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Welcome to NETWise. This is a podcast for neuroendocrine cancer patients and caregivers that presents expert information and patient perspectives. My name is Jessica Thomas, Director of Patient Education at the Neuroendocrine Tumor Research Foundation.

If you're a patient living with NETs, you probably have some experience of fatigue. Maybe it's hard to get out of bed in the morning. Maybe in the afternoon, you have to take a nap. Maybe you have less energy to cook dinner in the evening, or to spend time with friends on the weekend.

Fatigue can range from temporary to inescapable, and from inconvenient to debilitating. It can be frustrating, and stressful, and sometimes lonely – it isn't a symptom that's easy for others to see.

And although fatigue is extremely common, sometimes we can be so focused on the cancer itself that it doesn't get much attention.

But it can be useful to understand the different causes of fatigue that might affect NET patients – as well as some helpful strategies to address it.

So in this episode of NETWise, we're going to turn the focus on fatigue.

It's no secret to doctors that patients often feel exhausted.

Dr. Claire Mulvey is a thoracic medical oncologist at the University of California in San Francisco. She specializes in taking care of patients with lung NETs.

Mulvey: *It's a pretty common thing I've heard patients say is that they look fine, that people look at them and say, "You don't look like you have cancer, doesn't seem like you have cancer." But they don't feel fine. You know, when they look at their day and what they're able to do, they're not able to do the things that they could do before.*

Dr. Mulvey is also a researcher, whose work has been supported by NETRF.

Mulvey: *I have done research focused on quality of life for patients with neuroendocrine tumors, and fatigue has jumped out as a particular need for patients with NETs. And that's both- I think we see that in clinic and then also, as I'm starting to analyze some of the survey data from our studies, something like 40 to 50 percent of people have reported significant fatigue as a side effect.*

Fatigue is a persistent tiredness, or lack of energy and motivation. It is a normal biological response to exertion,

stress, or lack of sleep. But when you are fighting cancer, it can become extreme.

There are two main kinds of fatigue: physical and emotional.

***Mulvey:** I mean, I think they're sort of two sides to the same coin. But really, it's patients coming in saying, they're exhausted. That they can't do the things they normally want to do. That their day looks very different. It's that exhaustion, and it can be physical, it can be emotional. Often it's both.*

We're going to start with the physical.

There are multiple ways that NETs can cause the body to experience fatigue. The first is simply the existence of a tumor.

Dr. Scott Paulson is a gastrointestinal medical oncologist at Texas Oncology in Dallas, at the Baylor Charles A. Siemens Cancer Center.

***Paulson:** You get bulky tumors. It's like carrying around another living thing inside you. So it tends to start to steal away your nutrition. People tend to lose a lot of weight. It's tough to get the energy that you need.*

That kind of depletion can apply to any kind of large tumor. But the thing that sets neuroendocrine tumors apart is that many of them produce hormones. These are called "functional tumors," and the various hormones they produce can contribute to fatigue in unique ways.

***Paulson:** These tumors can make hormones that can make you feel better, make you feel worse, can mess with your blood sugar, can change how you absorb certain types of foods.*

Mulvey: *The most famous syndrome caused by neuroendocrine tumors really is carcinoid syndrome, which is a syndrome where you have a tumor, usually one that started in the small intestine or maybe the lung, that makes way too much serotonin. Serotonin, when it's not in your brain and it's out in your body, it tends to cause all this flushing. It tends to cause a lot of diarrhea. It tends to change how you absorb things, and it does tend to cause fatigue. Certainly with carcinoid syndrome, having to use the bathroom often definitely contributes to fatigue if you're having to get up in the middle of the night, because you're having diarrhea.*

That can prevent people from sleeping. It can affect their appetite. And then these problems snowball, you know, the carcinoid syndrome is getting worse than the sleep problem might get worse than the fatigue might get worse.

Serotonin is just one of many hormones that different kinds of functional NETs can produce. Other hormones can also cause fatigue.

Paulson: *Certain types of tumors called paragangliomas and pheochromocytomas, basically, the substance they can make is adrenaline. So they can dump constant stress hormones into the system, which can actually over time be very fatiguing and very tiring.*

Mulvey: *I mostly take care of patients with lung neuroendocrine tumors, and one of the hormones they can make is cortisol- or ACTH, which leads to cortisol production.*

So there are some patients who live with high levels of cortisol over time. And that can cause all sorts of problems. Cortisol is part of our body's normal stress

response. It's helpful in small doses at the right time. But if you're living with lots of cortisol over a long time, that's generally not healthy for the body and can contribute to things like fatigue and sleep trouble.

In addition to tumors and the hormones they sometimes produce, there is a second source of physical fatigue NET patients might experience. And that's treatment.

Treatments often cause the body to operate differently than it normally would, in order to fight off cancer. Many of the treatments commonly used for NETs are known to be fatiguing.

Mulvey: *Chemotherapy can lower the blood counts when your immune system is suppressed. Often people feel more tired if it lowers your hemoglobin and contributes to anemia.*

That can be another reason why people might feel tired. And that's true both for the oral chemotherapy medicines like capecitabine and temozolomide. And then, of course, also any IV chemotherapies like platinum and etoposide.

Paulson: *PRRT, a lot of folks report fatigue. I'm not quite sure it's the radiation dosing itself with PRRT, but it is reported all the time, and we do know that radiation is fatiguing. We like to think of PRRT as smart radiation and somewhat controlled, but still getting a very large amount of radiation dose inside the body and exposure to radiation makes people tired.*

So anybody who's getting radiation for, say, a cancer in the neck and just getting external beam radiation for 6 weeks, those folks always come out saying, "I feel exhausted."

Mulvey: Immunotherapy can cause fatigue. Um, through a variety of different mechanisms. It can affect the thyroid. That's pretty common. Rarely it can affect the adrenal gland. And then there are also patients where the numbers look fine, the thyroid adrenal function looks fine, but they're clearly tired from the treatment.

And then lanreotide and octreotide, I mean, they are hormones, right? So they're synthetic versions of natural hormones that we make. But they can affect sort of the whole endocrine system, I think in ways we may not fully appreciate.

Paulson: So many folks are on lanreotide and octreotide. That's our bread and butter, our staple of treatments.

Other treatments we use for neuroendocrine tumors can be exceptionally fatiguing. Sunitinib, everolimus, targeted therapies. Some other drugs that we think are going to be coming down the pipe, cabozantinib, these can be very tiring medications independently.

They basically are slowing growth patterns within a cell. Some of them are what we would call dirtier effects than others, meaning they hit multiple different processes and growing cells to turn them down and slow them down. And that can be very fatiguing.

In addition to the physical effects of treatment, the process of getting treatment can be exhausting in and of itself.

Paulson: The number of calls you got to do with an insurance company, the financial meetings, the- different taking time out of your day to go into the physician's office, getting treatments, getting shots, getting

infusions, just that whole process, which seems to never end.

This brings us to psychological fatigue. It's different from physical fatigue, in that it affects a person's cognitive and emotional functions.

You might have trouble concentrating, processing information or thinking clearly. You might feel more irritable, sad, anxious, or stressed.

And that stress doesn't just come from logistics. A cancer diagnosis often comes with a tidal wave of fear and uncertainty. This can be even worse when it's a diagnosis of NETs, which are rare and complicated.

Mulvey: *I come back to this idea of a patient saying, I look well, but I don't feel well. And I think there's a, a unique psychological stress from having these types of cancers. On the one hand, they're being told, you know, this is a good cancer to have, people do better than for some other cancers. And yet they're living with sometimes a lot of symptoms over time, both from their cancer and from treatment. There's a huge spectrum of how neuroendocrine tumors can behave. There are some that are very indolent, some that are very aggressive. Responses to treatment can be variable, and we do our best to make predictions based on what we know about someone's tumor.*

Paulson: *I mean, it's probably happened three times today, I think. I saw somebody with a new diagnosis of neuroendocrine tumor, likely has some small residual left over after a surgery, tiny, tiny amount, in a very difficult to remove lymph node. And my feeling is, well, we we ought to watch and see what that does before we*

do anything differently, because I'm not 100 percent sure, your PET scan wasn't conclusive on this.

And this particularly young individual, got two young kids. So he's saying, "Okay, now you just told me there's a tumor left over, or there may be one, but you're not sure, and we're just going to get a follow up scan in six months and see what's going on?" That- that doesn't sit well. And, having to live with that constantly I feel like is very difficult. It's a chronic disease state and it's constantly on your mind.

So I think that hangs with patients, and I think that tends to cause a lot of fatigue. It would make me tired thinking about it.

Mulvey: *I am a co principal investigator of a study called the E net study, which is looking at quality of life in patients with advanced neuroendocrine tumors.*

And one of the themes - we're still analyzing the data - but one of the themes that's starting to emerge is that the psychological symptoms are as prevalent, if not more prevalent, than some of the physical symptoms. And I do think these issues like uncertainty and, and just the chronicity of some of the symptoms and treatments may be contributing uniquely for neuroendocrine tumors.

(patient story)

Beth: *My name is Beth Leonard. I am 49 years old and I live near the Washington, D. C. metro area. And my diagnosis is neuroendocrine cancer. Stage 4 neuroendocrine cancer.*

They're not sure which is the primary, actually. So it's- just all they've been able to say is it's stage four. They know that for sure. And that's all I've got.

I struggle with going to sleep at the end of the day. I struggle with staying asleep in the middle of the night. And oftentimes can wake up very early despite all of that.

First and foremost, the anxiety of it all, right? When you're first diagnosed, especially, Google is your friend. Although they say not for it not to be, but Google is your friend.

So anytime I have a symptom, I don't know which doctor it goes to. I don't know what problem I need to attend to. Is it related to cancer? Is it something new? So when you first get diagnosed, all of these things are coming through your head and you're researching everything. And the quiet time for me was always at night. So I'd be on my phone looking, looking, looking, looking things up.

And then dealing with the normal relationships, work stressors; I take too much on; I'm a perfectionist. So all these things go through my head all night long.

The other contributing thing is that often my diarrhea will happen at 2 or 3 o'clock in the morning. And so it wakes me up and that disrupts my sleep. I don't know what it is, but that seems to be the 2 or 3 a. m. time frame and will often last until 5 or 6, sometimes 8 in the morning.

So I know that's a contributing factor to my fatigue.

I know that the endocrine system has an impact on sleep, fatigue and other things. And let's be honest, I have a chronic illness. I have a disease. I have cancer. I have

stage four cancer. My body's got to be working on overdrive all of the time.

So oftentimes I feel like I'm going through molasses. It's like you lift up a limb and you can barely get it up and it just wants to drop back down. So physically, my body has reached past its performance.

My mind starts feeling that, hearing that internally, and I get this repeat: can't do it anymore. I can't go on. I'm exhausted. I'm exhausted. I'm exhausted. I can just get through the day. I just got to get through the day.

I get through the day and I'm exhausted. Physically, mentally exhausted. And I'm not a quitter. So I keep pushing and pushing to get through the day. But just walking up the stairs is exhausting. I want to take a shower, just walking to do a shower these days is exhausting. I need to brush my teeth and I'm sitting here calculating the time in my mind how much time this is going to take me and take away from me trying to get to sleep. Should I wash my hair? So do I wash it at night or should I sleep in a little bit or try to sleep in a little bit and wash it in the morning?

I want to go and do things that I like to do and don't feel like I have the mental capacity. Because I think it's not even just the physical, it's the mental capacity of fatigue.

So emotionally it's been very challenging. Then you add and compound the medical stuff on top of all of that, not being able to sleep contributes to that emotional feeling of depression. Because you can't get out of it.

We want to take some time to talk specifically about sleep. When we talk about fatigue, it's often intertwined with sleep, which can be disrupted by cancer symptoms, treatment side effects, or stress and anxiety.

This lack of sleep can exacerbate both physical and psychological fatigue.

Amanda Phipps is an associate professor of epidemiology at the University of Washington and the Fred Hutchinson Cancer Center. Her research focuses on how different lifestyle factors impact patient survival among those with cancer.

Phipps: *The consequences of not getting enough sleep will really vary according to how consistent, or how long term the sleep deprivation is in a patient. I think we all can relate to the experience of not getting enough sleep one night and then the next day you feel a little more fuzzy, maybe a little more irritable, you're not as good about eating healthfully, and that of course is going to be true for patients with cancer as well.*

And in the long term, consistently not getting enough sleep, or sleeping poorly, can have all kinds of negative effects on our health

Phipps: *It can have an impact on things like our immune system. Our ability to fight off infection, our ability to fight cancers as well. Our body really relies on our immune system to help us repair damage that's done by cancer, help us to fight the cancer and help us again to protect us from infections while a patient has cancer.*

And certainly for many patients with cancer, when you are going through treatment, you may be in this

immunocompromised state. And so certainly in that state, your body needs sleep more than ever.

Dr. Jaspal Singh is a pulmonary critical care and sleep medicine physician in Charlotte, North Carolina, where he's a part of the Levine Cancer Institute at Atrium Health and Wake Forest School of Medicine.

Singh: *When you have a patient with cancer, you want that patient's body to have the best chance to fight that cancer.*

Then on top of that, patients with cancer are oftentimes treated with medications or other therapies, potentially, that also can weaken their immune system. So it's like when you're going into this battle, your cancer patients are going to want to have as much advantage as possible, or at least disadvantage as possible, and optimizing your immune system is important.

This can be especially important if you're receiving immunotherapy.

Phipps: *One hypothesis is that especially when you're looking at patients receiving treatments with immune modulated therapies, therapies that work through immune pathways, that not getting enough sleep, which then has an impact on your immune system, can impact a patient's ability to respond to those therapies.*

In addition to increasing physical fatigue and compromising the immune system, lack of sleep can have serious effects on our mental health.

Phipps: *We do see a link between certain mental health conditions and sleep patterns, like depression, for*

example. But there might be sort of a chicken and the egg situation, different mental health conditions may impact our ability to get good quality sleep.

Things like anxiety and stress can impact our ability to fall asleep at night and to stay asleep. But they also may have implications for our stress levels and our anxiety levels if we aren't getting enough sleep. So it works both ways.

These issues are all complex and interconnected.

Stress, anxiety, depression, cancer symptoms, treatment side effects...they all impact – and are impacted by – our quality of sleep and our level of fatigue.

Singh: *The idea of sleepiness and fatigue in a pure sense, they're different, but as you can imagine, they blur quite a bit. If you have a cancer patient and they say they're tired, for example, that's a common sort of concern of many cancer patients.*

They're always fatigued. They're always exhausted. But if they're falling asleep, like falling asleep while doing their usual activities, that's a different sort of animal. And I think sometimes it's hard to dissociate which is an extreme fatigue versus a sleep disorder. And I think skilled clinicians really try to separate those two and try to address them in a potentially concerted manner, but maybe separate strategies for the sleepiness versus the fatigue.

Those strategies can include exercise, good sleep habits, and medication. The goal is to put routines back in balance that may have been disrupted by cancer.

Phipps: *One thing that really motivates me and my work is the understanding that when a patient is diagnosed with cancer, there is so much that feels out of their control. But even in the midst of that moment of that experience of receiving a cancer diagnosis, there are things that patients can do that they do still have control over.*

So I think it's really empowering to focus on the things that a patient can control in that moment of receiving a cancer diagnosis, to think about ways in which a patient can impact their own treatment response, impact their quality of life as they go through this stressful experience of a cancer diagnosis and cancer treatment.

(patient story)

Carrie: *My name is Carrie Camino. I'm 54, and I live in Libertyville, a northern suburb of Chicago. I have neuroendocrine cancer, and it is grade 3, stage 4.*

I literally found this very much by accident. I had a small twinge of something in my abdomen, and it went away, and three days later it came back in exactly the same spot. And I like to say that there was no workout program that I was on at the time that was going to actually cause that small little muscle twinge feeling. And so I ended up going to see a new general practitioner, who was good enough to listen to my thoughts and concerns. She sent me for a CT scan and two days later, had to come back to me and tell me that she had found a mass in the head of my pancreas.

I have both, removed my primary tumor via a Whipple procedure, I've also been on CapTem chemotherapy. I was on that for nine months, and I've recently been on a six month holiday.

I use exercise as my main means of managing my stress.

The exercise regimen that I follow, it's a combination of cardio and weights and stretching and yoga. I'll incorporate some swimming in there. And not every day is like a big slog. Some days it's just walking the dog around the block. However, I will see very, particular impacts in terms of my ability to sleep at night based in, and directly correlated with, whatever my level of activity was that day.

And I sleep best and recover best when I've made the time for myself to exercise and to make sure that I'm taking care of my body. And that will definitely have a positive impact on my ability to, you know, face the next couple of days.

In particular, it's that ability to actually not stay awake, up stressing and thinking about this that I actually feel like is so helpful to me. Because you can really kind of spiral. And, and there was a point in time where I was. You know, I would definitely wake up multiple times during the night, and it was all I could think about, and that certainly wasn't helping anything, and then you just find yourself stressed out even more the next day. And so that's why for me, I've prioritized so heavily my ability to actually almost enforce a sleep schedule, by making sure that I'm staying so active.

The other part of this is to give yourself permission. I've always found myself, I think, in roles where I was very much attuned to the needs and managing towards the needs of others. And so shifting that focus around, was a pretty big pivot for me.

You know, there's nothing like having medical professionals, specialists, sit in front of you and say, "Look, the best thing that you can do for yourself right now is exercise every day and be focused every day on what you're ingesting and how it makes you feel and being thoughtful and mindful about your rest and your, physical state."

I was recently actually speaking with someone else who, unfortunately, had a diagnosis of pancreatic adenocarcinoma. And you know, the thing that I mentioned to him was, it's really hard to think about yourself as a cancer patient, especially when you actually feel good. And, to, to look in the mirror and kind of wrap your head around that is an important and significant step because it allows you to start to clear things out of your way. And to be okay with the fact that, you know, you now get to be a little bit selfish with some of those decisions. I think the other thing that it clears the way for is for you to give yourself some grace and realize that, you know, not every day is going to be exactly as it was yesterday, but you can still find some really amazing things ahead of you.

Like Carrie discovered in her NET journey, exercise can be one of the most effective strategies for managing some of the problems we've been talking about.

Mulvey: *It's good for sleep. It's good for fatigue. It's good for anxiety, stress, and depression. Now sometimes people are frail or have other health issues and it's hard to do really any sort of activity.*

So in those cases, we try to connect them with physical therapist. or exercise counselors where there's a supervised setting, trying to do some strength training, some mobility training. It's kind of paradoxical if you're

tired, you know, try to keep up your activity level, but it is one of the things people can do.

Something else people can do is pay attention to their sleep habits. This is often called "good sleep hygiene."

Singh: *Good sleep hygiene generally means trying to follow our natural biological clocks. For example, you want exposure to sunlight or outdoor light ideally during the day, if you can do that. Obviously with certain medications in certain situations, you probably don't want to do that. But paying attention to your- your body's clock, you might say. So when when it's nighttime, don't stay up use devices, electronics, and gadgets. You want to really have some decompression time and use the bed mainly for intimacy or for sleeping*

Phipps: *Sleep is something that we all have control over to some extent, but I think it's also important to set realistic goals. In talking to a patient with cancer who's experiencing disrupted sleep, if their treatment is causing them disrupted sleep because there are these side effects that have them up throughout the night, telling that patient that they need to get a solid eight hours of sleep every night is going to feel like an unachievable goal. But there are aspects of sleep that maybe might feel more controllable.*

I would encourage patients to think about what they do have control over and start with sustainable goals. Things like having consistency in what time you go to bed, what time you wake up in the morning, every day of the week. Thinking about the environment in which you sleep. How dark is it? How noisy is it? Are you setting yourself up for success? Think about the different aspects of your sleep that maybe

contribute, not just to the quantity of sleep that you're able to achieve, but also the quality.

Sometimes, these behavioral changes aren't enough, and patients still feel exhausted. At that point, medication could be a helpful intervention in treating sleep troubles and fatigue.

Mulvey: *So I've seen our palliative care symptom doctors recommend things like- so there's a little data for stimulants, some of the treatments that folks, for example, with ADHD might use like Ritalin or newer versions of that. I've had some patients have good luck, you know, they're short acting, they may take a dose in the morning. Sometimes that can help fight fatigue.*

So all of this, you know, has to be done carefully with pharmacy, but yeah, that's another tool in the toolbox.

Singh: *Sleep medications are commonly prescribed, especially in our cancer patients. If patients do need a medication, we try to first of all make sure that they're safe with their other biological therapies or cancer therapies. That's the first level. The second thing is we try to find medications that are the least sedating as possible.*

Because the more sedating a medication is, the more potentially it might add to the patient's fatigue. And we really don't want to add to more fatigue if at all possible. Some of the ones we might try are things like melatonin, for example, some of the shorter acting agents, if needed, with the caveat that we also know that the minute some of those medications are started, some of them can be habituating.

And so we really try to minimize using medications if at all possible, but in patients that we do need them we just counsel them appropriately, make sure we use the lowest dose needed for the shortest acting agent possible and hopefully try non pharmacological or non drug methods of managing the insomnia.

Phipps: *I would say anytime a person is considering sleep medication, it's something that they need to be talking about with their care provider and not something to take lightly and certainly not something that we want to see people using on a long term basis.*

Regardless of what strategies you might be considering, the place to begin is a conversation with your doctor. Fatigue might not be something they bring up with you of their own accord, and it's important to advocate for yourself.

Singh: *It's not unreasonable to talk with somebody and do a separate examination, do a focused history and physical on just those aspects and try to tease out, is there a sleep disorder hiding here? Is there just cancer related fatigue? Is there something else like a mental health issue or stress issue or something else socially happening with that patient that's contributing to all their symptoms? And I think it's very hard. Or is this expected with this type of therapy? Some of the newer therapies that we have, biologic- biological therapy, for example, can risk different manifestations of fatigue and sleepiness that we're not traditionally used to.*

Paulson: *On the physician side of things, we're not going to take care of every change in your lifestyle that could potentially be a benefit for you. Frankly, it's not how we're trained. We're very reluctant to dispense quite a ton of advice that is not clearly substantiated by high quality*

level of evidence. But we don't have a research trial to answer every question in life.

So because of that, don't necessarily always rely on your doctor. Really, neuroendocrine tumor research was moved forward by patients, these are great networks for it, do what's right for you, these are individual things, diet, exercise, how you approach sleep, how you approach fatigue, how you approach your job, your kids, your family, everything else, everybody's got to do it the right way for them.

It's really impossible for us to be prescriptive.

Ultimately, these decisions are in the hands of patients.

Your experience of fatigue can look different depending on who you are, what kind of tumors you have, and where you are in your treatment journey.

There's no one-size-fits-all solution to issues with sleep and fatigue, but trying to address them can lead to lifestyle changes that benefit your physical and mental health.

Paulson: *Just somebody I saw this morning, and this is fairly typical, fall into a very deep depression, stopped taking care of themselves, in this person's case started drinking too much, started not sleeping, completely disconnected from all of their normal things that they were doing, their friends, their family, everything else.*

And then over time, they were able to get back on a good sleep hygiene schedule, start taking better care of the nutrition, cut out bad stuff out of their life, and they're just doing a heck of a lot better. Do I think that it's killing off their neuroendocrine tumor cells? Maybe it is.

I don't know. Maybe it is. But even if it's not speeding up or slowing down the cancer, it's the difference between thriving with the cancer versus just surviving with it.

Mulvey: *I want patients to have both the assurance that it's not in their head, that these are common symptoms that a lot of people are dealing with. And to recognize that they have sort of an outsized impact on their overall day to day quality of life. That they can have the conversations with their doctors and that there may be things that they can do about it, that there are different contributions to why they might be having trouble sleeping or why they're fatigued. And also that there are things that you can do.*

Thanks for listening to NETWise. I'm Jessica Thomas, Director of Patient Education for the NET Research Foundation.

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Episode 30
Fatigue:
Transcript

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