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Breaking the Code: Mechanisms and Future Therapies for Refractory Chronic Cough

Announcer:
You're listening to CME on ReachMD, and this is *Deep Breaths: Updates from CHEST*. This activity, titled "Breaking the Code: Mechanisms and Future Therapies for Refractory Chronic Cough" is provided by The American College of Chest Physicians and is supported in whole through an unrestricted educational grant from GSK.

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And now, here's your host, Dr. Eric Merrell.

Dr. Merrell:
Hello and welcome to CME on ReachMD. This is "Deep Breaths: Updates from *CHEST*". I'm Dr. Eric Merrell, Pulmonary Critical Care Fellow at the University of Rochester. Today's episode is the second in a series about refractory chronic cough, or RCC, where we'll be focusing on mechanisms and future therapies. If you haven't yet listened to the first episode in this series titled "Diagnostic Challenges in Refractory Chronic Cough, from Burden to Solutions," we invite you to check it out on ReachMD.com/CME.

Joining me today to explore why cough persists despite appropriate evaluation, the neurobiology of cough hypersensitivity, and what emerging mechanism-based therapies may mean for patient care are Dr. Todd Schneider and Dr. Shahzad Mustafa. Dr. Schneider is an Associate Professor of Laryngology at the University of Rochester. Dr. Schneider, it's great to have you here today.

Dr. Schneider:
Thanks for having me.

Dr. Merrell:
Also joining us is Dr. Mustafa, who is Division Head of Allergy, Immunology & Rheumatology at Rochester Regional Health, and Clinical Associate Professor of Medicine at the University of Rochester School of Medicine & Dentistry. Dr. Mustafa, thanks for joining us as well.

Dr. Mustafa:
Thanks so much for having me. I look forward to the discussion.

Dr. Merrell:
So I'll start us off today by talking about what cough hypersensitivity syndrome is and the symptoms that should raise a red flag for clinicians. Cough hypersensitivity syndrome is characterized by an overresponsive cough reflex, in which stimuli that would not normally provoke cough trigger exaggerated responses. Clinically, patients often report persistent throat irritation and a strong urge to cough that feels automatic and difficult to suppress. A thorough history is very important here. Consistent trigger patterns, such as talking, laughing, odors, perfumes, cold air, and eating are indicative of a cough hypersensitivity phenotype rather than a self-limited post-infectious cough. Persistence beyond this eight weeks should raise a red flag and necessitate structured evaluation under a *CHEST* guideline-directed pathway.

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Turning to you now, Dr. Mustafa, what else should we keep in mind when it comes to cough hypersensitivity syndrome?

Dr. Mustafa:
Patients may have a normal chest examination and unremarkable imaging and still experience substantial cough burden, consistent with a hypersensitive cough network rather than structural lung disease. Upper airway laryngeal sensitivity can contribute to symptom generation and amplification, particularly when cough is triggered by talking, voice use or throat sensations.

Dr. Schneider, I'd love to get your perspective on counseling and management goals here.

Dr. Schneider:
Sure. So I've always like to tell the patients that this is one of the more common things that I see in my laryngology practice and that their symptoms are, or patterns are very common and that they're not making it up—because, usually, by the time they get to me, they're usually pretty frustrated with all the normal testing, but their symptoms are persisting. And so we really try to focus on a lot of the sort of quality of life aspects of the cough, you know including sleep, how the cough might be affecting their sleep, how their mental health and how—what ways this cough is affecting them outside of just the, physical aspects of the cough. And that's when I start talking about how we treat this with different modalities, one of them being sort of behavioral modification with our speech-language pathologists, in addition to some of the medications or injections to try to help lessen this cough sensitivity.

Dr. Merrell:
Thank you both for those great insights. Cough can be initiated through peripheral pathways. The irritant pathway is activated by external stimuli, such as cold air, aerosols and strong odors. This triggers cough via sensory nerve activation.

The pathologic pathway involves signals generated within the airway itself, particularly ATP, which activates sensory nerves through P2X3 and P2X2/3 receptors, amplifying cough sensitivity so that low-level stimuli provoke a strong urge to cough. Signals from both pathways converge at the brainstem cough center explaining why diverse triggers can produce a similar hypersensitive cough phenotype. After the workup is complete and we understand the mechanism, what do clinicians actually have available right now? in the United States, there are currently no FDA-approved therapies specifically indicated for refractory chronic cough. Surveying real-world data indicate frequent use of benzonatate and non-opioid antitussives with off-label neuromodulators used in selected patients and carefully monitored opioid therapy considered only in limited circumstances.

These approaches are largely symptom-focused rather than mechanism-based, which may help explain inconsistent clinical responses.

With all that being said, Dr. Schneider, could you tell us a bit about behavioral cough suppression therapy?

Dr. Schneider:
Absolutely. So there are the behavioral changes that we talked about earlier, and one of the main ones that we use is the behavioral cough suppression therapy, which is done by the speech-language pathologists, and there's good data that this is helpful for controlling these refractory chronic coughs. And it's both a combination of breathing strategies and along with the behavioral aspects of the cough, vocal hygiene, and counseling from a psychoeducational perspective to help folks suppress some of this hypersensitivity that they're feeling that's creating the cough. And it tends to be used by clinicians as a, a last resort, but we at the Voice Center, because we work directly with the speech-language pathologist, try to integrate it with our pharmacological therapy to use as an adjunct rather than a last resort or when everything else fails.

Dr. Mustafa:
And to add on to that, a key challenge in practice is the absence of standardized sequencing strategies once cough becomes refractory. A more effective approach is to define clear treatment goals, typically focused on sleep, daily function and quality of life. Select an intervention intentionally, and reassess using structured follow-up. Lack of meaningful improvement should prompt adjustment of therapy, escalation of care, or multidisciplinary referral, rather than repeated empiric switching.

Announcer:
For those just tuning in, you're listening to CME on ReachMD, and this is *Deep Breaths: Updates from CHEST.* We are speaking with Drs. Eric Merrell, Glenn Schneider and Shahzad Mustafa about the biology of refractory chronic cough and future therapeutic avenues.

Dr. Merrell:
Thank you. Now that we've covered cough hypersensitivity and the current gaps in care, let's talk about the emerging treatment pipeline and how we should counsel patients on investigational options.

The emerging RCC pipeline is increasingly mechanism-based, spanning both peripheral targets, such as P2X3 antagonism and voltage-gated sodium channel blockade, and central mechanisms, again reflecting the heterogeneity and cough hypersensitivity.

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P2X3 antagonism remains the most advanced approach. Gefapixant, a P2X3 antagonist, has been approved in Japan, Switzerland and the European Union for adults with refractory and unexplained chronic cough. However, it's not FDA approved in the United States. Next-generation P2X3 antagonists, such as camlipixant, remain investigational but are in phase 3 development.

In recent clinical trials, gefapixant improved cough-related quality of life and cough frequency versus placebo in phase 3b COUGH I and II trials. Both trials reported taste-related adverse events, such as a metallic taste, decreased taste and loss of taste in a majority of their patients, so this is a key tolerability consideration for this drug. Camlipixant, a more selective P2X3 antagonist, demonstrated placebo-adjusted reductions and objective 24-hour cough frequency by day 28 in the phase 2b trial SOOTHE, with taste adverse events only in a minority of these patients, I believe only up to 6.5%.

The pipeline is not P2X3 only. Investigational centrally acting agents, such as nalbuphine, a kappa opioid receptor agonist, and other non-P2X3 targets, such as NK(1) and NMDA, are understudied, underscoring the need for individualized interpretation of emerging data.

Coming back to you now, Dr. Schneider, what are some best practices for discussing these therapies with patients?

Dr. Schneider:
That's a great question. All the time when we're talking about these medications, it's always a balance between effect and side effect, and so it's just important that when we have access to some of these newer cough drugs, that we discuss the taste disturbance and balance the effect versus side effect, but then also make sure that we're also doing our behavioral strategies and still trying to combine that with the medications so that we can get some kind of a holistic treatment approach.

So, Dr. Mustafa, do you have any thoughts?

Dr. Mustafa:
I do. Shared decision-making should define success using patient-centered outcomes, such as sleep, function, ability to speak and participate socially, and explicitly discuss trade-offs, symptom improvement versus side effects such as taste effects, rather than implying a cure.

Dr. Merrell:
Now to contextualize this further in practice, what is one referral trigger from your specialty that should prompt timely multidisciplinary coordination in suspected RCC? Dr. Mustafa, let's start with you.

Dr. Mustafa:
Chronic cough lasts over eight weeks with repeated empiric treatments and persistent impact on quality of life. Initiate early specialist referral with clear documentation to avoid repeated empiric therapies and diagnostic testing.

Dr. Merrell:
Yeah, I agree. For me, it's persistent cough greater than eight weeks after a *CHEST* guideline-directed workup and empiric therapy of identified underlying conditions, be it asthma or nonasthmatic eosinophilic bronchitis, or GERD, or upper airway cough syndrome, with ongoing functional impairment, of course.

Dr. Schneider, how about you?

Dr. Schneider:
Well, a lot of the cough that I see is triggered by talking or with comorbid throat clearing, other upper airway symptoms, so that's why they end up in the laryngology clinic, and I like it that the patients show up having had some workup of the lower airways, just so we're not suppressing a cough that might cause other issues, like pneumonia, or that we're trying to suppress an asthmatic cough that could be treated with medications otherwise.

Dr. Merrell:
Thank you. As we start to wrap up, let's come back to how this translates into patient counseling. Dr. Mustafa, when you're talking with patients about current and emerging options for RCC, how do you keep conversation patient-centered and grounded in shared decision-making?

Dr. Mustafa:
Counseling should begin with patient priorities. Discrete choice data show patients tend to value reducing intense cough attacks most, with nighttime symptoms being ranked more important than daytime symptoms. Taste disturbance is important but not uniformly prohibitive to therapies. Validated patient-reported outcomes in questionnaires provide a structured way to capture baseline burden, monitor response and guide decisions about adjusting/escalating therapies over time or referral over time.

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Healthcare disparities must be addressed explicitly. Geography, access to specialists, insurance coverage and socioeconomic constraints can limit completion of evaluation and treatment. Proactively identifying these barriers and aligning plans to what is feasible improves follow-through and outcomes.

Dr. Merrell:
Yes, I totally agree. I'll add that patient preference data are particularly relevant when discussing investigational therapies where risk-benefit profiles vary by mechanism and individual tolerance.

Dr. Schneider, care to give us your final thoughts?

Dr. Schneider:
Happy to. I think positioning care as iterative and collaborative rather than just a single definitive decision helps manage the patient expectations and improves engagement when you're treating something difficult like this, and so integrating nonpharmacologic strategies like the cough suppression with the speech-language pathologist along with these pharmacologic options really reinforces that management targets the cough network, not just the symptoms, supporting adherence and sustained benefit.

Dr. Merrell:
Well, with those key takeaways in mind, I want to thank my guests, Dr. Todd Schneider and Dr. Shahzad Mustafa, for joining me to discuss the mechanisms of refractory chronic cough and what management looks like moving forward. Dr. Schneider, Dr. Mustafa, thank you both for being here today.

Dr. Schneider:
Thank you.

Dr. Mustafa:
Thanks so much for having me.

Dr. Merrell:
I'm Dr. Eric Merrell, and I thank you all for joining us on "Deep Breaths: Updates from *CHEST*." We hope these insights help bring greater clarity, confidence, and patient-centered focus to the care of people living with refractory chronic cough.

Announcer:
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