An Alternative Approach to the Chronic Refractory Cough?

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Therapeutic Options Beyond Our Pages highlights randomized controlled trials published in other journals of novel therapeutic options for the conditions treated by allergist-immunologists. Generally written by Editorial Board members with relevant expertise, this feature summarizes the methods and results of the study and then provides the author's perspective regarding the practical use of the information at this time.

The practicing allergist is often called upon to evaluate unexplained chronic cough in patients without obvious underlying cardiopulmonary disease. Clinicians who use a rational and evidence-based approach first consider the most common causes of chronic cough: upper airways disorders and postnasal drip (eg, allergic and nonallergic rhinitis), which are the single most common source of chronic cough; cough variant asthma; nonasthmatic eosinophilic bronchitis; and gastroesophageal reflux.[1,2] In most cases, a specific cause(s) can be identified that will lead to interventions to mitigate or eradicate chronic cough. It should be emphasized that multiple sources of cough can be identified in a single patient and may require multiple treatment interventions. A comprehensive evaluation of possible sources of chronic cough requires both objective diagnostic testing (eg, methacholine challenge testing to detect cough variant asthma) and/or empiric therapeutic trials of medications targeted at specific sources of cough, such as a proton pump inhibitor for gastroesophageal reflux disease or an oral antihistamine and/or decongestant for rhinitis and postnasal drip.

In recent years, nonasthmatic eosinophilic bronchitis has been added to the differential diagnosis and may explain 10% of patients with chronic cough. Nonasthmatic eosinophilic bronchitis is defined by sputum hypereosinophilia, the absence of airway hyperresponsiveness to methacholine, and a favorable response to inhaled corticosteroids,[3] Most clinicians do not have access to laboratories with the capacity to measure induced sputum eosinophils. In such cases, fractional exhaled nitric oxide may be considered as an alternative or surrogate biomarker that correlates with sputum eosinophilia and is predictive of a favorable clinical response to inhaled corticosteroids.[4]

Despite considerable advances in understanding and managing cough syndromes, some patients present with refractory cough that defies classification and is unresponsive to the aforementioned treatment interventions. A novel clinical trial that investigated gabapentin for patients with refractory chronic cough was recently reported by Ryan et al[5] in *The Lancet.* These investigators hypothesized that gabapentin could be effective because it is a structural analogue of γ aminobutyric acid, a neurotransmitter in the cerebral cortex, and could inhibit the release of excitatory neurotransmitters, eg, substance P, a peptide that stimulates cough. In this double-blind placebo controlled study, these investigators recruited 62 patients with refractory cough for more than 8 weeks.[5] To qualify, infection or active respiratory disease had been excluded. Only patients who failed prior treatments for rhinitis (ie, H1 antihistamines, nasal steroids), asthma, or eosinophilic bronchitis (ie, inhaled or oral corticosteroids), and gastroesophageal reflux disease (ie, proton pump inhibitors) were included. Demographics of the study population reflected previous reports of such patients, with a mean age of approximately 61 years old, more than 60% women, and most had been coughing for longer than 3 years. Qualified participants were randomly assigned to receive gabapentin (n = 32) or placebo (n = 30) for 10 weeks. Multiple efficacy outcomes were assessed, including a score from a cough quality of life questionnaire, which served as the primary outcome measure. During the first week of treatment, the dose of gabapentin or matching placebo was escalated to a maximal dose of 1800 mg or to a lower maximal tolerable daily dose. Compared with placebo, gabapentin treatment resulted in significant improvement in cough quality of life questionnaire and reduction in cough frequency and cough severity. Improvement in cough outcomes in the subjects treated with gabapentin relative to placebo, however, was not sustained after termination of the active treatment phase. Significantly, 31% of patients treated with gabapentin versus 10% in the placebo group reported adverse effects. Disorientation, confusion, dizziness,

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dry or wet mouth, and fatigue were most frequently reported, which required dose reduction in 6 patients treated with gabapentin (19%) and 3 patients with placebo (10%), and drug withdrawal in 2 patients (1 active and 1 placebo).

In addition, these investigators attempted to define the mechanism of action of gabapentin in treating refractory chronic cough. They postulated that gabapentin could either inhibit central reflex sensitization by modifying release of excitatory neurotransmitters in the central nervous system or by direct inhibition of the peripheral cough reflex. "Central reflex sensitization" was defined by patient-reported cough symptoms associated with laryngeal sensations of throat irritation, tickle, tightness, the presence of mucous, and something sticking in the throat and/or cough triggered by nontussive stimuli, including abnormal sensations in the throat, talking, laughing, eating, and drinking. Capsaicin challenge testing was used to identify subjects with "peripheral cough reflex sensitivity," which was proposed to mediate cough via capsaicin-triggered stimulation of a variety of airway chemoreceptors (eg, transient receptor potential vanilloid type 1 [TRPV1] receptors). Capsaicin challenge testing was conducted before and after 8 weeks of double-blind treatment and was performed by measuring the capsaicin inhalation dose required to elicit repetitive cough. The subjects were challenged with successive inhaled doubling capsaicin doses between 0.98 and 500 μM. Peripheral cough reflex hypersensitivity was identified in those subjects who coughed (ie, experienced 5 successive coughs) after challenge with <134.8 μM/L of capsaicin. No significant improvement in capsaicin sensitivity was observed after 8 weeks of gabapentin versus placebo treatment. However, patients treated with gabapentin and with central reflex sensitization appeared to have significantly more improvement in the mean cough quality of life questionnaire score versus patients treated without central sensitization.

If confirmed and replicated in larger studies, gabapentin may be considered as an alternative treatment for chronic cough.

This is the first randomized controlled study that evaluated gabapentin in treating refractory chronic cough. Based on a favorable response to gabapentin, it is reasonable to speculate that unexplained chronic refractory cough may originate from cough centers in the brain and, therefore, be particularly responsive to drugs that inhibit central nervous system receptors or neurotransmitters. Despite the interesting findings in this study, the precise mode of action of gabapentin in the treatment of chronic refractory cough remains uncertain. If confirmed and replicated in larger studies, gabapentin may be considered as an alternative treatment for chronic cough. Patients who have been treated should be closely observed for commonly reported adverse effects of dizziness, headache, somnolence, ataxia, and fatigue. Use of this agent at doses required to control cough could be limited by intolerable adverse effects in some patients.

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