay, thank you. Another question from our Web audience. "Of the areas that you discussed, so depression/anxiety, psychosis, ICD, and cognitive impairment, where do you see the focus is for new medication, for research to develop new medications?"

Daniel Weintraub, MD

Well the psychosis field I think had a major advance recently with the pimavanserin, and there's been a more recent study with pimavanserin showing its effect for dementia-related psychosis, including Parkinson's dementia, so that's been a big help recently. I think the depression field has had a lot of advances over the past ten years where we have evidence for four or five different compounds.

I think that the biggest unmet need – it's probably easiest for me to answer it this way – probably remains for cognitive impairment, number one, both milder changes and more severe changes such as dementia. Probably anxiety symptoms which, again, can be quite disabling for patients. And then

we're really kind of in the woods still about things such as apathy, about lack of motivation, how to impact on that.

There are drugs that are being tested for one or more of these, particularly cognition I would say, lots of which have novel mechanisms of action, which we really can't go into on the phone in detail today. I think the other hope for all of us is that the disease-modifying therapies that are being developed and tested, that if you can impact on synuclein, alpha-synuclein itself or the formation of Lewy bodies and somehow prevent their worsening, their spread, that not only is that going to help with the motor symptoms of Parkinson's disease but probably most of the nonmotor symptoms as well.

Rebecca Gilbert, MD, PhD

Thank you. We have another phone question.

Operator

Our next call is from Sue from Florida. Please state your question. Your line is now live.

Sue from Florida

Hi, thank you for all of your information. My husband has double and blurred vision, and he's been to all sorts of doctors and so on; and he last saw a neurological ophthalmologist, and he thinks that the double vision and the blurred vision is related to the Parkinson's. Is that common?

Daniel Weintraub, MD

Yes. And when I told you I probably forgot some specialists, to leave off, and certainly a neuro-ophthalmologist is on the list for some patients because visual changes are common in Parkinson's disease. Blurred vision, double vision, and it's probably due to multiple factors. You can actually have deposition or placement of some of the disease pathology, the alpha-synuclein and Lewy bodies in the retina and other parts of the eye, so that may help explain some of it.

My expertise doesn't extend to vision as a psychiatrist, so I probably can't say more than that, but I will say that visual changes are common, including things such as color discrimination, not being able to tell colors apart as easily. Those are pretty common in Parkinson's disease.

Rebecca Gilbert, MD, PhD

Thank you. We have another question from our Web audience. "My understanding was that Robin Williams suffered from Lewy body dementia and then was incorrectly diagnosed originally with Parkinson's. Is this a misunderstanding on my part?"

Daniel Weintraub, MD

No, it's not, and it's probably more a misunderstanding on all of our parts about how to label and diagnose these disorders because there is confusion. My recollection was that he was first diagnosed with Parkinson's disease and on autopsy was rediagnosed with Lewy body dementia. It gets quite

complicated though because we use these terms that don't really have a clear distinction from each other. Parkinson's disease is a Lewy body disorder, and you can develop dementia with Parkinson's disease, so Parkinson's disease dementia is really a Lewy body dementia. But then there's a syndrome, a clinical syndrome called dementia with Lewy bodies, which is really thought to be different from Parkinson's disease.

But where one begins and one ends is a matter of great controversy, and that's both at a clinical level and an autopsy level. So I'm sorry to not answer the question directly, but we can just leave it at the fact that he had some Parkinson's symptoms, he had some cognitive symptoms, he had some psychiatric symptoms; and what his exact diagnosis is less clear.

Rebecca Gilbert, MD, PhD

Yes, thank you. We have another question. "What is the best practice for managing anxiety and depression in the setting of cognitive impairment?" And then a related question, "What functional indicators do you look for to suggest that someone may not be able to live alone anymore?"

Daniel Weintraub, MD

Okay, so for the first question, I think that the general prescribing is not so different for people with cognitive impairment versus noncognitive impairment for psychiatric symptoms in terms of what we would like to use to get a benefit. The difference really becomes in terms of side effects. So, we have to use pure antianxiety agents or benzodiazepines, as I call them, less commonly or more cautiously in somebody with cognitive impairment because they're more likely to experience cognitive side effects.

There are certain antidepressants, a couple that I had mentioned, paroxetine, nortriptyline that have what are called anticholinergic properties. They block the neurochemical and the neurotransmitter acetylcholine. Blocking that chemical can lead to potentially cognitive worsening. So, we might use slightly different antidepressants or not use certain antidepressants in somebody with cognitive impairment. So, I'd say it's at that level that we think of different management strategies.

In terms of living alone versus not living alone, it does get quite complicated. It depends on multiple factors, but we do tend to look at what we call instrumental activities of daily living. Assuming somebody can cover their basic activities of daily living, that's things such as dressing, feeding, toileting, bathing, if they're able to do that, and some Parkinson's patients can't, but assuming they can do that, then we look at instrumental activities of daily living such as ability to handle transportation, ability to pay bills, ability to do grocery shopping and prepare meals. Those are the kind of things you need to be able to do day in and day out to survive by yourself, so there's a checklist. There are actually assessment instruments. We can actually test somebody in person and see how well they do on these different tasks, and that's probably the best indication of somebody's ability to live alone.

Closing Remarks

Rebecca Gilbert, MD, PhD

Okay, fantastic. There have been so many questions; and, unfortunately, I think we have to wrap up at this point. And so **[Slide 40]** I apologize to everybody that we didn't get to everyone's questions.

I want to thank so much Dr. Weintraub for joining us today, and I want to thank everyone for participating in today's telephone and Web education program. **[Slide 41]** There were so many wonderful questions, and we will try to answer them as we receive them in our Scientific and Medical Affairs department; and I encourage you to visit our website at apdaparkinson.org or call 1-800-223-2732, and you can ask additional questions there.

[Slide 42] If you enjoyed today's webinar, we hope you will consider supporting APDA with a donation. With your help, APDA can deliver more programs and services like this one which are needed now more than ever during these challenging times.

I also want to emphasize to everybody that we really do appreciate your feedback and comments and want to make sure that you complete the program evaluation form. To join us in this fight against Parkinson's and to learn more about the support APDA provides across the country, through our network of chapters and information on referral centers, as well as our national Research Grant Program and Centers for Advanced Research, please visit us at apdaparkinson.org.

We all agree that being informed about your disease and treatment options is the best way to empower yourself and take control of your care. We hope you have a wonderful rest of the day.