



Why Does it Take So Long to Develop a Cure for Parkinson's?

with Kevin Kwok

Davis Phinney Foundation

Melani Dizon (Director of Education, Davis Phinney Foundation):

Hi everybody. My name is Melani Dizon. I'm the director of education at the Davis Phinney Foundation. And I am here today with Kevin Kwok. Kevin has been living with Parkinson's for a long time. He's been a friend of the Foundation for a very long time. He's also on our board of directors and he's gonna talk to us today about why it takes so frigging long to develop a cure for Parkinson's. Hey, Kevin, how are you?

Kevin Kwok (Board of Directors, YOPD Council, Davis Phinney Foundation):

Doing great, Mel, a pleasure to be here.

Melani Dizon:

So happy to have you, really excited for you to talk. I know you gave this talk to a live audience, woohoo, a couple of weeks ago and everyone loved it. So, we're really excited for you to share this with our whole community. So, I am going to stop talking and let you dig into what you're what you know.

Kevin Kwok:

Great Mel. Well, thanks so much for the invitation to be here today. This is a topic very close to my heart because it really sort of converges all my backgrounds from multiple places. So, I'm giving this conversation from three different perspectives. The first is a 30-year executive from the pharmaceutical industry. The second is probably more important and that's someone who's been living with Parkinson's for more than a decade now. And the third is from someone who's very impatient and that's why I go from being an advocate to almost an activist. You know, we are living in really unprecedented times. It's been a world with COVID where we've gone from, I'm gonna use the term warp speed, but it's more like it is at the speed of light what has happened from the first diagnosis to actually having a vaccine that's been widely disseminated around the world, never in the world of innovation have we seen such a rapid innovation created and disseminated in such a broad way.

And it always leads me to people asking me the question. Well, if we can do it with COVID, why can't we do it with Parkinson's? And I remind people that disease and healing disease is not an easy task. If you think about cancer, Richard Nixon was the first person to wage the war on cancer. This is almost 50 years ago, and we have come such a long way with genetic research and modern technologies to advance our knowledge of cancer. But it's only the tip of the iceberg. We've had huge gains in the last few years, but it's taken decades and billions of dollars. So, keep that in mind, as you think about our situation here with Parkinson's and we're

gonna be talking about various things, which make it more particularly challenging and difficult in there. So, I mentioned as we go into this conversation that I'm an activist and activists are very impatient people, and generally I never use the term frigging in my lexicon. But I would use a word that's probably more emphatic, but we're in a friendly audience. So, why do you be more politically correct. And I started to think who even uses the word freaking. Well, so I searched my database, and I came up with a following.

This is our good friend, Dr. Evil, who had 1 million dollars of research spent on his research, Dr. Evil, meet Dr. Kwok, and let's go with this presentation. So, there's several objectives that I'd like to go through today. And let's just dive into what I'd like to walk away with an understanding of. The first is really understanding what is true and what are some of the myths when it comes to drug **R and D**. The next is understanding the process of clinical development, and there's gonna be a lot of jargon and drug terms. And so, I'm gonna try very hard to bring this to a level that we can all appreciate and understand. Nothing is worse than having a speaker just try to blow through talking with acronyms, which is so typical of people of my background. So, I'm gonna hold you to hold me to it, Mel, if I ask they or mention things that are not clear, ask me to go back. We'll discuss whether or not regulatory agencies like the FDA and the EMA are actually our friends and what role do they play? And I'll share some thoughts and just some historic tidbits about why the FDA came to existence. And then we'll go into just asking what actually constitutes a good drug protocol or clinical trial design. And then finally, what I like to do is share some personal insights as to why I volunteer for clinical trials. And then at the end, we'll discuss as we're going through this, what can we actually do today as people living with Parkinson's, thinking about where we go in this world of drug development as we're waiting for a cure.

So, the personal disclosure here is I am a retired pharma executive. I worked in this industry for more than 30 years and now thanks to going on disability and retirement. I've left the dark side. Now 10 years of those last 30 have been with the diagnosis of Parkinson's. And I have pivoted my career to become very involved in patient rights and patient engagement as part of my career. It's sort of one of those stop and breathe for a moment and say, what can I do now, knowing what I have. I'm a patient advisor to many different Parkinson's advocacy groups like the Michael J. Fox. I've been a patient advisor on two of their trials. I've been part of the Parkinson's Foundation's payer network, which, which tries to bridge people doing research with patients and bringing them together. And I've also been very politically active. So, I've testified at the FDA on living with Parkinson's and my thoughts on prevention have been presented to Congress, on exposure to toxic pesticides.

Prevention you'll find out from me is really, it's a hot button that I feel very strongly about. We'll come more back to that later. So enough of the personal disclosure, but let's move in now that you know my background.

So, there's a couple of myths here that I wanna first start with. The first myth is that the pharmaceutical industry is an evil empire destined to keep you shaking all the time, because it's of commercial value. That is such bunk. I hear this all the time, the evil pharma industry. And I will tell you that I've worked shoulder to shoulder with many scientists and executives whose sole intent is cure diseases in mankind and do the right thing and these are the hardworking people that are there every day at their desks working. Now, drug development is extremely time and resource intensive, hugely, so, it may be one of the most expensive industries we ever embark on. And so that adds some complexity when you're talking about not just millions, but billions of dollars now, sorry, billions of dollars that are that are required. It's not an industry for the faint of heart. It's a high-risk industry with more failures than successes. And this sort of dictates very much decision making by pharma as to what it can and cannot do, because it only has so many projects that it can move forward.

Now, with that, I will admit they're good and bad players. And the pharma industry is as someone who's come from the dark side, infamously bad for policing its own activity, but there are good people in that role as well. I think of people like Diane Stevenson, who's given her life towards bringing more programs into clinical development.

Her brother just recently passed from Parkinson's. And in some ways, I dedicate this presentation to people like Diane. Then there's the bad players, they're the people that are involved in op the opioid crisis or predatory prices like Martin Shkreli. These are the people that give a very bad name to what's going on in the industry. And the industry really has to self-regulate and check, people like that. But the most important thing is in looking at these corporations are, do they really have patient intent as a first priority and not as sort of a follow on. I hate being quote a subject and I hate to give myself as a market because there are people and I've been in meetings where I've heard those terms used by accident, but it reveals sort of a philosophy of a company. And it's very hard as an outsider to know that, but you have to ask questions to really peel away and see how behaviors walking the walk is more important than talking to talk.

So, myth one, here's just a slide here that shows the actual number of failures or if you wanna phrase it more in the positive term, the success rates based on each phase. And there are numerous studies out there. This is one taken from JAMA, which looked at a culmination of several drugs that were approved and then went ahead and looked at the success rates. So, you'll see here that if you are in phase one and I'll just read from the top line, only 14% of those drugs that go into phase one, actually make it to approval. It sort of doubles that 35% for phase two. And in phase three, you'll only see 59, even after a successful clinical trial, 20% of the programs still fail. Now also bring your attention to, if you go down on this slide and look at central nervous systems, which is more the area that we look at, you'll see that the percentage of failures is still pretty high on there. And we'll go into reasons why that is as we progress in the conversation.



So, myth number two, just because you see something in print doesn't mean it's real. Benzi Kluger, some of you may know him, puts out a newsletter called medical bullshit. And I think that the Davis Phinney Foundation has featured him on some of their webinars. I highly recommend you all listen to that because it puts in perspective what you see in the tabloids and you combine tabloids when you're sitting in line, getting your, paying for your groceries with the National Inquirer, along with social media, and you have a very dangerous recipe. For instance, this one was not an issue of deliberate, malicious intent. But a couple of years ago, there was a Georgetown study looking at the use of nilotinib, an approved cancer drug.

And the tabloids took that and ran with it saying that a cure for Parkinson's was imminent. Well, this is based on one trial, open label, which we'll go into what that really means, but it created such a consternation and frenzy in the marketplace that Michael J. Fox actually went out and tried to duplicate it and found out it could not actually get the same results. This is the balance of hope versus hype in here. And we'll talk more about hope and hype and intent, but in this world of media, we have to be very careful just because you read it doesn't mean it's true.

Now this is a true slide. So, I'll go into what has happened and again, there's a lot of great research. Some people say it's a good time to have Parkinson's because of this pipeline of multiple drugs going into drug research. I'm not asking for any detailed sort of conversation on any one of these agents, but more so putting this schematic in perspective. This slide shows all of the drugs in research as of 2021. And when I say research, these are the ones in clinical trial, the outer ring are phase one. And we'll talk more about what that means in phase one. The middle ring is phase two, and the third area are phase three looking at approaching registration. The bottom part of that sphere shows those that are just being designed for symptomatic relief. And the upper half of this circle are all the drugs looking at disease modification.

So, you can see there are a lot of programs right now. Now back in the day when I was first diagnosed, it was not a fraction of this. So, it speaks loudly to the industry and scientists working together to try to move things forward. Now, most of these programs unfortunately will fail and that's sort of the cold hard facts. We're gonna talk a little bit about a product that I have circled in the middle here under phase three. You can see it under right here, amprelosetine, this is a program that my company worked on before I left them for the symptom of neurogenic orthostatic hypotension, or nOH, low blood pressure, which plagues some of us with Parkinson's. We'll come more back to that, but I just wanted to show you a slide here to show you that help is on the way, and this is a good side, but between now, and when that help comes is still a lot of work that has to happen.

Michael J. Fox Foundation takes that same schematic and sort of summarizes it, this came out of their 2022 research newsletter into sort of four different areas of... So, I thought rather than to summarize individual drugs on there, I'd talk about themes. The first one is harnessing

natural immunity, and this includes the brain gut, which we've heard about from various speakers and inflammation and other things into thinking well, is there an immune component, like there was in oncology for Parkinson's and other neurologic diseases? I think this is a very exciting area. Reactivating the cells cleaning process. This is an area very close to my heart that I think of is how do we get rid of those alpha synuclein deposits in your brain? Are there drugs that we can give to get to do that? Can things like better sleep, help us eliminate these toxic proteins more readily?

It's a really exciting area. Replacing dopamine neurons. This has been around for a while. It's another way of talking about stem cell research. So, it's been around for quite a long time, but scientists are still making great strides in this area, although it's still very early. And then finally, there's this area of tapping the lrrk2 pipeline. Again, modern genetics is allowing us to find patients at risk and lrrk2 two may be one of those areas. So, going back from what is real to what is more fantasy, I found this recently on my email, which I thought was humorous. The individual here is not a medical authority. It's Herschel Walker who should probably stick to his political career and not talk about medicine, but in his recent, and this is a real interview and I actually listened to it to hear what he had to say.

He talked about having in his possession, a mist that would kill COVID on the spot. And he said that this mist was both approved by the FDA and the EPA. Well, first of all, I went and checked that and to best of my knowledge, that mist does not exist in there, but it did leave me to ask the question, what is the role of the FDA in all of this, and for those of you who, the drug industry was not always a heavily regulated industry. If you think back to, you know, the carnival days of going to a carnival and seeing a guy, you know, trying to pedal his snake oil on stage there, FDA at that time or not the FDA, but the industry at that time, didn't even have to ensure that what it said was in a contents of a bottle or a pill even existed.

And back then this is probably in the 1900s. There were situations where the interstate exploitation of agents didn't even contain drug. In fact, they contained toxins and there was cited cases of an antibiotic mixed with ethylene glycol, which is basically antifreeze you know, working for you and unfortunately many people died in that situation. The FDA has actually been reinvented many times. That was the onset of the founding of the FDA, but the more modern version of the FDA as we know it today happened in the late fifties, early sixties, there was a product called thalidomide. It was used to treat morning sickness in pregnant women. And it created such an issue with birth defects out there that the FDA reemerged, again, as sort of an agent of showing that making claims had to be validated with good research.

Now, the FDA has gone through a number of more significant recent changes, but the one that I'm most excited about is what they call patient focused drug discovery, PFDD you'll see the acronym, where they're actually encouraging the industry to seek input from patients in the development of drugs. And I think for me, this is a huge step in the right direction in here. So, more on what I think of in terms of where I'd like to see our industry go, but that's just a little

bit of thought on the FDA. Oh, one other point, when you watch those commercials on TV at night, and you see the commercial play like five seconds of grandpa playing, you know, in a garden with his grandchild, and then the next 40% or 60% of that ad talking about all the side effects. That's not the company wanting to do that. That's the FDA. And it's a balance to try to create companies, not necessarily promoting things as absolutely safe when they're not. And it makes our very annoying commercial, but there's reason behind that madness.

So, let's go a little bit into this stages of drug R and D. And first of all, R and D oftentimes gets clumped as one term. And we think of it as the same, but the way I define R and D, R is research, which is more what I think of test tubes and in silico on laptops while as development is when, once you get into humans in here, and oftentimes you get, you know, my mom is infamous for this, she'll say, oh, I was in the grocery store and I saw this positive National Inquirer ad saying, the Parkinson's cures are right along the way. And then they go, what do you think about this? And you start reading it and you realize this is still in rodents. It's not even in men or primates yet. And yet media loves to hype those kinds of situations.

There's a lot of work that has to go from basic research into human testing. And a lot of that preclinical research then results in a field called translational research. And that's when you start looking at when a concept or a molecule actually is a druggable target on there, and you start at that point in translational research, starting to look at things like, is it toxic? Will it cause birth defects? Can you actually give the drug that pharmaco connects, is the field of, can you get it, give the drug, get it into the body and to the site that requires the drug to actually hit. Then there's the issues of quality. Can you actually reproduce this drug in many ways? You know, and many drugs fail because you just can't manufacture it in a way consistently, and that all happens before you go demand.

At that point, R becomes D, and development then kicks in. And there's several phases on here, which we'll go into in more detail in a further slide, but this is when the costs and time really start escalating. And it's an exponential hockey stick when this happens. Now there's another interesting interplay between, there's a myth that scientists develop great drugs, but that's not true. The days of Alexander Fleming finding a little mold on a piece of bread and developing penicillin is a bygone, a remnant of a bygone era. That will never happen again. What often happens is to develop a drug, is, it requires a handoff. And that handoff goes from an individual with an interesting scientific discovery or notion to an engine that actually can fund and take the risk and do all of the things necessary to actually develop that drug.

And so then there's this interplay between what is big pharma and what is biotech or biopharma. And that often is the gray area. And those are the people that act sort of in this transitional place, in between translational research and human development. Now that used to be the old demarcation where biopharma would then sell the drug to a pharma company who would then take it to later stages of expensive clinical development, once the risk was removed. So, pharma as a whole in the past was not so good at research, but it was great at

development and marketing. But what we're starting to see now is this merge where pharma is becoming more like biotech and biotech is becoming more like pharma, and we don't have the time and the scope of today's conversation, but it's a very interesting dynamic that I'm seeing in the marketplace.

So, let's go and break out the bottom part of that chart on here, the different phases of clinical research. And you'll see here, I mentioned, what is, I've talked flippantly about phase one, but phase one are usually small trials that are done, not necessarily always in patients of disease, but they're in healthy individuals. And you're basically looking at whether or not this drug can be given safely and at what dose. So, these studies are usually less than 20 people. It can be, you may have to complete a number of phase ones, but it really just finds out can we put this phase one, is also known as first in man studies, and it's really there just to attest whether or not we can put this in a person and whether it's safe and at what dose, and as you could see here, only 14% of those candidates ever go further than at this stage.

Phase two is the, is when you actually take a disease population and now see whether or not the drug works and the way you like it to. These are called proof of concept trials. And these are where the smart scientists really have to figure out what do we look for? What end points? What are the aspects of that drug that are important to actually consider? And 35% of these candidates move on. And oftentimes phase two takes multiple tests because you don't really know, is our drug working, you know, in a patient population. Now you then go into the really expensive part and that's phase three. Phase three are otherwise known as registrational trials, but these are large. They can often be, the number that I often quote is 35 million to run a single phase three. And it can be a small phase three, if it's a small indication or like a vaccine, it can go up to 8,000 patients right in there.

A company that I was recently talking with mentioned that the cost of a single phase three patient in order to put them through the system was about 32,000 per patient on there. So, you start now seeing the issues. FDA usually tells you how many phase threes you need to do in order to get approved. And it's often not just one. It can be several on there. And then we eventually get into phase four. These are post-market studies that look at follow on, what happens when you get into a real population. Oh, and I might add that in phase three, you need very large populations to show that what you're looking at is not just the chance or that, it tries to eliminate investigator bias in there. So, phase one to phase four in and of itself is a very specific area of expertise that requires a lot of involvement in here.

So why do investigational drugs fail? Well, first and foremost, the obvious one is if you give them drug, and someone dies, or experience is a very negative, adverse event, that's safety. And those are oftentimes very easy to detect in there. But oftentimes what you see is a safe drug in phase two, doesn't really come out until bigger trials, and then you start seeing some of those side effects. So that's one of the reasons why programs often get killed later in their course versus early. Efficacy is more complicated. Is the drug not working because you used the

wrong dose? Did you not dose those patients for long enough? Are you measuring the right thing? Is this UPDRS the right thing that you need to be testing, right in here?

There's also the issue of patient selection. Are we looking at the right patient group and patients at different phases of their disease may act differently to products being given to them. And that's something to factor in. The other thing is that Parkinson's is not a simple disease that you can clump everyone all as the same. And what may be your pressing ailment may not be as pressing to someone else. And we'll come more to that. I have a very good example for that. Their quality issue, oh, and sorry. There's also the issue of placebo effect. I know that I can actually make my Parkinson's symptoms feel better just by the going into see an investigator or my physician. And you can actually influence the outcome of your study through the placebo effect. And scientists are going to great lengths to try to eliminate that placebo bias in there.

The other reasons drugs fail are quality. You can't make it in the quantities that you need safely. So, this comes up and then I put this catch all, the other areas, where sometimes you get a mixed result or what you get are biases either from the investigator or the companies that are moving these programs forward. We'll talk a little bit about that in a second. Now, Parkinson's, as I've seen from going to all of these various clinical meetings like World Parkinson's and others, is that Parkinson's itself lends even more complication than your typical drug being developed. You've all heard that term when you've seen one Parkinson's patient, you've seen one Parkinson's patient. That's a very convenient term used to try to show the difference between all of us with Parkinson's. And I'm so glad that this phrase is out there, but when it comes to drug development, this is a complicating factor, because if you can't look at one patient being the same as another, with the same needs and of treating their disease, it adds complexity to how do you measure if what you're doing is useful?

We'll come more back to that in a second. There's also a need for therapeutic biomarkers. That's a term that you may hear often. This is the number one area for the Michael J. Fox Foundation is finding a biomarker. If you have cardiovascular disease, you can use cholesterol or blood pressure. These are biomarkers and they're indicators of disease and if you lower them, it shows that perhaps you're adding benefit to that patient's cardiovascular disease. We don't have that right now in Parkinson's. And so, it's a very important area that we're looking for, you know, can we find a target and if we alter that target, will we actually affect the course of the disease? Now, the third point on here that I talk about is disease modification versus symptom control. You remember that graphic that I showed you with the upper and lower sphere?

Well, disease modification is something that we all strive for, but how does one actually get there? And what do you measure? How do you actually measure a slowing of disease in here and this is what scientists and clinical researchers sit in rooms for days talking about. It's a really important, it's not insignificant. Now, slow progressing disease is something else. Now, when

you have COVID or cancer, the cold hard facts on this is that you have it, you get hit with it, and you either die or your outcome is not a positive one in there, but it's relatively fast. It's in months and years. The problem with us with Parkinson's is our progression. I mean, it's one of the benefits is it is a slow progressing disease, but it just means that our timeline to measure the outcome is in often decades or even multiple decades.

And that poses a real problem in there when it comes to trying to find a cure. Now, areas like oncology have now shown that it's not a single bullet that actually works, but it's cocktails and so what they've now looked at is drug regimens that are four or five different drugs, depending on the stage of your disease, but because of the lifespan of oncology patients, it's easier within a decade to get multiple cocktails together. But if it takes us a few decades to find one drug, and then we wanna add another drug, you could see the complexity of actually developing a program of getting to that cocktail, which shows us that we're still a long ways away from finding the ideal treatment for those patients who are sort of midstream in our disease. Then what's also being looked at right now are late-stage patients versus early.

And a great area of research now is can we intervene earlier on and show greater benefit, but with that then becomes earlier detection and an admission that we are at risk. So, this is an area that I'm highly excited about and very interested, but it's got a lot of thinking to get, and then finally, there's a historic issue of many of the drugs that we go down, especially if you look at Alzheimer's they fail in late stage clinical development and often that's because of either a placebo effect or that the patients in larger groups just don't act and behave like smaller individual patients. So those are some of the complexities in Parkinson's drug development. And I know there are many others, but I just wanted to kind of have this conversation so that people realize that our disease is not a simple one.

Melani Dizon:

Kevin can I just ask a quick question about the idea of yeah, so when you see one person with Parkinson's, you've seen one person. So, part of the issue there is that if it's not something that is common right, then what are you creating a medication for? Right. If there's, everything is just so different and the group is so heterogeneous, but is there also talk in pharma around Parkinson's being many fewer people right that have Parkinson's than let's say cancer or something like that, where people are developing more drugs? The reason why I say that is I had a conversation recently with somebody who was working on an issue related to Parkinson's and they, you know, they went to a big company and they're like, oh yeah, we're really excited. What's this, how many people have Parkinson's? And he told them, and he said, oh yeah, no, we need a hundred million people to have it for us to work on it. So, what in the Parkinson's space and pharma space is discussed there, is there anything there that's kind of stopping what would be more robust research because of the numbers?

Kevin Kwok:

It's a fabulous question. And Parkinson's is one of those areas, which is kind of in the middle. You have what's called rare diseases and orphan diseases and you have, you know, like hypertension, which is affecting tens of millions of people. Parkinson's with its 1 million people right now is sort of in between and can be oftentimes viewed as in no man's land. One of the areas that I started talking to you about of biotech and pharma emerging sort of crossing over is this area of rare diseases in orphan disease. Because if you could find a drug that works well in a very rare group of patients, the studies may not need to be, you know, hundreds of people, you could get by with a registrational trial of 30 or 40 patients. And then what happens is you come out with this medication, and you see this astronomical pricing for that small group, you hear in the news of, we found a cure for these 200 patients.

Now that cure may be a million dollars a year, and insurance will have to figure out how it pays for that. But companies are moving more, very much to that very rare case because there are less barriers to try to succeed. And at the other side, what you're seeing in those very large trials is, indications that are huge, are that the trials that you have to run today are run into thousands of patients. So, it comes with its own headaches when you get to that part in there as well. But you're starting to now get into this whole ethical view of what is an attractive market. And I hate those conversations because as a patient, I was like, I am not a market. I am a patient, you know, in there, but I'd love to continue conversation on it, but it is an area that we face in Parkinson's that we're midstream.

I mean, the good news is on there that we are the fastest, "good news," the good news is that we are the fastest growing neurologic disease out there. And with COVID, we may see more of an emergence of neurologic diseases as we did after the Spanish flu. But I'd like to not think of people going into these because they find me as a lucrative market to enter, but more so it's an area that they wanna do good.

I'll continue this vein of conversation in the example that I'm about to go into, because it poses some of these ethical and corporate actions that very much address a subtype within a disease.

So, you're basically queuing me in on my next section of this talk here. I mentioned to you before that I worked on this product amprelosetine for nOH or neurogenic orthostatic hypotension. That's a big word for getting dizzy when you stand up because your blood pressure doesn't regulate. So my previous employer worked in this area and that was one of my big focuses was traveling the world, talking to patients who had nOH and in putting them back to my company, many of them who had never seen a patient because they worked behind, you know, in a lab or in an office and don't see patients. Well, based on positive, I mentioned proof of concept in phase two, the company had a meeting with the FDA and agreed that let's go into phase three and the phase three would comprise of two phase three programs. One was the 169 study, which is a four-week efficacy study to see if we actually saw an effect. And this was a group of multiple Parkinsonism patients. So, it not incl only included Parkinson's, it included patients with MSA and autonomic dysfunction.

Well, that was a four-week study. And then if those patients succeeded, they could roll into the 170 phase three, which was a long-term efficacy study to see if the effects were still durable over a long period of time. This was a very complex clinical trial design that required a lot of thought and a lot of moving parts in here. And then if everyone succeeded in those, they were then put into a long-term phase. It's not phase four because it wasn't approved yet, but a long term open label study, just to see for three and a half years, what would happen to those patients? Well, let me show you what happened.

So on September 15th, the company announced that it failed, that it missed its primary endpoint with amprelosetine to treat symptomatic nOH. And this was based on the randomized placebo-controlled trial that showed that its primary endpoint of improving low blood pressure, it was not met. And again, as I mentioned, this is in a group of mixed Parkinsonism patients. Parkinson's, MSA, NPAF, but interestingly enough, seven months later, oh, and so the company shut down the trial shut down that trial, the ongoing trial, and I don't know what happened to the ongoing extension trial, but it just said, all right, we failed let's, it is time to stop, right? Well, there were still a number of patients that hadn't been examined and seven months later, the company reissued a second press release, this time saying, well, actually, you know, unlike 169, we actually showed in the 170 study that patients that had MSA had a dramatic effect and it worked.

And this next slide actually goes to show that if you look at these four quadrants and each one of them has a chart in front of them with green and gray, if you look at the MSA patient group in each group, there was definitely a favoring, a results favoring positive effect. So, for some reason, the MSA patients were different than the Parkinson's patients, even though these were Parkinsonisms patients in here. And what was interesting here, Mel, is to your point, nOH is highly prevalent in MSA patients. 80% of all patients have nOH when they have MSA. In Parkinson's, it's anywhere from 10 to 30%, so much lower. And it's not always the main symptom that it's debilitating. It's one of many. So, you could see here that all patients are not alike, right? When it came to this trial. And if you look at this next slide on here, the individual breakdown going deeper into each of the symptoms on that scale.

Again, this is the MSA group. You'll see that dizziness, improved vision, improved weakness, fatigue, concentration, head, and neck discomfort, all greatly improved in the MSA group. So, the company has a dilemma because it shut itself down too soon. It also has now a market, which is much, much smaller than even Parkinson's on what it will do going forward on here. And so, the next chapter in this decision, and outcome still remains to be seen on what's going to happen. But it's an example of when you have a mixed result or you have a result that's prematurely ended. And what do you do now with this information? And these become the challenges of corporate executives on what we need to do when you have sort of in the gray zone. So, I hope that acts as an area for you to think about Mel.

Now, I mentioned in here that the trial design of the amprelosetine phase threes were stellar. I mean, they use randomized placebo control, blinded, multicenter trials. These are all terms that you'll hear of what is a good clinical design, but what they failed on was patient inclusion. And they failed to ask the question, are Parkinson's patients the same as MSA patients? And should we look at them differently in there and wait for a different kind of outcome? And unfortunately, that was an area that they missed, but the other aspects of this trial were all very highly and well-designed on here. So, one can't fault the design of the trial, except that at the fine nuance of all patients alike. And I'm thinking that that may be one of the biggest issues in the failure of many neurologic drugs, is that the patients aren't alike and hopefully through patient inclusion, we can find out more differences and hone in to better targeted focus on finding the right patient.

Melani Dizon:

Yeah. So, what, when you talk about patient inclusion, I mean, I know we're gonna talk about some of your experience with clinical trials, but is a typical trial, do they have people with Parkinson's as part of the design, or is that something that's becoming more frequent or where's the status of that?

Kevin Kwok:

Well, the answer to that is sometimes. Some companies are, have seen the light and they involve patients from the get go, even before they even move into, from research, they're talking to patients and saying, would this fit your needs? Can we actually just, what is the right profile of this chemical entity to meet your needs? And then every step along the way, they'll involve patients and say, you know, would you consider this a safe drug design? Would you consider this a good phase two? If I were to go into phase three, what are the complexities to you as a patient? Those are the companies I love dealing with because they are now bought into this whole concept of patient focused drug discovery.

Melani Dizon:

It seems it only is benefiting them. I mean, if they get more of that information on the front end from everything from, you know, the design to what could get in the way of compliance to all of those things, by talking to people with Parkinson's, that they have a, you know, only better chance to move it through.

Kevin Kwok:

I couldn't agree with you more, although what I will tell you is everyone, it's in to say that, oh, we all believe in patient care and patient input, and then they don't do it. And oftentimes the reason they don't do it is because these companies are running at the margin on expenses. And for any delay in enrolling the study and moving forward, it means they could run out of money and not keep the lights on. Right?

Melani Dizon:

Isn't that why we don't pay for prevention, but we pay for the problem. Right?

Kevin Kwok:

Well, so what happens is I've been told, as I've been trying to get patient groups together sometimes we go over protocols is that's great, Kevin, but if they tell us something that sets us back, we don't really want to hear right now. And that to me is a signal of not really being patient centric in here. And it's all companies still have this drive by corporate goals over patient needs, and ideally they should overlap. And that's what's called true patient centricity when that happens. But we may talk more later about what are ideal studies to work for or volunteer for. Those are the things that I find really, really important and history repeats itself. People who make those mistakes do it again and again, and those would be the trials that I would at least steer away from, or not prioritize as high.

But let me tell you why volunteering for trials works. This is a picture of me getting plasma from a young 40 year old man thinking that, and this is a study I did in Stanford, so, it was a controlled trial looking at whether or not plasma transfusions could actually change your outlook, not to go into detail on that study, but it was a study I volunteered for because I thought it was kind of cool and who doesn't want to be young again, right? But why do patients other than ego volunteer for trials? Well, the first and foremost is the most important thing is we, as patients would not be here today, if some patient didn't volunteer before. And so, one of the societal benefits that I believe in volunteering for patient trials is that I'm working and adding to the efforts and working off your shoulders on the people before me.

It's probably the most important thing on why we do clinical trial work. There are also sort of selfish reasons, too. It keeps me more in the know because now when I'm volunteering for a trial, I get to see my neurologist sometimes every other week versus every three to six months, you know, in there. And I've become much more integrated into that medical team in case I need some other help on there. So, my view is that knowledge is empowerment and that being involved in clinical trials allows me a better active control over my disease versus just being passive.

Well, what can you do today in your area to look at the trials that are happening in your area? Well, first of all, it's so important to read and look at all the information. And as you read more about clinical trials and what is a good study, you'll start being able to pick up the words in terms that differentiate good trials from bad trials. You can also find out about clinical trials from clintrials.gov. It's a listing of all the trials, and oftentimes has geography on when you can find them. Fox Insights actually is an offshoot of [clintrials](http://clintrials.gov), but the problem with [clintrials](http://clintrials.gov) and Fox insights is it's often not updated in time. So, when you actually reach out to them and find out about it, you'll find, oh, that study ended or that study was canceled. Well, one of the best ways is just going to your local, you know, your movement disorder clinic, and finding out what trials are they working on and be ready to question your medical team, bless you.

If you, unless you ask questions, you have a very short window when you're actually in with your physician. And usually that's not to go off on a tangent about volunteering for a clinical trial. You're talking about your dystonia, you're talking about your sleep. You're talking about the anxiety, your experience, and it usually doesn't also then add to, hey, by the way, can you spend another hour talking to me about this upcoming research that you're on? So, they forget about you unless you bring it up and flag yourself as an active person. But I would say, do volunteer that because you'll find yourself in a much richer conversation with your movement disorder clinic by getting involved. And then what you can do is you can actually help your fellow patients with this information, because now you are the person people seek out as saying, hey, you've heard about this clinical trial. What do you think about this for me? And so, you become almost at liaison, which is very effective.

So, here's some guidelines that I have, and this is an evolving list of things that I look for before I volunteer for a clinical trial. First of all, is it good science? For a non-scientist, this can be a little bit harder to really uncover, but you do wanna make sure that both the researcher that's doing the project has you in mind as a patient and not just thinking of you as a publication. I also, you asked me that question, do you get involved in studies that involve patient input? You would not believe the amount of naive conversations that come from a scientist who sits at a desk saying, oh, just add another three or four of these appointments, you know, to take, they don't realize that a single visit to a research center for a patient and a caregiver can be huge, you know, in there, and there are people in there who just think that, well, if three appointments are fine, two more won't make a difference.

So, you actually have to walk the walk and actually be a patient and involve patients dissecting, hey, do we really need, can you compress these two appointments into one? That's really important. So, if companies don't involve patients, I'm starting to lean away from getting involved in those trials. You hear this term patient partnership, but it's not really a partnership when you're calling your patients behind closed doors subjects in there, and you're working on timelines and not patient benefits. And so that's something I really look at is, is the company genuine in its patient partnership talk? Or is it just box checking? Because that's what's in with the FDA. Transparency and communication are so important. Are they telling you when things are going right when things are going wrong, or they just trying to hide stuff from you? But getting involved with good communication with the people doing the trials is so important.

Diversity of recruitment. This is a huge area because not everyone is a seventy-year-old white male with this disease of Parkinson's in there. But what's very hard for researchers to get people like the 40-year-old Asian American or the African American or women into these trials. So, unless diversity is really stressed, we're not moving the mark as much as we should in here. Be very careful of what are the motivations of the investigators and the sponsors? And if by asking a few questions, you don't feel comfortable. I think that's a good reason not to move forward. And then finally, here's where the rubber meets the road. How do they treat you after

the study's over? Do they send you the publication? Do they keep you updated? Do they let you know what's happening?

You know, as they go to manuscript. It's really important to see how these investigators and companies, if they're just using you for the one event, or do they really value your partnership? Then there there's other ways if you don't, if I haven't convinced you that being part of research is the only thing you can do, you can also work towards fighting for helping us increase funding for research. And that's where the activism comes into play. I'm here with a group of gentlemen, all either with Parkinson's or caregivers of people with Parkinson's. And we have moved from being just advocates to activists in here. We've been working this last year on trying to increase government of the department of defense fund spending into increasing the look at Parkinson's is part of that. And part of the things that I I'm very actively eager to help out with are neurotoxins and trying to prevent Parkinson's for the next generation.

To me, a prevention is a cure on here. So, I'm very, very vocal in my political outlook on this, but most importantly, what you can do right now is stay well. And that's really, really important because if you can't stay well, you're not gonna be around by the time some of these advances come out here. So, we've talked, and it's not the point of today's conversation to go into detail on living well with Parkinson's today. But it's really, really important in there. It's more important than I can ever stress and it's exercise it's. And this is an area that I'm becoming very keenly aware of in my disability days is the value of a good night's sleep. And I'm actually very involved with some sleep studies looking at that, in here. Mindfulness is another area that I've actually been involved in in clinical trials, is through mindfulness can you actually help yourself?

All of these areas need more study. So just because we do them doesn't mean we need more data. And so, supporting this type of research is equally important as well. So, with that Mel, I think I'm gonna call it, I've talked a lot about various aspects of clinical trial work, but let me just sort of stop now and say that it's a complex field, but it's a field very close to my heart. And I'm hoping that one day through all of our participation in research, our kids live in a Parkinson's free world.

Melani Dizon:

That is good hope. Thank you so much for doing this, Kevin. This is really great. I know everybody's gonna love it. And you mentioned a couple of the trials that you sort of have been involved with. I'm gonna share the links. So, Kevin did a mindfulness based one and they just, they published a paper about it, which I'm gonna share the link for that and real quick no names, no specifics of the trial, but can you tell us your very best experience of working on a clinical trial and your worst experience?

Kevin Kwok:

So, I've been involved for in a five-year study for deep brain stimulation. I have truly loved being part of those because I'm working on the next generation DBS, the smart DBS on demand. And

for me, being on the cutting edge of that research has been wonderful. So that's probably one of the real pros on there. A negative one? I can't think of any real negative ones. I could tell you a fun one that I'm working on.

Melani Dizon:
Great.

Kevin Kwok:
So, in the area of sleep there are a number of different protocols that I've been involved with. Meditation came to an end, but I definitely had benefits in terms of helping myself through a challenging time in lowering anxiety and depression and finding myself calmer. The next phase of that is something that I got involved in here and this is ongoing now, because I just went to my first appointment last week is the Amber study. And the Amber study is being conducted by the University of Colorado. And it's the study of the effects of THC and CBD on people over the age of 60. And we all talk about how it's so much benefit, but it's hard, it's all anecdotal at this point and you always hear more studies need to be done. Well, I volunteered for one of those studies and I'm working on a combination of CBD THC, looking at issues of cognition, which is really important to me on here. And I'm still midstream. They're actually, my next appointment's coming up in two weeks.

Melani Dizon:
Oh, that's very cool. I'll link to that study as well. Just so people can check out what's going on with it. Well, thank you, Kevin. I have a feeling that people are gonna really love this and if we have any further questions, I will get to you and maybe they'll be a part two, somewhere down the road.

Kevin Kwok:
I hope so. I really hope so. And if this conversation convinces you to delve further into what is good trial development, I will have done my job.

Melani Dizon:
Thanks, Kevin.

Kevin Kwok:
My pleasure, Mel. Great talking to you today.

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