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<https://reachmd.com/programs/cme/opening-a-new-chapter-on-the-diagnosis-and-management-of-unexplained-chronic-cough/12068/>

Released: 12/21/2020

Valid until: 12/21/2021

Time needed to complete: 15 minutes

ReachMD

www.reachmd.com

info@reachmd.com

(866) 423-7849

Opening a New Chapter on the Diagnosis and Management of Unexplained Chronic Cough

Announcer:

Welcome to CME on ReachMD. This activity, entitled "Opening a New Chapter on the Diagnosis and Management of Unexplained Chronic Cough" is provided by Prova Education and is supported by an independent educational grant from Merck.

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Dr. Canning:

Unexplained or refractory chronic cough causes significant impairments in quality of life. Effective assessment and treatment approaches are needed for these conditions. Are you doing everything you can to improve the quality of life in your patients?

This is CME on ReachMD, and I am Dr. Brendan Canning.

Dr. Dicipinigaitis:

And I'm Dr. Peter Dicipinigaitis.

Dr. Canning:

Let's get started. Dr. Dicipinigaitis, on the first podcast plus, I discussed in depth an overview of unexplained or refractory chronic cough. Can you please briefly sum up some of the key points for an introduction into this activity.

Dr. Dicipinigaitis:

Yes, thanks Brendan, because definitions really are very important as we begin a dialogue of cough. So chronic cough simply means that a patient has had a cough for more than 8 weeks, and at that point, it's important for the physician to look for underlying causes of cough that, if treated, will make the cough go away. Once all known reversible causes of cough are treated and the patient is still left with a cough, then it's appropriate to call the cough a refractory chronic cough. So it's very important that we thoroughly evaluate underlying causes before rendering this diagnosis.

Now, in the patients that I see at the Cough Center, the profile is very interesting. Although all types of patients of all ages and genders come to see me, the typical profile of a patient with chronic cough is a perimenopausal woman in her 50s and 60s. They are extremely troubled by their cough, and the cough is troubling in terms of its frequency. Some patients can cough literally hundreds of times a day, and in others, it's severity of episodes that are more bothersome, whereas a patient can have maybe 5 or 6 episodes during the course of a day, but those episodes are so severe, so prolonged, can cause vomiting or dizziness or fainting, and in women, very frequently urinary incontinence.

So it's really very profound what a quality of life issue chronic cough is. And as someone who tends to see patients later on in the course of their journey, it's remarkable that not uncommonly I'm the eighth or the tenth doctor these patients see because they have gone through, oftentimes, a number of primary care specialists and a host of subspecialists, including pulmonary, allergy, ENT, and GI, and unfortunately are still left with a cough that that hasn't been treated effectively. So I think we can underestimate the quality of life effect that a refractory chronic cough will have on a patient.

Dr. Canning:

And one of the important things in the field, Peter, is that when we talk about refractory chronic cough, we are usually excluding those patients that have a history of smoking.

Dr. Dicipinigaitis:

It's very interesting that those of us who run chronic cough centers – myself and colleagues in the US and abroad – we see a majority of our patients with refractory chronic cough actually being lifetime nonsmokers. So obviously, cough is a common associated symptom with COPD, for example, and asthma, but many of our patients at cough centers are, in fact, nonsmokers.

Dr. Canning:

Peter, keeping this information in mind, can you discuss some of the current guidelines on diagnosing unexplained or refractory chronic cough?

Dr. Dicipinigaitis:

Yeah, Brendan, in fact, there are two recent published guidelines by major medical societies. One is the American College of Chest Physicians, or CHEST, and then recently, just at the beginning of 2020, the European Respiratory Society published their guidelines. And in both of those guidelines, there is a very thorough discussion of a very important concept of the physician needing to very completely and systematically evaluate for reversible causes of cough. Those being what we now call upper airway cough syndrome, which used to be termed postnasal drip syndrome or rhinitis, also asthma and non-asthmatic eosinophilic bronchitis, which is a distinct syndrome, and reflux.

So it's very important to thoroughly evaluate and treat for these conditions and hopefully find an underlying cause of cough that can be reversed. Because if you are unsuccessful there, then it is appropriate to render the diagnosis of refractory or unexplained chronic cough, and unfortunately, at this point in time, we do not have good therapeutic options for refractory chronic cough. So very important to make sure we're not missing any reversible cough as we work up these very complex and challenging patients.

Dr. Canning:

And Peter, just to emphasize a point here, both you and I did work on the ERS and CHEST guidelines for cough. But what has become clear is that this group of patients, these unexplained or refractory chronic cough patients, are not unique to the United States or Europe, and in fact, we know that thoracic societies and medical societies throughout the world have produced guidelines which describe patients much the same that you'll find in the CHEST guidelines or in the ERS guidelines.

Dr. Dicipinigaitis:

That's right, Brendan. There are probably 10 or 12 national society guidelines published in the last decade or so, so the guidelines are out there, yes.

Dr. Canning:

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Brendan Canning, and here with me today is Dr. Peter Dicipinigaitis. We're discussing the optimal treatment strategies for unexplained or refractory chronic cough.

Peter, now that we have all the background knowledge discussed earlier in these podcasts, how do we translate this into current treatments?

Dr. Dicipinigaitis:

So Brendan, the reason I made such a big point earlier in this podcast and in the previous one about how crucial it is for a physician to very thoroughly investigate and evaluate for potentially treatable underlying causes of chronic cough is because if we're unsuccessful in finding an underlying cause, and we're dealing then with refractory chronic cough, unfortunately at this point in time, our options to treat this are not very good. And in fact, the landscape is quite bare.

And what we have at our disposal now as clinicians who are faced with a patient with refractory chronic cough are just opiates, such as morphine, which is used in the UK much more than the United States, and of course isn't a particularly satisfying option for something that may need chronic therapy.

The next big class of drugs that is used are the so-called neuromodulators, which are amitriptyline and gabapentin, and I do use these drugs when I'm faced with a refractory chronic cough patient, but unfortunately, my experience with these drugs has been very poor. Maybe 15% or 20% of patients are satisfactorily treated with these drugs because there are two challenges. Number one is you have to have a patient that actually has improvement in their cough from one of these drugs, and they have to tolerate the dose of the drug that gives them cough suppression. And especially with gabapentin, it's unfortunately often the case that patients just experience an intolerable amount of sedation, so that even if they do get some cough relief, they just can't tolerate the degree of sedation that the

gabapentin causes.

The other option is speech pathology, which very interestingly has been shown, actually in randomized controlled studies in the past decade, to improve cough and even cough reflex sensitivity. So I have been convinced in the last ten years or so that an involvement of a speech-language pathologist as part of the chronic cough treatment team can be a very, very valuable component of treatment.

Unfortunately though, very few speech pathologists are knowledgeable in and interested in chronic cough, so it's not like every town or office or even medical center will have such a person. But undoubtedly, speech pathology can be very useful in addition to pharmacological therapy for these very difficult patients with refractory chronic cough.

Dr. Canning:

So what I hear when I hear treatment strategies, which include morphine, amitriptyline, and gabapentin, and then the very hands-on approach of a speech pathology intervention, I hear a description of a condition in which patients and their treating physicians have reached really last resort area. And the fact that many of these approaches have benefits in only a subset of patients really speaks, to my mind, of the complexity of this disease and the severity of it and the need for new therapies for chronic refractory cough.

Dr. Dicpinigaitis:

Absolutely, and just a tremendous amount of frustration, both for the patient and for the physician alike.

Dr. Canning:

With that in mind, Peter, could you discuss some of the data on emerging therapeutics for treating unexplained or refractory chronic cough?

Dr. Dicpinigaitis:

Absolutely, I'm happy to, and I'm happy to report that I do have a lot to discuss. As we had mentioned in the previous podcast, you had reviewed all of the new learning on cough neurophysiology and cough pharmacology. And as we learned about the receptors and ion channels that are relevant in beginning the cough reflex, that led then to the discovery of drugs that are antagonists to these receptors and ion channels. And thankfully, we now have multiple clinical development programs of potential antitussives.

So clearly the area that has been most active is an area of purinergic receptor antagonists, or P2X3 antagonists. And with those drugs, there are actually 4 programs underway. One drug, gefapixant, has actually just recently completed phase 3 trials. Two large studies – one of about 900 patients and one of about 1,200 patients – and in those studies, there were two doses of gefapixant evaluated, 15 and 45 mg. And in both of those studies, the higher dose of the drug showed statistically significant improvement in the reduction of cough frequency versus placebo. So we're quite happy with those results and are looking forward to having the ability to use this drug as clinicians in the near future.

There are three other P2X3 drugs in development that are currently undergoing phase 2 trials. So this is the clinical development program that is furthest along, but there are some other molecules being looked at as well. For example, there's a neurokinin-1 receptor antagonist now being looked at. And neurokinins are likely involved both centrally and peripherally in cough. And earliest on in the pipeline, but also very interesting, are the so-called voltage-gated sodium channel blockers, of which there are at least two clinical programs going on. And these are lidocaine-type drugs that affect action potential and diminish the afferent signal that way. So thankfully, clinical drug development in cough is now a very active area, and we hope to have our first-ever drugs for chronic cough hopefully in the near future.

Dr. Canning:

One of the satisfying things – being a cough researcher over the past two decades, as you and I have been – has been the recognition by the pharmaceutical industry that this is a viable drug discovery area. And there are a couple reasons for that. First, I think, is the great advances that we've made in understanding the neurophysiology of cough. But I think equally important – comes from the clinical side – and that includes both the capacity to measure cough clinically with objective cough counting monitors that have emerged over the past 15 years, but also very reliable quality of life measures that have quantified this. And then in parallel has been the consistent messaging from clinicians such as yourself that have made clear that this is a serious problem for patients deserving of aggressive medical treatment and deserving of therapeutics designed specifically for the treatment of chronic refractory cough.

Dr. Dicpinigaitis:

That's exactly right, Brendan. And as you know, in the last 10 years or so, we in the cough community have also been very active in putting forth the concept that chronic refractory cough isn't simply a symptom of something else but its own inherent disease condition. And I think it's important that we think about it in those terms.

Dr. Canning:

As always, Peter, this has been an enjoyable conversation with you about chronic refractory cough. Just to conclude our discussion,

can you share with our audience your key takeaway?

Dr. Dicpinigaitis:

Yes, I think, certainly as we discussed, these are exciting times ahead. We will, for the first time ever, have drugs for chronic refractory cough, but I'll continue to stress the point that before we have the right to render the diagnosis of refractory chronic cough, let's make sure as clinicians that we have evaluated chronic cough and have truly excluded reversible, treatable, underlying causes of chronic cough.

Dr. Canning:

Yeah. I agree. So unfortunately, that's all the time we have today. I wanted to thank our audience for listening, and I wanted to thank Dr. Dicpinigaitis for joining me and sharing all of your valuable insights. It was great speaking with you today.

Dr. Dicpinigaitis:

Thanks, Brendan. It was a pleasure.

Announcer:

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