Potential Future Therapies for the Management of Cough

ACCP Evidence-Based Clinical Practice Guidelines

Peter V. Dicpinigaitis, MD, FCCP

Background: When the etiology of a patient’s chronic cough is established, specific antitussive therapy that is aimed at a particular cause of cough is highly effective. Nevertheless, in certain situations, therapy with cough suppressants, which previously were classified as nonspecific antitussive therapy, and which aim at suppressing the cough reflex regardless of the cause of cough, will be necessary.

Methodology: The data for this review were obtained with the aid of a National Library of Medicine (PubMed) search, which was performed in June 2004, of literature published in the English language from 1966 to 2004, using the search terms “cough,” “antitussive,” “pharmacotherapy,” “future therapies,” and “potential therapies.”

Results/conclusions: Currently available cough-suppressant therapy is severely limited by a dearth of effective agents and/or their unacceptable side effects. Several classes of pharmacologic agents are currently under investigation in an attempt to develop clinically useful cough suppressants.

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Key words: antitussive; capsaicin; cough; opioid; cannabinoids; future therapies; 5-hydroxytryptamine; potassium channel openers; tachykinins; vanilloid

Abbreviations: 5-HT = 5-hydroxytryptamine; NK = neurokinin; VR1 = type 1 vanilloid receptor

Multiple prospective studies have shown that antitussive therapy that is aimed at a specific etiology of cough is highly successful. Occasionally, therapy with cough suppressants, which were previously referred to as nonspecific antitussive therapy, and were intended to suppress the cough reflex regardless of the inciting factor, is necessary and appropriate. Such circumstances include chronic unexplained cough, which was previously referred to as idiopathic cough; cough due to irreversible causes, such as pulmonary fibrosis and inoperable lung cancer; and severe cough requiring transient relief while specific antitussive therapy takes effect. Unfortunately, the currently available suppressant therapy is limited by a lack of effective agents and/or their unacceptable side effects. Hence, a great need exists for more clinically useful cough-suppressant agents.

Below is a brief overview of several areas of current investigation, mostly in animal models, that may lead to the development of novel antitussive therapies (Table 1). The data for this review were obtained with the aid of a National Library of Medicine (PubMed) search, which was performed in June 2004, of the literature published in the English language from 1966 to 2004, using the search terms “cough,” “antitussive,” “pharmacotherapy,” “future therapies,” and “potential therapies.”

Vanilloid Receptor Antagonists

The tussive agent capsaicin, which is an extract of red peppers, has achieved common usage in clinical research because it induces cough in a reproducible and dose-dependent manner. The target receptor of capsaicin, the type 1 vanilloid (VR1) receptor, was discovered on peripheral pain-sensing neurons, as...
well as throughout the CNS. The isolation of the VR1 receptor creates the opportunity for the development of potentially useful antagonists.

**Selective Opioid Receptor Agonists and Opioid-Like Receptor Agonists**

Agonists of the μ-opioid receptor (such as codeine) suppress cough at the expense of adverse effects that may include sedation, respiratory depression, nausea, constipation, and potential for abuse. A more specifically acting agent that could inhibit cough without such undesirable side effects would offer significant benefit over the currently available narcotic antitussive agents. Selective agonists of the δ-opioid receptor have been developed, and have demonstrated antitussive activity in animals.

Opioid-like orphan receptors have been identified throughout the mammalian central and peripheral nervous system, including the lung. Nociceptin/orphanin FQ, an endogenous ligand of the opioid-like orphan receptor, has been shown to inhibit mechanically-stimulated and capsaicin-induced cough in animal studies. Furthermore, nociceptin/orphanin FQ has been demonstrated to inhibit capsaicin-induced tachykinin release and bronchoconstriction through a mechanism involving inward-rectifier potassium channel activation.

**Tachykinin Receptor Antagonists**

In human airways, inflammatory cells appear to be the major source of tachykinins, which include various neuropeptide transmitters such as substance P, neurokinin (NK) A, NKB, and calcitonin gene-related peptide. Animal studies have suggested that tachykinins, through stimulation of three receptor subtypes (ie, NK1, NK2, and NK3), induce neurogenic inflammation, bronchial hyperresponsiveness, and cough. Antagonists of the three NK receptor subtypes have been isolated and have demonstrated antitussive activity in animal studies.

**Endogenous Cannabinoids**

The endogenous cannabinoid anandamide has been shown in animal studies to inhibit capsaicin-induced cough and bronchospasm, while inducing bronchospasm in animals that are devoid of vagal tone. These contrasting effects are both mediated through peripheral cannabinoid type 1 receptors that are located in airway nerves. Subsequent trials in guinea pigs demonstrated that anandamide induces cough through the activation of the VR1 receptor. The development of more selective cannabinoid receptor agonists and antagonists may provide clinically useful antitussive agents.

**5-Hydroxytryptamine Receptor Agonists**

5-Hydroxytryptamine (5-HT) has been demonstrated to suppress experimentally induced cough in healthy volunteers. The 5-HT receptor agonist pizotifen was shown to counteract the inhibitory effect of morphine against capsaicin-induced cough, thereby implying a role for 5-HT receptors in the antitussive action, but not sedative action, of opioids. A better understanding of the role of 5-HT receptors in the human cough reflex may result in the development of antitussive agents lacking the undesirable characteristics of opioids.

**Large-Conductance Calcium-Activated Potassium Channel Openers**

Animal studies have demonstrated that the modulation of potassium channels can inhibit experimentally induced cough. In guinea pigs, for example, the benzimidazolone compound NS1619, which is a large-conductance calcium-activated potassium channel opener, inhibited airway sensory nerve activity and citric acid-induced cough. The antitussive action of the vasodilator pinacidil and the thiazolidine compound moguisteine were attenuated by glibenclamide, an adenosine triphosphate-sensitive potassium channel antagonist, thereby suggesting a role for adenosine triphosphate-sensitive potassium channels in the mechanism of action of both agents. Further elucidation of the role of potassium channels in pathologic cough may yield effective therapeutic agents in the future.

### Summary of Recommendation

1. For patients with cough, the aforementioned drugs, which are not commercially available in the United States for human use, should be evaluated in the setting of properly performed clinical trials. Quality of evidence, expert opinion; net benefit, intermediate; grade of recommendation, E/B

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