Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Stakeholder and Communication Conference Call

March 11, 2019

3:00 pm EST

Coordinator

Welcome and thank you for standing by. At this time, all guests will remain on a listen-only mode for the duration of today's conference. Today's conference is now being recorded. If you have any objections, you may disconnect at this time. I would now like to turn the conference over to Dana Brimmer. Thank you, ma'am, you may begin.

Dr. Dana Brimmer

Thank you. Good afternoon, everyone. My name is Dana Brimmer, and I am a contractor working with the ME/CFS Program at the Centers for Disease Control and Prevention.

On behalf of the program, I am pleased to welcome you to today's myalgic encephalomyelitis/chronic fatigue syndrome, otherwise known as ME/CFS, stakeholder engagement communication conference call, which we shortened to the SEC.

Our primary purpose here is to share information with a large number of people with interests in ME/CFS as part of our regular outreach and communication series. Before we get started, I want to review how the SEC calls work. Notification of calls will be sent by e-mail and information is also posted on the CDC ME/CFS website.

There's no need to register or RSVP for the call. Simply dial the 800 number and use the participant code provided in the e-mail or sign on the website. Due to the large

number of call participants, we are unable to have call lines available in speak mode. Therefore, we will take questions via e-mail using the ME/CFS SEC call e-mail system.

Please note that this e-mail address cannot respond to inquiries. Please note that due to time constraints, CDC and the guest speaker will not be able to answer all questions, but the CDC ME/CFS program looks forward to reading all of them that we receive. Our guest presentation today is titled “Orthostatic intolerance, research and clinical insights” by Dr. Benjamin Natelson.

First, we will hear from Dr. Elizabeth Unger, who will provide updates about the CDC’s ME/CFS program. After Dr. Unger, and our guest speaker, we will answer questions submitted via e-mail. I will first read the questions out loud and then our speaker will answer each one. I’m going to read a quick disclaimer before we hear from Dr. Unger.

These calls are open to the public. Please exercise discretion on sensitive content and materials as confidentiality during these calls or items submitted via e-mail cannot be guaranteed. Today’s call will be recorded and transcripts will be available at a later date on the CDC website.

The views of non-CDC presenters expressed during this conference call are their own and do not necessarily represent the views of the United States Department of Health and Human Services or the Centers for Disease Control and Prevention. I’d now like to ask Dr. Elizabeth Unger, Chief of the Chronic Viral Diseases branch at CDC, to start the call. Welcome, Dr. Unger.

Dr. Elizabeth Unger

Thank you Dr. Brimmer and welcome to all. Quickly, for those of you who are new to our forum, we initiated these calls to provide regular communication and engagement with the ME/CFS community about CDC’s activities and, equally importantly, to allow experts external to CDC to share information about the ME/CFS-related work.

We invite speakers based on their expertise and availability and we are extremely appreciative of their willingness to participate. Each speaker prepares their remarks independently. If you have suggestions for speakers or topics for future calls, please send them to the SEC call e-mail. That's mecfs@cdc.gov. This is the same address you would use if you'd like to be added to receive e-mail notifications, as well as to ask questions.

As you probably have learned, the charter for the HHS chronic fatigue syndrome advisory committee (CFSAC) was not renewed. We've taken several steps to help maintain the collaboration and momentum fostered by CFSAC. The interagency communication is continuing through a working group of the National Advisory Neurologic Disorders and Stroke Council focused on advancing ME/CFS research. I am serving as an ex-officio member of this workgroup.

In addition, we at CDC plan to increase the number of our SEC calls and we already have our next call planned, which will be in late May or early June, featuring Dr. Alison Bested whose presentation is entitled, "Pacing: Learn How to Stop Crashing and Increase Your Energy."

Now, I'd like to give you an update on some of CDC's recent activities and I'll start with our surveillance efforts. Last fall we awarded a contract to the National Association of School Nurses to conduct school-based surveillance of students with chronic absenteeism. A study suggests that ME/CFS is a major cause of missed school attendance.

This surveillance program will allow detection of pediatric and adolescent ME/CFS. To collect accurate data at the level of schools on the number of children who are chronically absent and the reasons for the repeated absenteeism, school nurses will be educated about how to recognize ME/CFS in their student population. Because school nurses are on the frontline of monitoring student health, this effort has the potential to

efficiently identify and track ME/CFS in school-aged populations. This could lead to a national school-based surveillance project for pediatric and adolescent ME/CFS.

We have also initiated surveillance activities with a managed-care organization through the Vaccine Safety Datalink program. The managed-care organization has developed a protocol to identify those with ME/CFS among their organizations' patient population.

A structured medical record review will be used to validate the diagnosis. Initiating this surveillance activity has highlighted ME/CFS for that particular managed care group. If the electronic medical records protocol successfully identifies patients with ME/CFS, this could provide a unique approach to monitor how clinicians diagnose and treat ME/CFS, and to investigate associated preceding illnesses or vaccines.

I'll round-out our surveillance activities with a quick update on the behavioral risk factor surveillance system, the BRFSS. For those new to this initiative, CDC's BRFSS program partners with state health departments. It was established in 1984 with 15 states participating and it now includes all 50 states.

In April 2018, based on our proposal and advocacy support, the BRFSS committee incorporated ME/CFS questions as an optional module into the 2019 state-based survey. Participating states will gather data to monitor ME/CFS prevalence, healthcare access, risk factors, and comorbidities.

The ME/CFS module includes those used as state-added questions in the 2014 and 2016 BRFSS surveys. Those questions are, "Have you ever been told by a doctor or other healthcare professional that you have chronic fatigue syndrome, CFS, or myalgic encephalomyelitis, ME?" If the response is yes, the second question is, "Do you still have CFS or ME?"

The optional module includes the third question, which was added to probe disability. “Thinking about your CFS or ME during the past six months, how many hours a week on average have you been able to work at a job or business for pay?”

We don’t know yet how many states will include this module for the 2019 BRFSS survey; however, we’ve secured funds to continue the optional ME/CFS module in the 2020 survey as well. Leveraging this existing surveillance system is a cost-effective way to monitor prevalence trends and risk factors associated with self-reported provider diagnosis of ME/CFS in the U.S. This is similar to the Canadian community health survey. This will make the U.S. the second country tracking ME/CFS to an ongoing surveillance system.

Now, I’d like to shift to updates on the multi-site clinical assessment of ME/CFS study, also referred to as MCAM. In the interest of time, I’m only going to briefly touch on a few items.

As a quick review, the study design required the use of a standardized approach for collecting the information on patients participating in the study at their respective sites. MCAM study information can be found on the CDC’s ME/CFS website under the program tab.

Last October, CDC hosted the 8th annual contract meeting for the MCAM study. During the two-day meeting, participants discussed the steps to close out four areas of the study that included: the ME/CFS clinical longitudinal adult cohorts that included homebound and incident cases, as well as healthy controls, cognition and exercise testing, and the natural killer cell function assessment. Study efforts are ongoing, focusing on children and adolescents with ME/CFS and adults with other conditions sharing some similarities with ME/CFS that is ill comparison groups.

I’d now like to provide some information about our educational initiatives.

Dissemination of information to the general public and healthcare providers is still a critical need. A new continuing education Medscape course entitled, “Diagnosing ME/CFS: the Expert’s Way In,” launched February 25th, 2019.

This course includes expert panelists Dr. Lucinda Bateman of the Bateman Horne Center, Utah; Dr. Natalie Azar, New York University Langone Medical Center; Dr. Nancy Klimas, Nova Southwestern University in Florida; and Dr. Jose Montoya, Stanford University, California. It includes pre- and post-test questions as well as questions required for earning continuing education units.

During the first week, the course had 2,146 learners and 715 certificates were issued. We will continue to update you on progress in future calls.

We are partnering with the Georgia chapter of the American Academy of Pediatrics to raise awareness among their members about ME/CFS. They have invited an ME/CFS expert to speak at their annual meeting in the summer, and used a banner ad in their December newsletter to raise awareness about ME/CFS in children and to highlight the CDC webpage as a source of information. Through interactions with this organization at a state level, we hope to build towards collaboration on the national level with other healthcare professional organizations.

In August 2018, CDC hosted the 2nd ME/CFS stakeholder roundtable meeting. About 40 people attended the meeting including state and federal partners, patients and advocacy groups, ME/CFS clinical experts, and representatives from various medical educational and professional organizations. The meeting was instrumental in gathering input on the type of educational materials providers need and would use.

Patients and advocates were able to share their perspectives about the kind of information they wanted their healthcare providers to know. Based on small-group calls prior to the meeting, we prepared drafts of educational materials. On the day of the roundtable, these drafts were distributed to help focus discussion. CDC received

valuable feedback from individual perspectives that will help create materials that are informative and useful to their intended audience.

Hopefully everyone is aware of this by now, but it is still worth noting that CDC's ME/CFS website has been updated. This was facilitated by the first roundtable, and we would like to thank participants for their diligent work, effort, and time on this project. In July, we posted the updated section for healthcare providers.

The section for the general audience, as well as healthcare providers, are currently being translated into Spanish, and we hope that this Spanish version will be available by the end of the summer. We have also added a section that includes first-person accounts of what it is like to live with ME/CFS. We plan to continually add to the "voice of the patient" section.

CDC is committed to working with our partners to achieve the goal of improved healthcare access and quality for patients with ME/CFS. Treatment guidelines for ME/CFS could contribute to this goal and the first step towards guidelines is an updated, systematic review of the literature. We have contracted with the Pacific Northwest evidence-based practice center at Oregon Health Sciences University, OHSU, to conduct this review. As you may be aware, systematic reviews start by framing the questions to be answered, as well as the particular population, interventions, comparators, outcome settings, and timings that will be considered.

These key questions are extremely important to assure the youthfulness of the review. This week, OHSU conducted interviews with key informants representing advocates and ME/CFS clinicians to help refine these questions. The discussion was very helpful and OHSU will finalize the key questions prior to initiating the evidence review.

Finally, a quick reminder that May 12, 2019, marks the 27th International Awareness Day for ME/CFS and Fibromyalgia. We will be using CDC's feature homepage, as well as CDC's social media outlets, to publicize the awareness day.

So I'm going to stop for now with our updates. Thank you for your attention and participation, and at this point, I would like to turn the call over to Dr. Brimmer so she can introduce our guest speaker.

Dr. Dana Brimmer

Thank you. Dr. Benjamin Natelson is the Director of the Pain and Fatigue Study Center at Mount Sinai Beth Israel in New York, New York, where he is also a professor of neurology at Mount Sinai Icahn School of Medicine. Dr. Natelson received his bachelor and medical degrees from the University of Pennsylvania in Philadelphia and then did his neurology residency at the Albert Einstein College of Medicine in New York City.

He also completed two post-doctoral fellowships, one in behavioral neurosciences at Cornell University Medical Center and one in physiological psychology at the Walter Reed Army Institute of Research. In 1991, he shifted his research to studies of people with CFS and fibromyalgia. Dr. Natelson has over 250 peer-published papers and has authored three books. Welcome, Dr. Natelson.

Dr. Benjamin Natelson

Thank you very much Dr. Brimmer and Dr. Unger for allowing me to interact with patients with ME/CFS. I'm particularly interested in doing so because most patients get confused about who I am. They say that Dr. Natelson, he's a research doctor.
I am a research doctor, but I am very much also a clinical doctor who's interested in seeing new patients with ME/CFS, so I can help figure out how to get them on the road to wellness. My mission really is clinical care, clinical definition of disease, how to reduce symptoms, and how to understand ME/CFS so we can develop new treatments.

So, the first thing I want to do with your listeners is to explain to you the difference between participating in the research and seeing a doctor, because even when you're doing the research, you may see a doctor, but research requires two things. First of all, no research in America can be done without your informed consent.

That means someone is going to say to you, “Are you interested in participating in research where we’re going to do such and such?” And if you say yes, then the research person will sit down with you and give you a few pages that lay out what the study is and if there are any risks to you, what those risks are, and essentially step you through the research plan. So you have to sign your informed consent.

Another thing that often, but not always, separates research from clinical care is you’re not going to be paying to do it. You either will not be charged to participate in the research study or you will actually get some reimbursement for the time you’ve spent to participate in it.

So, informed consent and no cost to the research volunteer is what research is. Clinical care, you all know about. You make an appointment to see your doctor. Your insurance reviews, pays the doctor for services at (length) of care, and the doctor works in the time with you to answer your questions and help do what I said I want to do, which is to put you on the road to wellness.

When you do research, that’s not part of the time you’re going to be spending. There, the doctor or the research staff are not going to be working with you to specifically help you feel better, but they’ll be working with you on the research problem.

Is the research problem trying to understand whether the brain is normal or abnormal in ME/CFS, or is the research problem there’s a new drug out, does that drug improve or does it reduce the symptoms of severe fatigue in ME/CFS?

So instead of the researcher or doctor saying to you “How can I help you feel better?”, what the research doctor says, “Please spend the following amount of time participating in this study,” which will do whatever the study is supposed to do… try out a new drug, figure out what’s wrong in ME/CFS, etc.

So, while there is research going on in many different sites, and you can explore these on the Internet, I want to tell you a little bit about the few… the several research projects that are going on at the Mount Sinai School of Medicine.

And I should just note that I've recently moved my offices north of Beth Israel for people who know Manhattan. I'm now at the Main Medical School campus on the upper eastside. So the studies we have going are several, funded by taxpayer dollars. The first is a follow-up study using spinal fluid, which we've collected from ME/CFS patients who are on no brain-active medications.

Now I have to explain, why do we want to do this? Well, spinal fluid -- as soon as you're taking medicines -- things change and indeed, if you study the brain, the brain can change just from brain-active medicines, and brain-active medicines are medicines for pain, bad sleep or psychological problems.

So, collecting spinal fluid in individuals not on those medicines is difficult, because many patients are on those medicines and we just can't ask them to volunteer, but we do have about 40 samples that are going to be analyzed to look at the research question of whether ME/CFS occurring without severe body-wide pain is the same as ME/CFS occurring with severe body-wide pain, aka fibromyalgia (FM).

Our research position is that the two illnesses and two diagnoses, ME/CFS alone and the ME/CFS with FM are different, and we've done a bunch of studies, which tend to point to that being true, and the next step is now to look at the spinal fluid of patients with ME/CFS alone, compare it to the spinal fluid of patients with ME/CFS and FM, and to healthy control spinal fluid.

And there is a method now that lets us identify every single protein that dissolves in the spinal fluid and we expect, based on an earlier study, to be able to identify proteins that are unique to ME/CFS, that differentiate it from ME/CFS and FM, and will be step one toward biomarker development.

Biomarker development has been a part of everything I'm doing as a researcher, because right now ME/CFS and FM are diagnosed based on what you, the patient, tell me, and we have no way of separating out the myriad different subgroups that fall within the diagnoses of ME/CFS alone and ME/CFS with fibromyalgia.

What we need is biomarkers and as soon as we have a biomarker that identifies a group of patients, either those with ME/CFS alone or those with FM, we can take a knife to the pie and cut out a slice and say these patients with the biomarker are different from the ones who don't have the biomarker. That means their underlying biology is different and means that the treatments are probably going to be different.

So I, and my colleagues, at Mount Sinai are devoted to biomarker development and, number one, we're going to do that with analyzing the spinal fluids we collected, and then starting spinal taps on patients, who give us their permission and their informed consent, so that we can have more samples to further answer the question of whether ME/CFS is the same or different from FM.

The other study that we are doing at Mount Sinai is a study of sleep, and we won't be having subjects sleep overnight. We're just going to start doing nap studies, where an individual will come into the sleep lab, and we will attach leads to their head and face as we've done in the regular sleep study, and ask them to nap.

In the hopes that we can figure out whether the way they nap differentiates patients who have ME/CFS alone from patients who have ME/CFS plus fibromyalgia. Again, I want to answer that research question, because if the two ailments are essentially the same that means the underlying biology is the same and would suggest that the underlying treatments are going to be pretty much the same.

But if, as our research to date has pointed out, the two ailments are different, that means different biomarkers and different avenues of treatment. So those are two studies that we're very excited about and are going right now or will be starting soon.

We are expecting to do a treatment study down the pipe on ME/CFS and expand our existing study on gulf veterans, with Gulf War illness, to people who have fibromyalgia. Just a quick aside about Gulf War illness.

I was very interested in it, because when I read about the symptoms that troops returning from the 1990-1991 conflict in the gulf reported, I thought they had chronic fatigue syndrome and indeed they had a markedly increased rate of chronic fatigue syndrome.

And so we have gotten funding from the Department of Defense to treat those veterans who also complain of body-wide pain with not a medicine, but a neuro-modulatory device that is stimulating the nerve in the neck and we're hoping soon that we're going to expand that study to patients who also have medically, unexplained pain.

Now having talked to them about what research is and how it's different from clinical care, I want to move on to the question of orthostatic intolerance. What it is, and how to identify it, and what, if anything, can be done about it?

What is orthostatic intolerance? Well, it's when a patient says that they were standing up, they feel worse than when they're either seated or lying down and they complain of light-headedness. They could have nausea. They can feel their heart beating in their chest, a whole host of uncomfortable symptoms.

One of the symptoms that some patients complain of is that their ability to think and concentrate, which is affected just by ME/CFS, but is worse when they're upright. So what is orthostatic intolerance biologically? Well, when you go from lying to standing, your body moves a pint of blood from your thorax, your midriff -- if you will -- into your

legs, so all of a sudden when you go (and that's why, by the way, so often people feel like a moment of dizziness if they go from lying to standing, because it takes the body a few seconds to adjust to the fact that there's less blood in the whole system because there's more blood in the legs and pelvis.)

The thing that complicates things for ME/CFS is apparently many ME/CFS patients have less blood in their blood vessels than is normal and the word for that - the medical word - is hypovolemic, which is less volume in their blood supply than is normal. So let's just say that a normal person has 100% and a ME/CFS patients has 80% of the normal amount of blood and both of them stand up.

The normal person may have a second of feeling lightheaded, but the ME/CFS patient who goes from lying to standing, all of a sudden the blood vessels in their chest don't have as much blood as is necessary, and there are receptors in the major blood vessels in the chest, in the thorax, that can sense changes in blood pressure. Those are blood pressure receptors. Now they are there to help a person live through a hemorrhage, so if you were to lose 1-1/2 or 2 pints of blood in a very short amount of time, (your bodily fluid), you would become hypovolemic.

And even if you weren't standing, but especially so if you're standing, the blood pressure receptors in the major vessels in the chest would say where's the blood and it's not there and those neurons would be activated, and what they do is they trigger a reflex that protects you from low blood pressure by increasing your heart rate.

So that is the normal bodily response to hemorrhage. Well, thank God our ME/CFS patients are not hemorrhaging, but they, let's say some of them, only have 80% of the blood volume of healthy people and when they stand, it's as if they're hemorrhaging.

Their blood pressure receptor, in their major vessels in their chest say 'where's the blood, it's not here, we need to compensate by raising the heart rate' and that is called orthostatic tachycardia and has been nicknamed POTS. POTS is just the addition of the

word postural. Postural orthostatic tachycardia syndrome (POTS). Now what does POTS translate? How do we make that diagnosis? Well, when you come to see me at Mount Sinai, or at many centers where physicians are expert in ME/CFS, they ask you to lie down in a face-up position for up to 10 minutes to allow your biology to come back to normal.

You may have had to walk or dash to the office. This is where blood pressure and heart rate begins to return to normal and then after things are back to normal, see you have a heart rate of 70 or 75, which is a normal heart rate per minute.

In our center where we have not done tilt testing, but we are about to start it, but without the tilt table, we just piloted a test that NASA has used over the years to see whether individuals who've been sent out in space develop orthostatic intolerance, and a quick aside, when you're in zero gravity, you develop orthostatic intolerance.

And when you lay in bed for prolonged periods of time, you develop orthostatic intolerance. So one of the things I do with my patients is I tell them that they should spend as little time flat in bed as possible, because prolonged bedrest, which can often be caused by feeling so ill with malaise and fatigue, can lead to prolonged bedrest, and prolonged bedrest in itself can lead to POTS.

So that I encourage people not to lie horizontally, but to sit up and try to stand and walk based on their abilities. So there you are, lying flat in our office, 75 degrees and then we do the NASA test, which is simply to lean you against the wall. And on our Facebook page, if you go to the Facebook page for our website, which is www.painandfatigue.com, you will see what it looks like, where you're leaning against the wall and we can measure your blood pressure and heart rate.

And so if your heart rate goes up by more than 30 beats, that is, 75 lying flat and it goes above 105 while leaning for a 10-minute lean test, that's POTS. Now I'm probably the only doctor in the New York area who adds something to the assessment for orthostatic

intolerance, so in other words you can complain that you feel worse, you are upright but when you develop POTS, you're having an objective marker orthostatic imbalance.

We extend this to another measure and that is freezing rate and the consequences of other rapid or deep breathing. So we do that by attaching a cannula to a patient's nose so we can look at exhaled (inaudible) composition of the exhaled air that individuals produce as they breathe out and in.

So this little device looks at the last bit of air that is exhaled with every breath, and what we're looking at is the exhaled carbon dioxide. Now I have to explain to you a little bit about the biology of carbon dioxide. So when you eat food, the food goes to cells within the body which use it for energy to stay alive.

And the product of that energy use is the production of carbon dioxide and water, and (typically) the cell then lets carbon dioxide out into the bloodstream where it's brought back into the lungs for you to exhale, and normally we exhale just the right amount of carbon dioxide because if we have chronic obstructive pulmonary disease (COPD), where our lungs have been destroyed by some disease process, our CO_2 can't go into the breathing spaces in the lungs, known as the alveoli, because they've been destroyed.

And so the CO_2 levels in the blood build-up and then that can produce horrible symptoms and even, if there's too much carbon dioxide, that's called hypercapnia, hyper is too much, capnia is carbon dioxide. But there is another thing that can occur if you have orthostatic intolerance -- whether it be from being in space for two weeks, being flat in bed for two weeks, or by having the problems in the nerves to the blood pressure receptor and heart and blood vessels. The so-called autonomic nerves, which are responsible for POTS, and what I'm about to explain to you which we have labeled as POSH, postural orthostatic syndrome of hyperventilation. And what POSH is, is an individual who's lying flat on his or her back, has the normal exhale values for carbon dioxide, but then when he or she leans against the wall, whereas in the tilt test, the

carbon dioxide value goes down to low values that produce tingling around the lips, tingling in the fingers, and make you feel awful, and that is due to your over-breathing.

So the person with COPD can't try to exhale the carbon dioxide, but that individual has lung disease, which interferes with the carbon dioxide going to the blood into the breathing spaces. What happens in POSH is individuals breathe too deeply, and so they exhale too much carbon dioxide and the levels get very, very low.

And when they get very, very low, you have orthostatic intolerance. Now what does that? Well, in the same way that the chest has receptors for blood pressure, it has receptors for carbon dioxide level and when your carbon dioxide levels get low, your brain gets activated and says 'something is amiss' and turns on nerves to the heart and makes you breathe even faster sometimes.

And so patients that have POTS and POSH, a very fine researcher in Westchester Julian Stewart, has reported that the POSH is produced by the POTS, and that occurs because of changes that the reduced levels of carbon dioxide do in the brain to activate the brain. And one way of dealing with low carbon dioxide in an emergency situation, as if you were hemorrhaging, is to increase the heart rate.

So, in addition to this orthostatic hyperventilation, some patients have it just while sitting. And we doctors were originally taught that hyperventilation is a bodily manifestation of anxiety or nervousness and, in some people, it clearly is. If I see a patient who's had a long history of troubles with anxiety and worry (being worried) and they are over-breathing while sitting in front of me that may be anxiety.

But a large number of people have it because of this gravitational problem, again that their, even when you're sitting, you're auto-transfusing - I shouldn't use auto-transfusing - even when you're sitting, blood shifts from your body into your pelvis and legs, not as much as when you stand, but it still does and that, Julian Stewart has called

gravitational stress, the same thing as standing of course, which can produce orthostatic intolerance.

Some individuals have orthostatic intolerance just sitting. They'll have either a high heart rate, or they will have reductions in their exhaled carbon dioxide, and so both resting reductions in carbon dioxide and resting high heart rate could be…when I say resting, I mean sitting as a patient would in front of me when I do my clinical intake, would suggest that when they stand they're going to get worse and we often see that.

And so we think that these individuals do not have anxiety as the cause of their over breathing, but instead have this response to gravitational stress which turns on these nerves to the heart, the blood pressure, the autonomic nerves, and produce either over-breathing and/or high heart rate.

So POTS or POSH, now let me just talk a little bit about how reductions in the exhaled carbon dioxide can occur, and there are two ways that this can occur voluntarily. We can either pant like a puppy, so if our normal respiratory rate is 12 breaths per minute, okay, so that's a breath what, every six or seven seconds, which is sort of normal. But if we then breathe at 25 breaths per minute, we may be moving more air than is necessary, and we may exhale more carbon dioxide to produce reduced levels in carbon dioxide, a way we measure with a nasal cannula, which would be over-breathing or hyperventilation by that method.

But it turns out that a much more common method is not increasing respiratory rate, but it is increasing depth of breathing. So instead of breathing at 25 breaths per minute, someone who has this problem could be breathing normally at 10 to 12 breaths per minute, but instead of moving a certain amount of air, they may be moving 150% more air.

That is they're breathing much more in and much more out, which does the same thing as taking carbon dioxide out of the breathing space - out of the blood into the breathing

spaces - and then exhales into the environment. So both of these methods can reduce the exhaled carbon dioxide and lead to orthostatic intolerance.

Now what can be done with that? Well, I've already said that one thing is to not lie flat, so I often tell patients with markedly bad orthostatic intolerance to put several bricks under the head of the bed so that they're lying on a small angle, but again not lying flat, so that's Number 1.

Number two is you can wear support stockings that are available in the - can be available - in surgical supply houses, but I've learned that some of the athletic clothing that people wear are support. The only thing about these, though, is you just can't wear them to the knee. They have to be tight so that you are able to (inaudible) and why do you wear these, why the tights or these support hose? Why do they help prevent POSH and POTS, well again when you stand up, you auto-transfuse. You shift a pint of blood from your body to your legs, and if you have this tight garment on your legs up to your waist, there's less room for the blood to pool so the blood stays up in the chest so that's one way to do it.

And then there are various medical ways that can be used, which we could talk about if you were ever a patient. So one word about my clinical practice, because I love new patients, is our website, www.painandfatigue.com, where you will see that I ask you to fill out a health screen form, which then gets sent to us, that we review, and then we see you.

And we spend quite a bit of time with our new patients, because so many patients have a lot to tell us, and we need time to listen. So I think that's it, Dr. Brimmer, in terms of my comments. Let's see, how are we doing on time?

Dr. Dana Brimmer

We're doing well on time. We can move on to Q&A now or if you have any last thoughts, please feel free to share.

Dr. Benjamin Natelson

Well, let's think. Let me summarize, so what I've tried to do today is to explain to you what research is. (And) research is not going to necessarily make you feel better, at least not right then, but it's going to collect knowledge that will improve knowledge about ME/CFS and then allow doctors to work on biomarkers, which are critical for pulling out groups of patients who have things in common, as compared to people who don't have the biomarker.

And that's number one, and of course as I told you, you have to sign informed consent and you do not pay for research. Clinical care, on the other hand, is oriented toward you and your symptoms, how to reduce them, and how to put you on the road to wellness.

And again for patients interested in either research or seeing me as a physician, www.painandfatigue.com. So that's it. I think we can take some questions now, Dr. Brimmer.

Dr. Dana Brimmer

Great, well thank you. So I have the first question for you and that is "Are you seeing hypoxia within patients? Blood-oxygen levels on my pulse oximeter have been fluctuating based on position. I have heard this among other patients as well."

Dr. Benjamin Natelson

Okay, so the answer is no. During waking, none of my patients have abnormalities.. well I shouldn't say none…it is very rare patients, when they're upright, have problems with oxygen, blood-oxygen levels, but it's not the blood-oxygen levels that I track because they're nearly, 999 times out of 1000, they're normal, but it's the exhaled carbon dioxide that I track.

That is a much more often normal. (And) in collaboration with researchers in the CDC, we've looked at the relation between POSH and POTS, and we found that one patient

can come in one day, sitting, with low levels of carbon dioxide and they come in the next day, they may have POTS. That is everything is fine when they're sitting, but when they stand up, their heart rate goes up. And then, on another visit, they may have POSH, that is, they come in and when they're sitting, their carbon dioxide levels that they're exhaling are normal, but when they stand and lean against the wall, their carbon dioxide levels fall.

So there's an interaction among these diagnoses that we are researching at CDC to try to understand who gets these problems, and what are the associated biological abnormalities that come with them in terms of breathing, blood pressure, and heart rate.

Dr. Dana Brimmer

Okay, a second question for Dr. Natelson, "My question is on the objective measurement of the SEID symptom like CPECSs or the tilt test. Are these measurements clinically reliable, and what are the cutoff points to clinically diagnose ME/CFS based on these measurements? Are there any research on these objective measurements?"

Dr. Benjamin Natelson

Well, the answer is there is plenty of research on tilt and lean, and let me take that tilt and lean first. So, I spent the past 15 minutes talking about tilt and lean, the abnormalities that you see.

These are rather reliable. Again, in our CDC study, we've had starting with 76 patients with ME/CFS, and by the third visit we only were able to ask 30 or 32 that returned for the third visit, and each visit is a year apart, but we have identified the fact that many patients who have biological evidence of orthostatic intolerance have it over those three visits, but its form can change, that was the point I just made prior to this question.

That is one time it can be POTS. That is, everything is fine with the patient lying supine, but when he or she leans against the wall, their heart rate zooms, and another time they

could have POSH, that means their exhaled carbon dioxide is normal lying, but when they lean up against the wall, the exhaled carbon dioxide falls to low levels which in and of itself can produce symptoms, and as I indicated earlier can also produce an increase in heart rate.

So there's been a lot of work. Individuals that have physiological manifestation of orthostatic intolerance basically could be a resting high heart rate and in some patients it could be resting low levels of exhaled carbon dioxide, and then of course, if they're normal resting and then they lean against the wall, POTS or POSH, these are biological manifestations. And they're often, but not always, repeatable, but they often a consistent and a target for my treatments, because patients feel awful if they have orthostatic intolerance when they're up. And that encourages them to rest more and if they rest in the lying-down position, they're going to get more orthostatic intolerance because bed rest simulates life in space, which we know produces orthostatic intolerance.

So that's the question for tilt testing, or as we do lean testing, and that's what NASA essentially uses leaning against the wall as a simple version of the tilt test. What's the tilt test? That's a horizontal table that tilts a patient up so that they may be anywhere from 45 to 70 degrees upright, and it's also a gravitational stress the same way as resting.

In terms of a stress test, the CPET (cardiopulmonary exercise test), that is not useful for ME/CFS unfortunately, because we have done studies and we have been very, very careful to compare our ME/CFS patients with individuals who are also very inactive just due to the fact that their life is television and resting and their biology on stress testing is the same.

So ME/CFS is not a reliable, I'm sorry, a stress test is not a reliable way of separating an ME/CFS patient out from a healthy control.

Dr. Dana Brimmer

Okay, thank you. Dr. Unger, I have a question for you. The question is “I heard earlier today from the CDC update that patients are being tracked through a vaccine awareness program. That makes sense, because a lot of us think this was caused from vaccines or having (medical) exposure. Does the CDC think this is vaccine-related?”

Dr. Elizabeth Unger

Thank you, thank you for that question, and the opportunity to clarify. That study with the managed healthcare is being leveraged through the vaccine safety data link, and we’re still early on in the process, but the reason that we went to the vaccine safety data link was, because we wanted to provide more evidence about the relationship between ME/CFS and vaccines.

To date, the vaccines have not been causally linked to ME/CFS, but we understand that there is a concern in the community. (And) we want to provide as robust data as possible, and that will require tracking widely because ME/CFS is not you know (inaudible), establishing that link will be very difficult.

And so as a very, very first step to that, we need to be able to find if we can use electronic medical records to do a very large, broad-scale surveillance, but just let me reassure you that CDC does not have any evidence that ME/CFS is related to vaccines.

Dr. Dana Brimmer

Okay, well thank you so much to both Dr. Unger, and many thanks to Dr. Natelson for taking the time to be with us today, and to our participants for your time and interest. To submit questions, ideas for future topics, and speakers, please direct all correspondence to mecfssec@cdc.gov.

More information about the CDC ME/CFS program is available at the CDC website. Thank you again everybody for your participation.

Dr. Benjamin Natelson

Dr. Brimmer, can I just say one last thing to your listening audience before we stop the webinar?

Dr. Dana Brimmer

Oh yes, please do.

Dr. Benjamin Natelson

I want to again remind patients that I am a doctor, as well as a researcher. And individuals in the Northeast that can get to Manhattan, I love new patients. I want to help you feel better, and I want to thank you for the opportunity to speak to you about clinical care and research. Thank you.

Dr. Dana Brimmer:

And thank you everybody for participating today.