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Current and future centrally acting antitussives☆

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Abstract

The purpose of this review is to highlight some important issues regarding current centrally acting antitussive drugs as well as discuss the implications of these matters on the development of future cough suppressants. Drugs that act in the central nervous system to inhibit cough are termed centrally acting and this designation is based exclusively on evidence obtained from animal models. This classification can include drugs that act both at peripheral and central sites following systemic administration. These drugs are intended to reduce the frequency and/or intensity of coughing resulting from disorders of any etiology. There are a number of central cough suppressants identified by their efficacy in animal models and the most prominent of these are codeine and dextromethorphan. Although the exact neural elements on which these drugs act are currently unknown, they are thought to inhibit a functionally identified component of the central system for cough known as the gating mechanism. The efficacy of codeine and dextromethorphan in humans has recently been questioned. These drugs are less effective on cough induced by upper airway disorders than in pathological conditions involving the lower airways in humans. The reasons for this difference in antitussive sensitivity are not clear. We propose that sensory afferents from different regions of the airways actuate coughing in humans by antitussive sensitive and insensitive control elements in the central nervous system. This hypothesis is consistent with results from an animal model in which laryngeal and tracheobronchial cough had different sensitivities to codeine. Other factors that may be very important in the action of central antitussive drugs in humans include the role of sensations produced by a tussigenic stimulus as well as plasticity of central pathways in response to airway inflammation. Resolution of these issues in the human will be a challenging process, but one which will lay the foundation for the development of more effective cough suppressants.

Keywords

Antitussive; Cough; Codeine; Dextromethorphan; Cough suppressant

1. Introduction

Drugs that act in the central nervous system to suppress cough have classically been designated as centrally acting antitussives. By definition, this classification recognizes the existence of elements of the central nervous system that have an important role in the production of cough and are also sensitive to antitussive drugs. This class of antitussive drugs is considered separate from peripherally-acting antitussives which are thought to act selectively on elements of the peripheral nervous system that are important in the generation

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of coughing. Several informative reviews exist on the centrally-acting antitussives and their proposed mechanisms of action (Bolser, 1996; Chung, 2002; Chung and Chang, 2002; O'Connell, 2002; Belvisi and Geppetti, 2004; Dicpinigaitis, 2004).

This class of antitussives includes the well-known compounds codeine and dextromethorphan, as well as a several other drugs for which evidence of cough suppressant activity exists in humans such as morphine (Fuller et al., 1988), hydrocodone (Stolz et al., 2004), pholcodine (Belcher and Rees, 1986), and baclofen (Dicpinigaitis et al., 1998) as well as drugs that have been tested only in animal models of cough (Bolser et al., 2001; McLeod et al., 2002). For the most part, the specific pharmacologic receptors to which these drugs bind are known, and include but are not limited to opioid, GABA-B, tachykinin, non-opioid (NOP-1), and sigma receptors (Chau et al., 1983; Bolser et al., 1993, 1997, 2001; Dicpinigaitis, 1997; McLeod et al., 2002).

Centrally acting antitussives (as well as peripherally-acting drugs) are intended to reduce the frequency of occurrence and/or intensity of coughing that results from pathological conditions. It is well-known that bothersome coughing can be associated with a variety of disease states (Irwin et al., 1993, 1998; O'Connell et al., 1994). The successful identification and specific treatment of these pathological conditions usually results in amelioration or resolution of coughing (Irwin et al., 1993; O'Connell et al., 1994). This clinical paradigm, known as the anatomical-diagnostic protocol, was pioneered by Irwin et al. (1993, 1998). This approach also addresses centrally acting antitussive drugs and differentiates this type of therapy from the specific approach (i.e., treating the disease rather than the cough) based on accurate diagnosis by using the term *nonspecific* to describe antitussives. Nonspecific antitussives are intended to be effective in reducing cough resulting from any disorder. The term nonspecific conflicts with the known specificities of these drugs at pharmacologic receptors. We have proposed that this terminology be changed to suppressant therapy (Bolser, 2006b), to better reflect the concept that these drugs actually are intended to modulate the expression of cough.

The classification of drugs as central is based on the results of specific experimentation in animal models. There are several methods used to obtain evidence of a central action of an antitussive drug including but not limited to: intracerebroventricular administration of the drug or its antagonist, identification of drug in CNS tissues after systemic administration, and ratios of intra-arterial and intravenous potencies (Bolser, 1996). These methods typically yield conclusions that are in good agreement. However, the real strength of these methodologies is in identifying drugs that have a central component to their actions. Some classical centrally-acting drugs may have a peripheral component to their action (Karlsson et al., 1990).

2. Efficacy of central antitussive drugs in animal models

Codeine and dextromethorphan are effective cough suppressants in animal models. These drugs suppress cough by 50–100% depending on the particular experimental model used (Chau et al., 1983; Adcock et al., 1988; Karlsson et al., 1990; Bolser et al., 1993; Kotzer et al., 2000). The dosage ranges required for cough suppression by these drugs are not typically associated with respiratory depression (Adcock et al., 1988). These antitussives not only can decrease the number of induced coughs, but also can reduce the magnitude of motor drive to expiratory muscles (Bolser et al., 1993). As such, they can modulate both the intensity and occurrence of coughing. This pattern of action is shared by a number of other antitussive drugs (baclofen, morphine, tachykinin antagonists CP99994 and SR48968, nociceptin, and the sigma receptor agonist SKF-10,047), in the anesthetized cat model (Chau et al., 1983; Bolser et al., 1993, 1994, 2001). We have proposed the existence of a common central

element that is sensitive to antitussive drugs (Bolser et al., 1999, 2002). This element, known as a gating mechanism, is hypothesized to control the excitability of the brainstem cough pattern generator as well as provide excitatory input to expiratory premotor pathways (Bolser and Davenport, 2002).

The identity of the neural elements that make up the gating mechanism is unknown. The specific effects of central antitussive drugs on the cough motor pattern and their lack of effect on breathing (at cough suppressant doses) provide evidence that the antitussive-sensitive elements are unlikely to be part of the core respiratory network (Bolser et al., 1999). Previous investigators have shown that microinjection of codeine or dextromethorphan into the nucleus of the tractus solitarius suppressed cough (Kito et al., 1977). However, the doses that were injected were large (10 μg) and significant diffusion of the drugs to anatomically distant sites within the brainstem could have occurred. (Xie and Hammarlund-Udenaes, 1998) measured striatal tissue concentrations following intravenous infusion of a dose of 10 mg/kg of codeine in rats and found unbound concentrations of this drug in the low μg/ml range. Intravenous administration of codeine in the 0.3–1.0 mg/kg range completely suppresses cough in the cat (Bolser et al., 1993). Using this information as a guide, we estimate that brainstem concentrations of unbound codeine associated with significant suppression of cough are probably in the ng/ml range. This estimate is subject to caveats regarding the different species involved (rats versus cats) and different experimental conditions between the studies. The doses used by Kito et al. (1977) were in the microgram range, approximately 3 orders of magnitude higher than our estimates for effective brainstem concentrations for the suppression of cough.

The analysis delineated above raises an important issue regarding the identification of specific central sites that are sensitive to antitussive drugs. Microinjection (or microdialysis) methods will be very useful in animal models to investigate the central actions of anti-tussive drugs. The concentrations of antitussive drugs that are delivered by this method should approximate the local tissue concentrations that occur following systemic administration of effective doses of these same compounds. In the absence of specific information regarding brainstem tissue concentrations of an antitussive drug, the risk of microinjecting amounts that are substantially higher than the maximally effective dose is high. To our knowledge, no studies have determined brainstem tissue concentrations that resulted from systemic doses of antitussive drugs that suppressed cough.

3. Efficacy of antitussive drugs in humans

Codeine is widely accepted as an effective cough suppressant in humans. However, the efficacy of codeine has recently been questioned (Hutchings and Eccles, 1994; Freestone and Eccles, 1997). Indeed, codeine was ineffective to suppress cough at doses of 50 mg in several double-blind placebo controlled studies (Hutchings and Eccles, 1994; Freestone and Eccles, 1997). Conversely, several older placebo controlled studies have demonstrated efficacy of codeine over a similar dosage range in patients with lower airway disease (Sevelius and Colmore, 1966; Sevelius et al., 1971). These older studies were conducted in small numbers of patients. An important difference between the more recent studies and the older ones was patient population. Codeine was found to be ineffective in patients with cough due to upper airway disorders, whereas in the older studies codeine was found to be efficacious in cough due to lower airway disease (Sevelius and Colmore, 1966; Sevelius et al., 1971; Aylward et al., 1984). Limited efficacy (less than 20% suppression of cough) of dextromethorphan also has been reported in patients with cough due to upper respiratory infections (Parvez et al., 1996; Pavesi et al., 2001). A hypothesis that can reconcile these apparently conflicting results is that the segment of the airway involved can influence the efficacy of an antitussive drug in humans. Pathological conditions that involve the upper

airway may actuate central mechanisms that are relatively insensitive to codeine (and/or dextromethorphan). On the other hand, disorders involving the lower airways may induce coughing by central mechanisms that are more sensitive to suppression by these antitussives. This hypothesis is supported by work in an animal model showing that cough induced from the larynx is less sensitive to suppression by codeine than tracheobronchial cough (Korpas and Tomori, 1979). Moreover, we have proposed a central control system that accounts for differential regulation (and codeine sensitivity) of laryngeal and tracheobronchial cough (Bolser and Davenport, 2002) through the existence of separate control elements for each type of expulsive behavior.

An issue that may be related to this matter is that some of the expulsive behaviors that are produced during upper airway infections may not be cough but expiration reflexes. Expiration reflexes are unique behaviors that are composed of a sudden expulsive effort with no prior inspiration and are specific to laryngeal stimulation (Korpas and Tomori, 1979). These expulsive behaviors are insensitive to codeine treatment in animal models (Korpas and Tomori, 1979). It is unknown if expiration reflexes are sensitive to suppression by codeine in humans. However, the presence of codeine-insensitive expiration reflexes during upper airway infections may make it difficult to detect a suppressive effect of codeine on coughing in humans.

A related matter is the concept that first generation H1-receptor antihistamines are more effective in the treatment of cough due to upper respiratory infection than nonsedating antihistamines (Packman et al., 1991; Irwin et al., 1998; Muether and Gwaltney, 2001; Dicpinigaitis and Gayle, 2003). The mechanism for this effect is assumed to be related to anticholinergic activity of these drugs, but double-blind placebo controlled studies of specific anticholinergic agents on cough in humans have yielded inconsistent results (Bolser, 2006b). The inconsistent effects of anticholinergic agents on coughing do not support the concept that first generation H1-antihistamines exert their anti-tussive effects via muscarinic receptor blockade. A similar difference in efficacy exists between first and second-generation antihistamines for sneeze (Muether and Gwaltney, 2001). These investigators have proposed that first generation antihistamines are suppressing sneeze by a central action. If first generation antihistamines also are suppressing cough by an action in the CNS, then this suggests that H1-histaminergic central pathways could be involved in the production of cough due to upper airway infection. Indeed, it further implies that the distinction between cough suppressants and specific pharmacologic therapies may be less well defined then was previously thought (Irwin et al., 1993). In particular, it may be possible for centrally acting antitussives to have a suppressant effect on cough induced by specific disorders. This specificity could occur if reorganization of central cough pathways results from chronic inflammation of selected segments of the respiratory system. That is, there may be a relationship between the anatomic location of the inflammation and specific changes in the central circuitry (and neuropharmacology) of the cough pattern generation system.

4. Considerations for the development of new centrally-acting cough suppressants

Given the efficacy of codeine has been questioned recently, the matter of whether newer centrally acting drugs should be developed requires some discussion. Codeine elicits significant side effects, such as sedation (Kim et al., 2002) and is usually administered 4 times daily. Newer drugs could be developed that are relatively free of these side effects and/or are administered once per day. Indeed, the rationale for the development of peripheral cough suppressants is based partly on reduced sedation potential. However, dextromethorphan is not associated with significant sedation (Weinbroum et al., 2001). In an animal model of cough, sedation potential of a group of centrally penetrant H1-

antihistamines was not associated with their ability to suppress cough (McLeod et al., 1998). In essence, simply because a cough suppressant drug acts in the CNS is not evidence that it will exhibit sedation as a side effect in humans.

To be sure, a peripherally-acting antitussive drug would be expected to have few if any CNS side effects. However, an important justification for the development of a new centrally acting cough suppressant drug must be efficacy. However, there is no rationale that favors central over peripheral cough suppressants based on efficacy in animal models. Furthermore, based on the classical understanding of the central physiology and pharmacology of cough, there is no rationale that would support a potential for greater efficacy of central antitussives over those that act peripherally. Why then should a new centrally acting antitussive drug be developed? Aside from the aforementioned issues of improved side-effect profile and/or dosing, the answer may lie in our emerging understanding of the central mechanisms that produce cough.

Our understanding of the genesis of coughing in awake humans is rapidly evolving. Recent work has raised the concept that cough is not simply an involuntary behavior that is produced solely by pulmonary sensory receptors and brainstem mechanisms. Cough can be associated with significant sensations. One such sensation has been termed “urge to cough” and this sensory modality increases in an intensity-dependent manner with cough number (Davenport et al., 2002). The presence of this sensation indicates that in humans, sensory information associated with coughing reaches locations in the brain rostral to the brainstem. Cough can be voluntarily suppressed and this finding also supports the involvement of suprapontine (presumably cortical) pathways in the control of this behavior (Hutchings and Eccles, 1994). The extent to which a centrally acting antitussive drug might act in areas rostral to the brainstem to suppress sensations that are associated with coughing is unknown. Furthermore, the role of sensations in the production of cough is not fully understood. The functional organization of the central cough system and the elements that are sensitive to antitussive drugs may be very different in awake humans than in anesthetized or awake animals. Indeed, we have proposed that voluntary control of coughing is mediated by control elements that are separate from those in the brainstem (Bolser et al., 2006). In such a control framework, a centrally acting cough suppressant drug could act at more than one CNS location resulting in robust inhibition of coughing.

The justification for the development of novel centrally acting cough suppressants may also be tied in to our increasing understanding of the effect of airway inflammation on the central nervous mechanisms for this behavior. The central organization of cough pathways and the sensitivity of their elements to cough suppressants may change in response to chronic airway inflammation. Central hyperresponsiveness resulting from chronic activation of nociceptors is a clinically important consideration in the treatment of pain (Melzack et al., 2001). This “transformation” of central pathways in response to sensory afferent feedback is known as plasticity. Mechanisms of plasticity in peripheral sensory afferents are discussed elsewhere in this special issue. Central plasticity could contribute to the presence of chronic coughing for an extended period of time after an upper airway infection (Irwin and Madison, 2000). That is, the excitability of central pathways mediating cough could be enhanced for an extended period of time such that previously innocuous stimuli elicit coughing. In this scenario, a peripherally acting antitussive may be ineffective in suppressing the coughing. As stated earlier, centrally-acting antihistamines appear to be more effective that peripheral drugs of this class in the suppression of cough due to upper airway infection (Irwin et al., 1998). In animal models, central plasticity occurs in response to chronic exposure to cigarette smoke or mechanically-induced chronic airway irritation (Joad et al., 2004). Joad et al. (2004) showed the microinjection of a tachykinin receptor antagonist into the nucleus of the tractus solitarius (NTS) inhibited cough in animals that were chronically exposed to

cigarette smoke. However, microinjection of this drug had no effect on cough in air-exposed animals. Their results indicate that in the NTS, plasticity occurred sufficient to "expose" a site of action for a cough suppressant that was not available in naive animals. Furthermore, systemic administration of tachykinins receptor antagonists can inhibit cough by a central action in animals with no underlying airway disease (Bolser et al., 1997). Presumably, cough suppression in naïve animals by centrally active tachykinin receptor antagonists occurs at a site different than the NTS. Taken together, these results are consistent with the idea that central plasticity in response to airway inflammation can result in the appearance of multiple sites of action for selected antitussive drugs. The extent to which these mechanisms occur in awake humans is not well understood. The identification of central plasticity in humans leading to recruitment of multiple sites of action of antitussives is likely to be a challenging process. The successful development of novel centrally acting antitussives may yield important tools that will allow more specific information regarding the organization and potential for plasticity of the central neurogenic mechanism for cough in humans.

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References

Adcock JJ, Schneider C, Smith TW. Effects of codeine, morphine and a novel opioid pentapeptide BW443C, on cough, nociception and ventilation in the unanaesthetized guinea-pig. Br J Pharmacol. 1988; 93:93–100. [PubMed: 3349236]

Aylward M, Maddock J, Davies DE, Protheroe A, Leideman T. Dextromethorphan and codeine: comparison of plasma kinetics and antitussive effects. Eur J Respir Dis. 1984; 65:283–291. [PubMed: 6539224]

Belcher N, Rees PJ. Effects of pholcodine and salbutamol on citric acid induced cough in normal subjects. Thorax. 1986; 41:74–75. [PubMed: 3518130]

Belvisi MG, Geppetti P. Cough. 7 Current and future drugs for the treatment of chronic cough. Thorax. 2004; 59:438–440. [PubMed: 15115877]

Bolser D, Poliacek I, Jakus J, Fuller DD, Davenport PW. Neurogenesis of cough, other airway defensive behaviors, and breathing: a holonarchical system? Respir Physiol. 2006; 152:255–265.

Bolser DC. Mechanisms of action of central and peripheral antitussive drugs. Pulm Pharmacol. 1996; 9:357–364. [PubMed: 9232675]

Bolser DC. Cough suppressant and pharmacologic protussive therapy: ACCP evidence-based clinical practice guidelines. Chest. 2006b; 129:238S–249S. [PubMed: 16428717]

Bolser DC, Aziz SM, DeGennaro FC, Kreutner W, Egan RW, Siegel MI, Chapman RW. Antitussive effects of GABAB agonists in the cat and guinea-pig. Br J Pharmacol. 1993; 110:491–495. [PubMed: 8220912]

Bolser DC, Davenport PW. Functional organization of the central cough generation mechanism. Pulm Pharmacol Ther. 2002; 15:221–225. [PubMed: 12099768]

Bolser DC, DeGennaro FC, O'Reilly S, Chapman RW, Kreutner W, Egan RW, Hey JA. Peripheral and central sites of action of GABA-B agonists to inhibit the cough reflex in the cat and guinea pig. Br J Pharmacol. 1994; 113:1344–1348. [PubMed: 7889290]

Bolser DC, DeGennaro FC, O'Reilly S, McLeod RL, Hey JA. Central antitussive activity of the NK1 and NK2 tachykinin receptor antagonists, CP-99,994 and SR 48968, in the guinea-pig and cat. Br J Pharmacol. 1997; 121:165–170. [PubMed: 9154323]

Bolser DC, Hey JA, Chapman RW. Influence of central antitussive drugs on the cough motor pattern. J Appl Physiol. 1999; 86:1017–1024. [PubMed: 10066718]

Bolser DC, McLeod RL, Tulshian DB, Hey JA. Anti-tussive action of nociceptin in the cat. Eur J Pharmacol. 2001; 430:107–111. [PubMed: 11698070]

Chau TT, Carter FE, Harris LS. Antitussive effect of the optical isomers of mu, kappa and sigma opiate agonists/antagonists in the cat. J Pharmacol Exp Ther. 1983; 226:108–113. [PubMed: 6864534]

Chung KF. Cough: potential pharmacological developments. Exp Opin Investig Drugs. 2002; 11:955–963.

Chung KF, Chang AB. Therapy for cough: active agents. Pulm Pharmacol Ther. 2002; 15:335–338. [PubMed: 12099788]

Davenport P, Sapienza CM, Bolser DC. Psychophysical assessment of the urge-to-cough. Eur Respir Rev. 2002; 12:249–253.

Dicpinigaitis P. Use of baclofen to suppress cough induced by angiotensin-converting enzyme inhibitors. Ann Pharmacother. 1997; 30:1242–1245. [PubMed: 8913404]

Dicpinigaitis P, Dobkin JB, Rauf K, Aldrich TK. Inhibition of capsaicin-induced cough by the gamma-aminobutyric acid agonist baclofen. J Clin Pharmacol. 1998; 38:364–367. [PubMed: 9590464]

Dicpinigaitis PV. Potential new cough therapies. Pulm Pharmacol Ther. 2004; 17:459–462. [PubMed: 15564092]

Dicpinigaitis PV, Gayle YE. Effect of the second-generation antihistamine, fexofenadine, on cough reflex sensitivity and pulmonary function. Br J Clin Pharmacol. 2003; 56:501–504. [PubMed: 14651723]

Freestone C, Eccles R. Assessment of the antitussive efficacy of codeine in cough associated with common cold. J Pharm Pharmacol. 1997; 49:1045–1049. [PubMed: 9364418]

Fuller RW, Karlsson JA, Choudry NB, Pride NB. Effect of inhaled and systemic opiates on responses to inhaled capsaicin in humans. J Appl Physiol. 1988; 65:1125–1130. [PubMed: 3182481]

Hutchings HA, Eccles R. The opioid agonist codeine and antagonist naltrexone do not affect voluntary suppression of capsaicin induced cough in healthy subjects. Eur Respir J. 1994; 7:715–719. [PubMed: 8005254]

Irwin RS, Boulet LP, Cloutier MM, Fuller R, Gold PM, Hoffstein V, Ing AJ, McCool FD, O'Byrne P, Poe RH, Prakash UB, Pratter MR, Rubin BK. Managing cough as a defense mechanism and as a symptom. A consensus panel report of the American College of Chest Physicians. Chest. 1998; 114:133S–181S. [PubMed: 9725800]

Irwin RS, Curley FJ, Bennett FM. Appropriate use of antitussives and protussives. A practical review. Drugs. 1993; 46:80–91. [PubMed: 7691510]

Irwin RS, Madison JM. The diagnosis and treatment of cough. N Engl J Med. 2000; 343:1715–1721. [PubMed: 11106722]

Joad JP, Munch PA, Bric JM, Evans SJ, Pinkerton KE, Chen CY, Bonham AC. Passive smoke effects on cough and airways in young guinea pigs: role of brainstem substance P. Am J Respir Crit Care Med. 2004; 169:499–504. [PubMed: 14644932]

Karlsson JA, Lanner AS, Persson CG. Airway opioid receptors mediate inhibition of cough and reflex bronchoconstriction in guinea pigs. J Pharmacol Exp Ther. 1990; 252:863–868. [PubMed: 2156065]

Kim I, Barnes AJ, Oyler JM, Schepers R, Joseph RE Jr, Cone EJ, Lafko D, Moolchan ET, Huestis MA. Plasma and oral fluid pharmacokinetics and pharmacodynamics after oral codeine administration. Clin Chem. 2002; 48:1486–1496. [PubMed: 12194925]

Kito G, Kase Y, Miyata T, Takahama K. Neural mechanism for production of spasmodic expiratory response like cough induced by amygdala stimulation in the cat. I Pathways from the amygdala to the lower brain stem. Arch Int Pharmacodyn Ther. 1977; 229:116–128. [PubMed: 337914]

Korpas, J.; Tomori, Z. Cough and Other Respiratory Reflexes. S. Karger; Basel, New York: 1979.

Kotzer CJ, Hay DW, Dondio G, Giardina G, Petrillo P, Underwood DC. The antitussive activity of delta-opioid receptor stimulation in guinea pigs. J Pharmacol Exp Ther. 2000; 292:803–809. [PubMed: 10640321]

McLeod RL, Bolser DC, Jia Y, Parra LE, Mutter JC, Wang X, Tulshian DB, Egan RW, Hey JA. Antitussive effect of nociceptin/orphanin FQ in experimental cough models. Pulm Pharmacol Ther. 2002; 15:213–216. [PubMed: 12099766]

McLeod RL, Mingo G, O'Reilly S, Ruck LA, Bolser DC, Hey JA. Antitussive action of antihistamines is independent of sedative and ventilation activity in the guinea pig. Pharmacology. 1998; 57:57–64. [PubMed: 9691225]

Melzack R, Coderre TJ, Katz J, Vaccarino AL. Central neuroplasticity and pathological pain. Ann N Y Acad Sci. 2001; 933:157–174. [PubMed: 12000018]

Muether PS, Gwaltney JM Jr. Variant effect of first- and second-generation antihistamines as clues to their mechanism of action on the sneeze reflex in the common cold. Clin Infect Dis. 2001; 33:1483–1488. [PubMed: 11588693]

O'Connell F. Central pathways for cough in man—unanswered questions. Pulm Pharmacol Ther. 2002; 15:295–301. [PubMed: 12099782]

O'Connell F, Thomas VE, Pride NB, Fuller RW. Capsaicin cough sensitivity decreases with successful treatment of chronic cough. Am J Respir Crit Care Med. 1994; 150:374–380. [PubMed: 8049818]

Packman EW, Ciccone PE, Wilson J, Masurat T. Antitussive effects of diphenhydramine on the citric acid aerosol-induced cough response in humans. Int J Clin Pharmacol Ther Toxicol. 1991; 29:218–222. [PubMed: 1869343]

Parvez L, Vaidya M, Sakhardande A, Subburaj S, Rajagopalan TG. Evaluation of antitussive agents in man. Pulm Pharmacol. 1996; 9:299–308. [PubMed: 9232667]

Pavesi L, Subburaj S, Porter-Shaw K. Application and validation of a computerized cough acquisition system for objective monitoring of acute cough: a meta-analysis. Chest. 2001; 120:1121–1128. [PubMed: 11591548]

Sevelius H, Colmore JP. Objective assessment of antitussive agents in patients with chronic cough. J N Drugs. 1966; 6:216–223.

Sevelius H, McCoy JF, Colmore JP. Dose response to codeine in patients with chronic cough. Clin Pharmacol Ther. 1971; 12:449–455. [PubMed: 4936034]

Stolz D, Chhajed PN, Leuppi JD, Brutsche M, Pflimlin E, Tamm M. Cough suppression during flexible bronchoscopy using combined sedation with midazolam and hydrocodone: a randomised, double blind, placebo controlled trial. Thorax. 2004; 59:773–776. [PubMed: 15333854]

Weinbroum AA, Gorodezky A, Niv D, Ben-Abraham R, Rudick V, Szold A. Dextromethorphan attenuation of postoperative pain and primary and secondary thermal hyperalgesia. Can J Anaesth. 2001; 48:167–174. [PubMed: 11220426]

Xie R, Hammarlund-Udenaes M. Blood-brain barrier equilibration of codeine in rats studied with microdialysis. Pharm Res. 1998; 15:570–575. [PubMed: 9587953]