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Emerging Treatment Strategies for the Management of Patients with Chronic Cough

Announcer:
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Dr. Garrison:
Hello. On behalf of the American Thoracic Society and partnership with AKH, I want to welcome you to this webinar and the management of patients with chronic cough. My name is Garth Garrison. I'm a pulmonologist at the University of Vermont, here in beautiful Burlington, Vermont, where I also direct our pulmonary and critical care fellowship training program. I'm joined today by my good friend and colleague, Dr. Prema Menon. Dr. Menon, would you like to introduce yourself?

Dr. Menon:
Yes. Thanks, hi everyone. I just want to thank everyone as well for joining today. My name is Prema Manon. I'm also pulmonary and critical care at UVM, and I'm the director of our interstitial lung disease I'll give it back to you, Garth.

Dr. Garrison:
Thank you. Today we'll be addressing chronic cough and current recommendations for management. Specifically, we will be addressing the prevalence of unmet clinical needs and impact of chronic cough in patients who do not find relief in recommended management strategies; analyzing clinical trial data and mechanisms of action of emerging therapies for patients with refractory chronic cough; and summarizing the current guidelines and emerging treatment strategies for management of these patients.

I'll start off with just a couple of definitions. Cough can be described as acute, sub-acute, or chronic. Acute cough- is defined as a cough lasting three or fewer weeks, whereas sub-acute cough can last between three and eight weeks. For the purposes of this discussion, we will be defying chronic cough as a cough lasting greater than eight weeks, although a cough greater than twelve months is used in many chronic coughrelated clinical trials.

Chronic refractory cough is a cough that lasts more than eight weeks, despite a thorough evaluation and therapeutic trial. For this discussion today, we will not be specifically discussing chronic cough related to structurally abnormal lungs, such as with idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, or bronchiectasis. That said, some of these chronic cough management strategies may be considered in those populations.

As many of you can attest, chronic cough is a very common complaint. That appears to be true not only just in North America and the United States, but really throughout the world. How common is chronic cough? Well, the data is somewhat hard to evaluate given different definitions and populations studied, but it's estimated that the worldwide prevalence of chronic cough may be as much as 10%. There are interesting data from Canada just published recently demonstrating a prevalence of 15% in adults over age 45. It's more common in smokers, but present in10.8% of never-smokers. That's an amazingly-high number. It appears more prevalent in Europe and North America overall when compared to countries in Africa and Asia.

In 2014, a group called the International Cough Registry, which is a collection of cough specialty clinics published retrospective data

from referred patients to describe the demographics of chronic cough. In this group of patients, two out of three were women, and the most common age at presentation was between the fifth and sixth decades. In China, cough may present earlier, being more common between the third and fourth decades. In the aforementioned Canadian study, chronic cough was actually more common in men with an increase in incidence throughout the decades. Obesity appeared to be associated with more complaints of cough in that population.

Dr. Menon:
So, moving to assessing cough symptoms, I think it's really important to understand that, as Dr. Garrison mentioned, as prevalent as cough is, it's really important to understand how we're gonna quantify or really understand how severe cough is. We know that people with chronic cough have reduced quality of life. Quality of life is really reduced primarily because of a variety of different things. There's a significant impact on social interactions, for example, patients may not feel comfortable singing in their choir or in their chorus group, they may feel uncomfortable being in public while coughing and this leads to a significant sense of isolation and resultant depressive symptoms.

Additionally, things like stress incontinence and chronic chest pain that can be associated with chronic cough are also factors that really increase the risk of developing depression and anxiety. And these symptoms can be so bothersome that they're really the reason that they come patients come for evaluation.

We also know that adequate treatment of cough symptoms actually improves quality of life. So how a patient perceives their cough, their intensity, the disruptiveness, , is really key to understanding how we should be approaching treatment. This makes it really important to be able to assess the impact of cough on patients.

And so, I'm going to take some time to talk about some tools that are available to assess the actual impact of cough. I think we all know that these tools exist but may not be as familiar with them. Just in general, there are two broad categories of subjective assessments: those that focus on cough severity and those that are more widely addressed, things like cough and the effects of cough on general health status.

So, the most commonly used cough symptom focused tool is the Leicester Questionnaire. This is a validated tool with high internal consistency and repeatability of scores. It's very responsive to successful treatment of cough. So, what it is is it's basically a nineteen item questionnaire that addresses physical, social, and psychological domains. So, each, domain or each item will have a seven-point Likert scale, ranging from one, being all of the time to seven, none of the time, and it really reviews symptoms over two weeks. As an example, in the last two weeks, have you felt embarrassed by your coughing? In the last two weeks, have you felt frustrated, or have you gotten more hoarse? So it's basically the minimal clinically important difference in this scale between any time we evaluated a p- is, is about one and, one and a half to two points. So the LCQ, which is the way I'm gonna refer to the Leicester Cough Questionnaire from now on, the LCQ has been widely translated and validated for acute, sub-acute, and chronic cough and is actually a really good tool to use for comparative purposes, both clinically and in clinical trials.

Another tool that is available, it basically focuses on cough symptoms only and this is the visual analog scale. Because of its simplicity, like many of these visual scales it's probably the most used in clinics for immediate assessments. It's quite easy to use. It's basically a 0 to a 100 mm linear scale, and again, this has been tested, and higher scores indicate higher severity. So, when a patient comes in, you ask them to, kind of, mark on this scale how disturbing it is, their cough symptom is. and a minimally a minimal clinically important difference in this case would be about a 17 mm difference between. The biggest kind of issue with the visual analog scale is that there really is very limited data on reliability and validity of this. But, again, for ease of use, it's definitely one that can be used in clinic quite quickly.

So, there are again, a variety of other tools that we can use to assess cough, particularly related to quality of life. So, a couple that I'm going to talk about in specific, I think many of us know about the short form health survey in St. George's Respiratory questionnaire, but there is a cough-specific quality of life questionnaire that comprises twenty-eight items in six domains. So, it's about, takes about as long as doing the Leicester Cough Questionnaire, but it has a lot more to do with quality of life. So, it looks at physical complaints, extreme physical complaints, emotional well-being, personal safety, fears, and functional abilities. In this case each item is rated with a four-point Likert scale, with a maximum total of 112 points, with a difference in score about 22 points being clinically significant.

So, again, in addition to these, we've got the usual quality of life questionnaires, but I think that the cough severity diaries are also kind of the next best used tool. So, the cough severity diaries, for example, is a seven-item outcome measure with an 11- point Likert scale. And so, it's said to be as easily used as the visual acuity scale, but cough severity diary questionnaire is such, though it's short, there's really been tested and validated when used with a diary of daily symptoms. So, you know, I think, figuring out which is the right combination for your own clinical practice or which you feel makes the best sense for use in your clinic is the most important. But I do think it's of the utmost importance to really understand who to assess and document that, formally.

Dr. Garrison:
So, I'm gonna touch on the pathophysiology of chronic cough and I think this helps to understand where we might be going with current therapies and how current therapies might be working. It's an amazing complex process with a number of definite protein modulators. Speaking broadly, upper airway disease, lower airway disease, and esophageal dysfunction are most commonly thought of as inside pathologies. As you can see, there's a lot of potential for interplay between these. And these inputs interact with the nervous system to ultimately manifest as cough.

The cough reflex is initiated through stimulation of vagus nerve afference. As you will recall, the vagus nerve, also known as cranial nerve 10, arises from the medulla. The broncho-pulmonary branch of the vagus nerve arises in the inferior and superior vaso- vagal ganglia, also known as the nodose and jugular ganglia, which are located in the jugular foramen. Cough related to vagus nerve afference includes C fibers and cough receptors.

C fibers are unmyelinated fibers that exist in the airway and vascular walls, as well as the pulmonary interstitium. These fibers are sensitive to a number of chemical stimuli and the mechanisms of stimulation are areas of significant interest in the development of novel therapies. Note that these receptors do not respond to mechanical stimulation. Two important receptors for stimulation of cough are the transient receptor potential vanilloid 1 or TRPV1 and the transient receptor potential ankyrin 1 or TPRA1. Interestingly, these receptors are also important for nociperception with TPRV1 having a role in perception of heat and TPRA1 having a role in the perception of pain, itch, and cold.

Bradykinin appears to sensitize the airways to cough interactions with TPRV1 and TPRA1 signaling. Capsaicin and acid are also potent stimulators of TPRV1. As you know, capsaicin is responsible for the sensation of spice in food. Ozone and isothiocyanate are triggers for TPRA1 signaling. Isothiocyanate is responsible for the pungent taste of wasabi. Bradykinin pathway antagonism, as well as TPRV1 AND TPRA1 inhibitors, are potential targets for potential cough suppression therapy.

Another really important receptor for cough is the purinergic P2X3 receptor. P2X receptors are cation channels that respond to extra-cellular ATP. ATP-induced signaling can lead to pain, inflammation, and pertinent to us, cough. Stimulation of cough occurs via ATP activation of the P2X3 receptor. P2X3 inhibition as a cough suppressant may actually be available soon.

Cough receptors are myelinated fibers found in the extrapulmonary airways, including the larynx, trachea and bronchi. This are mechano-receptors and are not sensitive to chemical stimuli, aside from acid. Primarily, these result in cough from direct mechanical stimulation of the large airways.

Ultimately, the cough sensory input signals interact with the nucleus tractus solitarius while the stimulation of these afferents can lead to cough via reflex pathways.The cough reflex has the potential for significant central modulation. The central nervous system can play a minor role, can be inhibitory, or can even trigger a cough without stimulation. Indeed, most people perceive an urge to cough when stimulation occurs, proving, some opportunity to suppress a cough voluntarily. This central modulation presents an avenue for therapy using speech pathology interventions. Speech pathology interventions, definitely can help patients with chronic cough. It's worth noting that patients with chronic refractory cough often present with other laryngeal complaints, including vocal cord dysfunction, and muscle tension dysphonia, which may also benefit from the expertise of a speech pathologist. A speech pathology intervention for chronic cough consists of at least four components: education, psychologic support, cough suppression strategies, and reduction of irritants. During these sessions, patients are educated about their condition and pathophysiology, provided information on importance of adherence, and identifying emotional barriers. There are taught laryngeal re-posturing techniques and other ways to deflect cough sensation. They're instructed on ways to avoid irritants like alcohol and reflux and to reduce certain phono-traumatic behaviors.

Although typically small, multiple studies have shown that speech pathology interventions can lead to statistically significant improvements in quality of life for patients with chronic cough and they also improve cough severity, cough frequency, and urge to cough sensation. Speech pathology evaluation should be considered for patients with chronic cough, particularly those with refractory symptoms despite medical therapy. There's certainly room for studying the timing, patient selection, and therapy dosings in the future.

Dr. Menon:
So, I'd like to go from there and talk a little bit about cough hypersensitivity syndrome. It's been hypothesized that some, if not potentially all, cases of chronic refractory cough may belong to a specific phenotype, namely the hypersensitivity of the cough reflux. The term 'cough hypersensitivity syndrome' or 'CHS' relates to the specific entity characterized by an enhanced cough reflux. The concept of cough hypersensitivity really helps explain how cough can continue even when an irritant exposure is decreased. It also helps to explain how chronic cough could arise from a variety of different processes, and it's hypothesized that neuropathic mechanisms involving transient receptor potential nociceptors, similar to the ones that Dr. Garrison was talking about earlier in the pathophysiology are not similar, but those are actually considered to play in important role and are probably central in the determination of cough hypersensitivity syndrome. Understanding and addressing this hypersensitivity may help to reduce chronic cough, particularly in patients in whom the

underlying disorder has been treated, but there remains a significant cough.

So, there's been a variety of different therapies that I'll discuss in a minute, that have been looked at for cough hypersensitivity syndrome. Historically there were two tests to assess cough sensitivity. Both of these tests were essentially single breath inhalations of either capsaicin or citric acid. So when we're looking at cough hypersensitivity syndrome, specifically, research surrounding that, these are usually the tests that are used for that. The capsaicin challenge is one in which there's an inhalation of a capsaicin aerosol in doubling concentrations using single breath methods with, kind of, a compressed air-driven nebulizer and it's very controlled breath-activated nebulizer. So, cough is essentially counted for ten seconds after each dose inhalation. This is very similar for citric acid inhalation tests, except, obviously, the dosages would vary. What we look at is what is the lowest concentration that causes two coughs, and five coughs and we kind of compare and look to see whether that would be a positive test or not.

Now, the issue with these tests, although they're I think really interesting and have been very helpful in, kind of, getting some understanding about this hypersensitivity syndrome, the issue is they really have not been shown to be specific or useful from a diagnostic perspective on an individual level. So again, we're trying to do studies and group people it might be useful, but more often than not, we may get negative tests in people who still have that. So, it's really important, more from a historical standpoint and to consider these neuropathic mechanisms as a potential for treatment for cough hypersensitivity even, again, when usual causes for cough, COPD, asthma and reflux seem to be under good control.

I'm going to just talk briefly about a couple of studies that have been looked at related to this cough hypersensitivity syndrome. Opiates have long been considered for therapy of suppression in cough, but there have really been very few trial data to support these recommendations. In 2007, Alyn Morice and his colleagues actually conducted a small perspective trial looking at twenty-seven patients, which unfortunately many of our trials that we look at with cough patients are actually quite small, but twenty-seven patients with chronic cough that were randomized to low-dose morphine versus placebo. And there was a significant improvement in the Leicester Cough Questionnaire between the two groups of about 3.2 points, and if you remember before, 1.5 to 2 points is considered clinically significant, and a reduction by 40% overall in cough scores. At the end of that study, a dose increase crossover was available, and what they found was that there's no difference between people who responded to 5 mg - they didn't necessarily respond better to 10 mg but interestingly, non-responders, initial non-responders actually did respond to the higher dose of morphine. Also what's I think is interesting is between these groups, there was actually no difference between the citric acid challenge between both responders and non-responders.

Another kind of drug given the hypothesis of increased sensitivity, and, in an effort to really reduce that central sensitization,, we've tried looking at the neuromodulator gabapentin. In this study by Nicole Ryan and colleagues, there's sixty-two subjects who were randomly assigned to gabapentin versus placebo. Gabapentin significantly improved cough -specific quality of life in 74% of subjects compared to placebo. There were about 31% of subjects on the gabapentin arm that had significant side effects, specifically nausea and fatigue so choosing the patient population is important.

And then lastly, I'll just briefly talk about another neuromodulator which was used with cough because of its relatively low side effect profile, which is amitriptyline. It's been considered for treatment of chronic cough, essentially this study looked at it in post-viral patients, thinking about a post-viral vagal neuropathy. So, in this study, twenty-eight patients were randomized to amitriptyline versus codeine and guaifenesin combination at a dose of 10 mg of amitriptyline per day. A majority of the patients in the amitriptyline, actually twelve out of fifteen, achieved a complete response, on the 10 mg compared to no patients who achieved a complete response on the codeine/guaifenesin group. Obviously, this is a pretty small trial and only two arms with no placebo, so, not really sure what we can make of that, but we'll talk about that later, as we get into our overall guidelines.

Dr. Garrison:
So, I'd like to now take a few minutes to talk about how chronic cough starts. Ultimately, whatever pathology leads to cough may develop into a chronic cough hypersensitivity syndrome. An inciting disease process can most often be identified in chronic cough, as much as 95% of the time. I'd like to take some time now to discuss a few of these classic cough phenotypes. These are important considerations when approaching a patient with chronic cough. Classically, the most commonly described cough phenotypes are asthma, non-asthmatic eosinophilic bronchitis, gastroesophageal reflux, and upper airway cough syndrome. Other syndromes include iatrogenic and somatic cough syndromes relative to the structural lung disease can present as chronic cough syndrome -be sure that your evaluation screens for these conditions.

Asthma is the most likely etiology to be diagnosed as an inciting event during thorough evaluation of chronic cough. This may be seen with or without typically allergic symptoms. Both traditional flow variable asthma and cough varying asthma may be seen. Classically, these patients identify triggers for cough that may include allergens or irritants like temperature change. Diagnostic options to identify asthma include bronchodilator testing, bronchoprovocation testing, and possible allergy evaluation. Identifying eosinophilic inflammation

in this setting may help to guide therapy.

Non-asthmatic eosinophilic bronchitis is another common diagnosis identified during the evaluation for chronic cough. Similar to asthma, patients may describe irritants leading to cough, but spirometric testing and bronchoprovocation testing should be normal. Clues to this diagnosis may include elevated exhaled nitric oxide testing or presence of pseudo-eosinophils, if you have the capacity to send those. On occasion, bronchoscopy and bronchial wash may reveal the presence of eosinophils, allowing the diagnosis to be made.

Both asthma and non-asthmatic eosinophilic bronchitis are best treated with inhaled corticosteroids. Indeed, the high incidence of these two conditions during cough evaluation may justify empiric therapy, if there are no clues based on history or physical exam for an alternate diagnosis. In 2004, Chaudhuri and colleagues showed that a trial of fluticasone was associated with a significant benefit in reducing cough severity. This involved a trial of one hundred and twenty patients randomized to fluticasone for fourteen days versus placebo. Exhaled nitric oxide, pseudo-eosinophils and total IgE were predictors of successful trials in this study. The role of inhaled corticosteroids in non-eosinophilic disease is questionable currently.

Now, gastroesophageal reflux is also commonly cited as a cause of chronic cough. The role of GERD in the in chronic cough is actually a bit controversial. In reflux, clearly acid can contribute to cough via multiple mechanisms, however non-acid reflux may be equally as important. Reflux, does not need to even reach the larynx to stimulate cough as stimulation of the upper esophagus may lead to vagus stimulation leading to cough. There is some thought that esophageal-laryngeal reflux in patients with esophageal dysfunction may also cause chronic cough in addition to gastroesophageal reflux. However, in patients with chronic cough due to reflux, reflux symptoms really should be noted. Empiric therapy for acid reflux, absent reflux symptoms is not likely to be successful. Aside from a thorough history, an esophagram may help to identify esophageal dysfunction and ambulatory pH probe testing may help to clarify the role of acid-related reflux treatment.

This recommendation is backed up by several studies, including one by Faruqi in 2011 where fifty adults with chronic cough were randomized to empiric therapy with esomeprazole versus placebo. In the primary outcome of cough severity, there was no change in cough scores eight weeks. In those with dyspepsia, there was a trend towards improvement but it wasn't statistically significant. Also, in 2011, Shaheen and colleagues randomized forty patients without reflux symptoms using high dose esomeprazole at 40 mg twice daily. Again, no observable benefit was noted on the cough questionnaires.

Another commonly cited cause of chronic cough is upper airway cough syndrome. This is defined as persistent rhinosinusitis in conjunction with chronic cough. Note that the classic sensation of post-nasal drip is not required for diagnosis of this condition. However, it's not really clear that there's a mechanism for which this can cause chronic cough. Perhaps, there's mechanical stimulation by a thick mucus. Clearly throat clearing occurs, but in terms of ongoing chronic cough, there's not a clear signal that would be anticipated to trigger the cough reflex on an ongoing basis. The unified airway hypothesis suggests that the upper airway disease may be mirroring conditions in the lower airway, and therefore cough and rhinosinusitis may be occurring concurrently rather than by causation.

Remember that medications too most classically ACE inhibitors can cause chronic cough. Chronic cough is noted in up to 15% of patients taking an ACE inhibitor. This is thought to be due to accumulation of bradykinin. Drug withdrawal is typically the only effective therapy. During an evaluation, be sure to screen for ACE inhibitor use. Other medications may cause cough through unclear or perhaps idiosyncratic mechanisms. Attention to any recent changes in medications prior to onset of cough is definitely warranted.

Psychogenic cough and habitual cough have been re-termed somatic cough and tic cough. Somatic cough should only be diagnosed following a thorough evaluation of alternate causes and a failure of multiple treatment courses. And somatic cough diagnoses should meet the DSM criteria for somatic disorders.

Post-infectious cough can be seen as a sub-acute or sometimes a chronic cough. This is classically due to pertussis but other infections can certainly initiate this disorder, including influenza and mycoplasma. This usually occurs in the absence of eosinophilic inflammation and often resolves with time, or corticosteroids can useful to reduce the cough severity.

Dr. Menon:
Alright, just as we move next, I'm sorry, the title says "*Morphine and Chronic Cough*" but what we're going to be talking aboutis actually, kind of, how to take all of that information that we just talked about -- how bad cough is, how can we assess it, and the variety of different treatments and data that's available and look at our guidelines, put them together and try to think about how it might actually change our practice. So, what I'm going to look at is our CHEST guidelines as well as ERS guidelines. And so, fortunately, there's a, quite a bit of overlap, so as I go through this, I won't necessarily go through everything twice. But, I would like to just go through what the guidelines look like. So, with our CHEST most recent guidelines from 2018, I'm going to go through this entire schema, but just an idea of how we should be looking at things. So, you know, if there's a chronic cough, the first thing, obviously to do is to take a history, and then really thinking about which direction we need to go to. And there's clearly at the bottom of this, a very nice area that shows some red flags.

And so, identifying those red flags early in the history is going to be very important.

So, basic things which would be, you know, initial evaluation, get a thorough history and physical, see if there is anything that you can clearly identify as a potential source of the cough. Usually a chest x-ray is in that initial evaluation especially through CHEST, and ideally identifying those red flags. So, what are the red flags? And basically, red flags are anything that might identify a much more, kind of life-limiting or life-threatening process that's going on that needs more urgent workup. So, things like hemoptysis, risk factors for cancer or, kind of, things that trigger your thought for cancer. Nocturnal dyspnea associated with cough, worsening hoarseness with cough, especially if that's kind of the first symptom, is hoarseness over cough. Things like systemic symptoms that might make you think of underlying malignancies or infections, and kind of, the list goes on from there. And again, one of the things to remember is anything that might, in an abnormal X-ray for example tell us about underlying known lung diseases like interstitial lung disease that might cause cough that are not necessarily part of what we are talking about today.

So the first step would be initial management, which is, as Dr. Garrison mentioned, really looking through basic things that could cause cough in stopping those offending medications. In the CHEST guidelines, stop the medications and then re-evaluate in four to six weeks. If there is some clear symptom, say you know, reflux that's very symptomatic and you treat them and re-evaluate in four to six weeks. Again, thinking about this more common causes of cough that Dr. Garrison mentioned, doing specific evaluation for the upper airway cough syndrome thinking about sinus imaging, asthma, thinking about doing formal broncho-provocation studies, allergy testing, if needed, etc. And then once you've decided kind of what those things might be, considering initiating that therapy right away, and then again doing about a four-to-six-week trial. This is looking at starting things like antihistamines and decongestants for asthma, then inhaled corticosteroids as Dr. Garrison mentioned for asthma and, allergic eosinophilic disease, and then treatment for reflux. And then thinking, if these diseases still exist and there's refractory cases, kind of, before you move towards that chronic hypersensitivity syndrome of cough, really thinking about is there more that needs to be done? So, if you treat GERD but they still have GERD symptoms, thinking about things like being much more aggressive with the testing, twenty-four hour testing, a swallow function, if you have sinus disease and you've treated them but they still have SMS, really thinking if there are other things that need to happen, surgical interventions, and such as that. So, really thinking is the underlying diagnosis well-controlled.

The only other thing that I would just mention is that it's not in the 2018 guidelines but have been in previous CHEST guidelines and remain something that we should talk about is, what if you have unexplained chronic cough? So, you've treated all of the SMS seem to be improved from the asthma, from the reflux, from any of those things that I talked about, then it's really considering other reasons. So, consider referral, again, similar to what Dr. Garrison mentioned for multi-modality speech therapy, considering therapeutic trials for gabapentin or low-dose morphine. And then remembering two things that I just wanted to reiterate that Dr. Garrison talked about, which is really avoid just using inhaled corticosteroids for cough unless there's real evidence of bronchial hyperresponsiveness or eosinophilia or something that makes you think that they might respond. And the same would go with avoid trials of acid suppression unless there's active symptoms of reflux.

So, getting through to the ERS guidelines, just making sure I'm OK on time. So, I think again, there's a lot of overlap so I won't go specifically into too much detail, about all of these things, but I think it's important to recognize that you know a couple of things that are pointed out in the ERS guidelines are in addition to the history and physical exam but really doing an assessment of cough scoring, so that we have some documentation and understanding of response to therapy. And then again, most of the therapies that we're talking about are, are essentially the same. I will say that in the ERS guidelines, there is more conversation about a longer trial on all of the therapies. So, rather than six weeks, maybe, you know, eight to twelve weeks. And again, initial evaluation, thorough history and physical, doing some form of cough assessment, identifying other risk factors and then very similar to what the CHEST guidelines say, additional evaluation as needed. Again, I won't go into all of this, but you can see that very similar, thank goodness, somewhat overlapping trials with the big, or recommendations with the big difference being three month, therapies considered before we consider a failure of therapy or something of that sort. And then at least three months before we also attempt tapering medications.

So, in the ERS guidelines, they have some very specific questions that I think many of us often think of, and I'll just review some of them which are you know, should a chest CT be routinely performed on chronic cough patients with normal chest radiograph and physical examination? And the recommendation is that a CT chest is not recommended for initial evaluation of chronic cough and especially even if during the evaluation, even if chest X-ray and physical exam are normal. Obviously depending on what we find with lung function testing and other things, we can then move forward with a CT scan, if needed.

And then should pheno or blood eosinophils be used to predict treatment response to corticosteroids or antileukotrienes in chronic cough and, you know, unfortunately there's no real evidence that this is going to guide clinical management, and so no recommendation for following that specifically.

Next, should antiasthmatic drugs be used to treat patients with chronic cough? Interestingly, there is a suggestion in the ERS guidelines

that a short two to four week trial of ICS would be suggested, and a short trial of leukotriene modifier might be suggested as well as, a combination inhaled corticosteroid and long-acting bronchodilator could be considered but it would be a short period to see if there's any improvement in cough.

Should drugs with promotility activity such as reflux inhibitors, and macrolides be used to help treat patients with chronic cough? And their recommendations are there's really no evidence for use for either of those without symptoms, but you could, consider one month trial of macrolide therapy was recommended based on some data in patients who have a diagnosis of chronic bronchitis and subsequent cough.

And then which neuromodulatory agents would be used? Here, again, thinking about pregabalin, gabapentin, tricyclics, and opiates. Their recommendation was a trial of morphine, the low to medium dosing, would be suggested for refractory cough. A trial of one of the neuromodulators could also be suggested. And, you know, one of the things that have been talked about in the CHEST data about amitriptyline is that potentially when we're thinking about other drugs, potential considering what other associated comorbidities there are. So, for example patients who have had chronic cough for a long time and might have significant depression or fatigue and really making sure that you're using amitriptyline or gabapentin accordingly.

Then the last question that I'll just discuss here will be, you know, should non-pharmacologic therapy or cough control therapy be used to treat patients with chronic cough? And again, for refractory cough, where there is no clear etiology and/or everything has been treated - other than cough there's really no other symptom left of the underlying disease, a trial of cough control therapy with speech pathology is certainly suggested based on the ERS guidelines.

Dr. Garrison:
OK. A whirlwind tour through a lot of guidelines. So we've talked so far about the current evidence, emerging trends in those guidelines in the management evaluation of chronic cough. Now I'd like to look towards the future, to talk about additional medical therapies that may be available. This is a graphic highlighting some of the potential therapies under development. You can see that there are multiple P2X3 antagonists that are being evaluated by several other companies. Given the prevalence of chronic cough and the impact on quality of life, this is certainly an area of significant investigation.

To focus for a minute on the P2X3 inhibitors, Gefapixant has been the most rigorously studied to date. You may have heard of this drug, which is currently under review at the FDA with application received in March and decision on approval due somewhere around December 2021. Gefapixant has been studied in two completed phase 3 trials that were called COUGH-1 and COUGH-2. Prior to these trials, phase 2 studies showed significant reduced, significantly reduced cough at a 600 mg dose, but essentially, all patients experienced loss of taste. At lower doses, this side effect was improved, the tradeoff was lower efficacy of cough suppression. COUGH-1 and COUGH-2 looked at 15 mg and 45 mg doses. These studies included 1,907 patients with chronic cough. In COUGH-1, subjects were treated for twelve weeks and twenty-four weeks in COUGH-2. There was a notable placebo response, but Gefapixant at 45 mg was associated with improvement in cough severity. However, over 50% of patients experienced taste-related side effects, at that dose. There are other P2X3 antagonists under development. Gefapixant does cross-antagonize P2X2 and it is proposed that more specific P2X3 inhibition will lead to cough improvement without alterations in taste.

One interesting small study published in 2011 described the utility of capsaicin desensitization. This involved taking twenty-four patients with unexplained chronic cough and fifteen controls, randomizing them to oral capsaicin for four weeks, versus placebo, and the primary outcome of improvement in capsaicin cough sensitivity, there was a significant decrease in both the chronic cough and healthy controls in terms of their cough sensitivity. So, just, sort of, interesting and remember that the capsaicin receptor is one of the main triggers for chronic cough.

There are a whole host of other targets under development. Remember the mechanisms for cough are very complicated, and there's a lot of different inputs. So, gamma receptor antagonists are being evaluated, as are sodium channel blockade, sodium cromoglicate, TRPA1 inhibition, TRPV1 inhibition, TRPM8 antagonism. These are all in various stages of development with primarily pre-clinical and very, very limited clinical data supporting their use. But we may see clinical trials involving these compounds in the future.

So, just to bring us back around, I'd like to leave you with these thoughts. Chronic cough is common and impairs quality of life. The development of chronic cough is complex and may result from several different insults leading to a syndrome of hypersensitivity. Most cases can ultimately be attributed to an underlying diagnosis. Asthma and non-asthmatic eosinophilic bronchitis, reflux, and upper airway cough syndrome are the most common diagnoses identified during evaluation with asthma and non-asthmatic eosinophilic bronchitis being the most common. For patients with chronic refractory cough, treatment with speech pathology interventions and neuromodulatory therapies can be considered. Novel therapies for cough are under development. Remember we have multiple high-quality guidelines from CHEST and ERS that can be used to help you develop an evaluation and management plan for your patients.

Announcer:
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