

Cough: New Pharmacology



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List of Design Committee Members: Jaclyn A. Smith, PhD, and Huda Badri, PhD (authors); Robert S. Zeiger, MD, PhD (editor)

Learning objectives:

1. To recognize the range of new therapies, their development stage, and potential for success.
2. To comprehend how cough is being evaluated in clinical trials and therefore interpret the evidence that these therapies are effective.
3. To appreciate the new insights into the mechanisms underlying chronic cough provided by these therapies.
4. To understand the possible means by which these new treatments might be incorporated into clinical practice.

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Chronic coughing has a significant impact on the sufferer's quality of life. Despite this, licensed therapies are currently lacking, and until recently novel efficacious therapies for the treatment of chronic cough have remained elusive. In recent years, a first in class P2X3 antagonist has been found to be efficacious in patients with refractory chronic cough, stimulating much interest in the development of therapies for this problem. The aim of this review is to summarize the current state of

development of novel therapies acting both in the peripheral and central nervous systems. Most programs are focused on treating patients with refractory chronic cough, but chronic coughing is also a problem in common respiratory diseases in spite of standard care. However, unraveling of the pathophysiological mechanisms underlying cough will ultimately be needed to identify the relevant drug targets, better characterize patients, and match them to the most

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Abbreviations used

CNS- Central nervous system
 COPD- Chronic obstructive pulmonary disease
 IPF- Idiopathic pulmonary fibrosis
 NaV- Voltage-gated sodium
 NK-1- Neurokinin 1
 nTS- Nucleus tractus solitarius
 PRO- Patient-reported outcome
 RCC- Refractory chronic cough
 TRP- Transient receptor potential
 TRPV1- Transient receptor vanilloid-1

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In a healthy subject, the cough reflex plays an important role in protection of the airway from environmental irritants and the entry of foreign bodies; however, in disease excessive coughing has a significant impact on the sufferer's quality of life.¹ Despite this, efficacious therapies for the treatment of cough have remained elusive. The last new drug to be licensed for cough in the United States was dextromethorphan, more than 50 years ago. Many over-the-counter medicines containing a range of active ingredients are available for the treatment of cough associated with viral upper respiratory tract infections, but evidence of the effectiveness of these treatments is lacking.²

Currently there are no licensed therapies for patients suffering from chronic coughing; however, the interest in developing such therapies has grown, especially after reports of the unprecedented effect of Gefapixant, a P2X3 receptor antagonist in patients with refractory chronic cough (RCC)³ (Figure 1). Therefore, in recent years, a range of novel therapies have undergone preclinical and

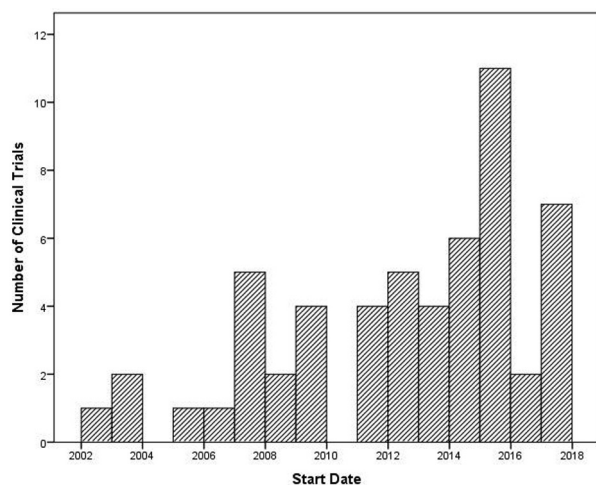


FIGURE 1. Number of interventional clinical trials of new pharmacologic therapies for chronic cough registered on either clinicaltrials.gov or ISCTRN by start year.

clinical evaluation for the treatment of chronic cough, and the aim of this review is to focus on novel therapies undergoing active development.

NEUROPHYSIOLOGY OF COUGH

A basic understanding of the neuronal pathways, receptors, and ion channels involved in evoking cough is essential to comprehending the mode of action of novel pharmacologic agents. Coughing occurs when vagal sensory nerve fibers in the larynx and airways are activated by irritant chemicals or the mechanical stimulus of excess mucus and/or a foreign body. Based on preclinical studies in the guinea pig, 2 categories of fiber are thought to be most important in mediating cough: unmyelinated predominately chemosensitive C fibers and thinly myelinated Aδ fiber mechanoreceptors that are also activated by changes in pH and osmolarity. These fibers have their cell bodies in the jugular and nodose ganglia of the vagus nerve (respectively) and synapse in the brainstem in the nucleus tractus solitarius (nTS) and the paratrigeminal nucleus (Pa5). In the brain, a complex neural network is responsible for coordinating the motor cough response as well as associated sensations of irritation/tickling in the throat and an urge-to-cough. A wide array of ion channels, receptors, and neurotransmitters have been implicated in the pathways controlling cough.⁴ Those being targeted by new pharmacologic interventions for cough are summarized in Figure 2.

PATHOPHYSIOLOGY OF COUGH

Excessive coughing in disease is a consequence of repetitive activation of the neuronal pathways mediating cough. There are 2 broad mechanisms via which this may occur:

- (1) increased exposure of the sensory nerve terminals to chemical irritants (eg, PGE₂, ATP) or excess mucus
- (2) changes in the excitability of the neuronal pathways that may affect airway sensory nerves and/or their central nervous system (CNS) connections.

The plasticity of the nervous system dictates that increased stimulation of peripheral nerve fibers can result in changes in their excitability, for example, through changes in receptor expression^{5,6} and subsequent modification of synaptic transmission in the brain,^{7,8} further increasing the gain in the system. It is therefore unlikely that these processes occur in isolation, although in subgroups of patients, certain mechanisms may predominate. The terms peripheral and central sensitization, borrowed from the literature on neuropathic pain, are sometimes used to describe the alterations in airway nerve function; however, very little is known about the receptors and neurotransmitters involved in clinical disease. Increasingly, we are starting to understand more about disease mechanisms through interventional studies of novel therapies when the specific mode of action is known.

ANTITUSSIVE THERAPY: AN UNMET CLINICAL NEED

Currently most studies evaluating cough treatments are focused on RCC, defined as a dry cough of >8 weeks' duration that is unresponsive to the treatment of potential underlying conditions such as asthma, gastroesophageal reflux, or nasal disease; this includes the small proportion of patients who have no evidence of any underlying condition, sometimes referred to

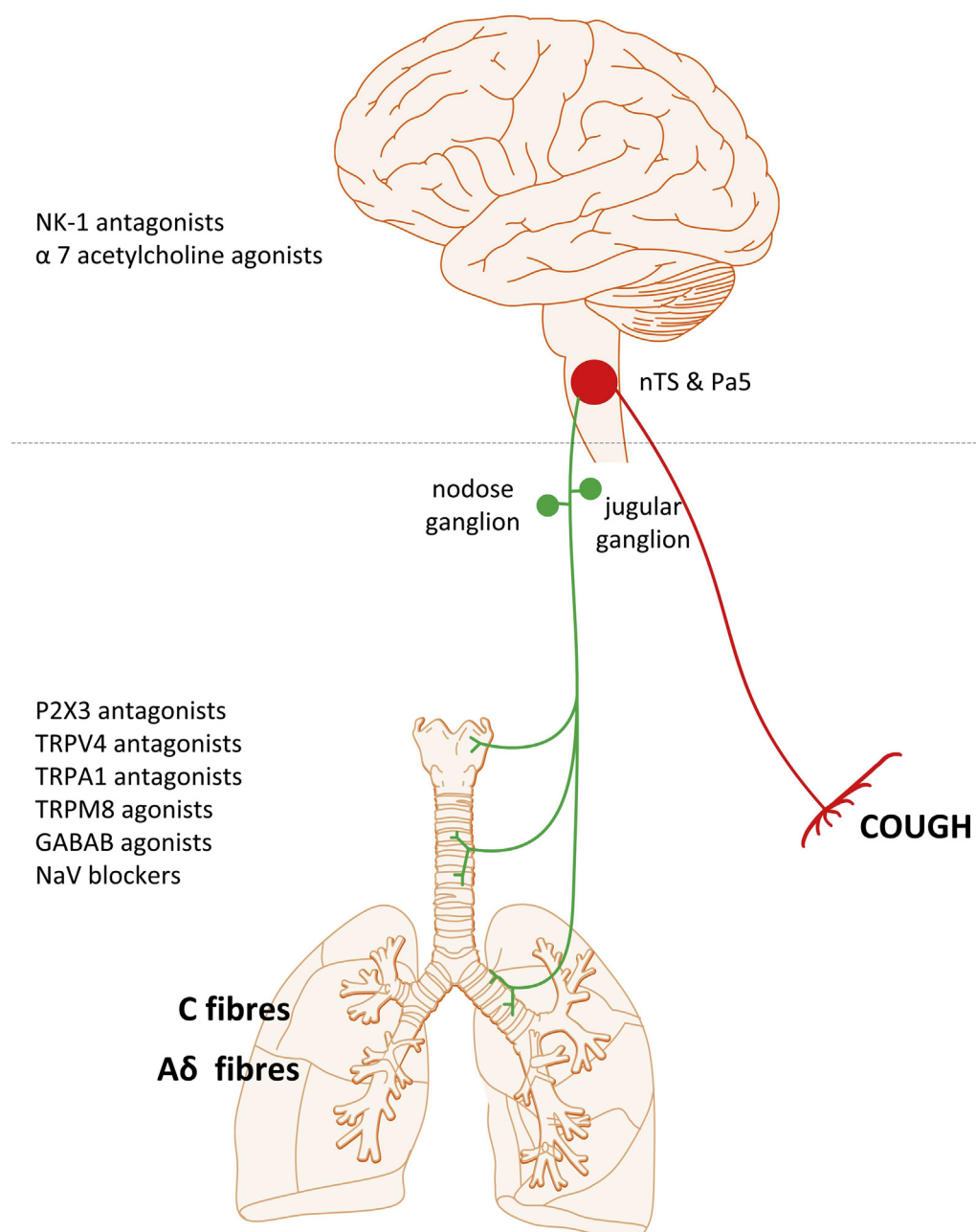


FIGURE 2. Novel targets for antitussive therapies in the central and peripheral nervous system. *NaV*, Voltage-gated sodium; *NK-1*, neurokinin 1; *nTS*, nucleus tractus solitarius; *TRPA1*, transient receptor potential ankyrin 1; *TRPM8*, transient receptor potential melastatin 8; *TRPV4*, transient receptor vanilloid-4.

as unexplained chronic cough. A cough severity visual analogue score of >40 mm is often an eligibility criterion, with the aim of targeting those patients with the highest cough frequencies. This patient group is attractive for testing novel therapies as they have high cough rates that remain relatively stable over time and currently no licensed treatments are available for this condition.

Antitussive therapy also has potential value in patients with cough associated with chronic respiratory diseases; cough in these conditions persists despite standard care.⁹⁻¹² The mechanisms underlying cough in such patients are likely to be different from RCC.^{5,13} Furthermore, there is evidence of responders and nonresponders in studies of effective treatments for patients with

RCC.³ Ultimately, a stratified medicine approach is likely to be required to match patients to the appropriate intervention.

One concern in treating cough is the potential risk in those with mucus hypersecretion such as chronic bronchitis in patients with chronic obstructive pulmonary disease (COPD) or bronchiectasis. It is possible that reducing cough in this context could increase the risk of lower respiratory tract infections.

OLD PHARMACOLOGY FOR COUGH

Currently, the treatment of chronic cough relies on the cough responding to the treatment of any underlying condition

identified as there are no licensed therapies for refractory or unexplained chronic cough. A small number of randomized controlled trials have provided some evidence for benefit from neuromodulating therapies licensed for the treatment of pain, for example, amitriptyline,^{14,15} gabapentin,¹⁶ pregabalin,¹⁷ and low-dose morphine sulphate.¹⁸ These therapies are thought to act in the CNS and although their precise mechanisms of action are unclear, their effects on mood are well described. The trials of these agents to date have relied on subjective quality of life tools as their primary outcome measures, which should be interpreted with caution for mood modulating therapies. For example, the study of pregabalin versus placebo as an adjunct to speech pathology suggested significant improvements in cough specific quality of life and cough severity scores with pregabalin in the absence of any improvement in cough frequency.¹⁷ Although it is theoretically possible that the intensity of cough improved without any change in cough frequency, the most plausible explanation is that changes in mood modulated the perception of cough rather than any true antitussive effect occurring. Currently, objective evidence for antitussive effects is lacking for pregabalin, gabapentin, and amitriptyline, although some evidence suggests that responders to low-dose morphine experience reductions of approximately 70% in cough frequency over placebo.^{19,20} Nonetheless, significant side effects are common with these unlicensed therapies.

ENDPOINTS IN ANTITUSSIVE CLINICAL TRIALS

The ability to objectively quantify changes in cough frequency using acoustic cough monitoring systems has changed the standards by which antitussive therapies are evaluated. Currently, the VitaloJAK (Vitalograph Ltd, Buckinghamshire, UK) is the only device with the regulatory approvals suitable for regulatory trials (Food and Drug Administration [FDA] 510k and Conformité Européenne [CE] mark). Patient-reported outcomes (PROs) are complimentary, confirming whether improvements in cough frequency are accompanied by perceived improvements in cough severity and impacts on quality of life, see [Table 1](#).

PERIPHERAL NEURONAL TARGETS FOR ANTITUSSIVE THERAPY

The advantages of targeting peripheral nerves when developing antitussive agents are the potential avoidance of common CNS side effects such as drowsiness and the possibility of delivering therapies directly to the airways reducing the overall risk of systemic adverse events (see [Figures 2 and 3](#)).

P2X3 receptor antagonism

P2X3 receptors are ATP-activated ion channels found almost exclusively on sensory nerves. Each channel consists of 3 subunits; these may be identical P2X3 subunits or contain a single P2X2 subunit, known as P2X2/3 channels. Currently, at least 4 companies are developing P2X3 antagonists for the treatment of RCC, after the initial results generated by Afferent Pharmaceutical Inc. with Gefapixant (previously AF219/MK7264). In a phase IIa proof-of-concept study, this therapy produced a 75% reduction in cough frequency over placebo at 600 mg BID, but 100% of patients complained of loss of taste/taste disturbances.³ Furthermore, phase IIa studies explored lower doses of this therapy and suggested that although antitussive efficacy was maintained at doses as low as 30 to 50 mg, the reporting of taste improved.^{24,25} Subsequently, a large-scale phase IIb study was undertaken and demonstrated a 37% reduction over placebo at 50 mg BID.²⁶ Interestingly, in this study, there was a 30% reduction of cough frequency in the placebo arm perhaps due to a change in patients' expectations of cough therapies. Phase IIa studies in patients with idiopathic pulmonary fibrosis (IPF) and acute viral-induced cough have been conducted but little information is in the public domain; the study in acute cough was terminated as at interim analysis the data did not support the study endpoints for acute cough.^{27,28} Large-scale phase III trials in refractory cough are currently recruiting globally (Merck Inc.) evaluating doses of 15 and 45 mg, with objective cough frequency and safety as the primary endpoints for both studies.^{29,30}

The main liability for Gefapixant is the tolerability of taste disturbances, thought to be explained by its modest selectivity for P2X3 over P2X2/3 channels; studies in double knockout mice have implicated P2X2/3 channels in taste mediation.³¹ Consequently, molecules exhibiting greater selectivity for P2X3 compared with P2X2/3 are under investigation (Bayer,^{32,33} Bellus,³⁴ Shionogi³⁵). The extent to which this strategy will retain antitussive efficacy/mitigate taste effects is difficult to predict, and so the results of the first clinical studies with more selective agents are eagerly awaited.

Transient receptor potential receptors

Transient receptor potential (TRP) channels are a family of cation channels found on a diverse range of cell types including neurons, functioning as polymodal cellular sensors of a diverse range of stimuli resulting in the perception of light, temperature, pressure, and pain.³⁶ Twenty-eight mammalian TRP channels

TABLE 1. Summary of endpoints used in clinical trials assessing potential therapies for cough

Endpoint	Utility	Tools	Clinically important change in refractory chronic cough
Cough frequency monitoring	Objective measure of cough frequency	VitaloJAK Leicester Cough Monitor	Reduction of 20% to 30% ²¹ Unknown
Cough severity	Patient's perception of cough severity	Cough Severity Visual Analogue Scales Cough Severity Diary	Unknown Unknown
Cough-specific quality of Life	Patient's perception of impact of cough	Leicester Cough Questionnaire Cough Quality of Life Questionnaire	Increase of 1.5 to 2 points ²² Reduction of 10.6-21.9 ²³
Experimentally evoked cough	Target engagement, mechanistic insights	Capsaicin/Citric Acid/ATP/Hypertonic Solutions/"Fog"	Not applicable

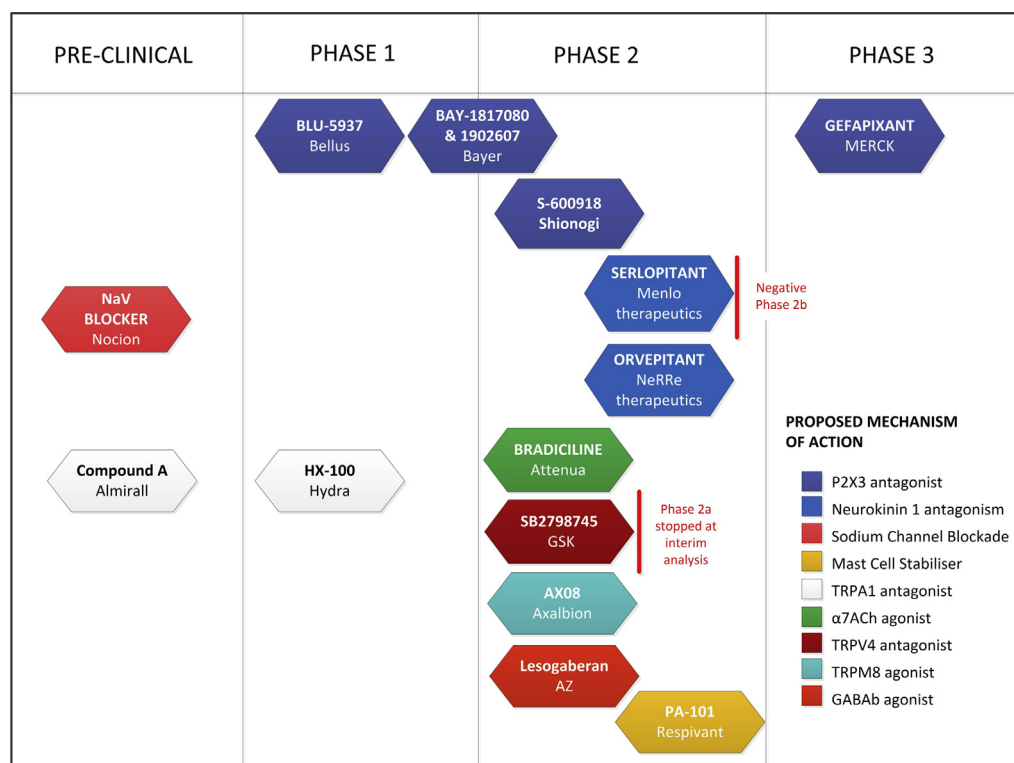


FIGURE 3. Current stages of development of agents for the treatment of chronic coughing. *NaV*, Voltage-gated sodium; *TRPA1*, transient receptor ankyrin 1; *TRPM8*, transient receptor potential melastatin 8; *TRPV4*, transient receptor vanilloid-4.

have been identified, but relatively few are implicated in the cough reflex.³⁷

TRPV1 antagonism. C fiber sensory neurons, including those in the airways, typically express Transient Receptor Vanilloid-1 (TRPV1) channels through which they respond to heat, acidity, and capsaicin (chilli pepper extract). As inhaling capsaicin readily evokes cough, and patients with chronic cough exhibit heightened responses to capsaicin, the testing of compounds antagonizing this receptor was an obvious step in the search for novel antitussive therapies.^{38,39} SB-705498 (GSK Ltd) has been evaluated in RCC and XEN-0501 (Ario Pharma Ltd) in patients with RCC and COPD selected for cough responses to capsaicin.⁴⁰⁻⁴² In all 3 studies, target engagement in the lung was confirmed through significant inhibition of coughing on capsaicin inhalation. Although XEN-0501 appeared more potent than SB-705498, neither agent had any effect on spontaneous cough frequency in any patient group. Whether TRPV1-mediated responses are important drivers of cough in conditions other than RCC and COPD remains to be determined.

TRPA1 antagonism. Transient receptor ankyrin 1 (TRPA1) receptors have been shown to play a role in evoking cough in animal models and possibly also in humans through the inhalation of cinnamaldehyde.⁴³ TRPA1 receptors are an attractive target as they are activated by irritant chemicals reported by patients to evoke coughing, for example, chemicals in cigarette smoke, perfumes,⁴⁴ and also environmental exposures thought to be important in respiratory disease, for example, diesel.⁴⁵

Only 1 compound (GRC 17536; Glenmark Pharmaceuticals Ltd) has been tested in patients with RCC but had no effect over 4 weeks compared with placebo on cough frequency;⁴⁶ the study remains unpublished, and so it is unclear whether there was any evidence of target engagement. Furthermore, the drug was inhaled at a single dose, and as little is known about the optimal dosing and airway deposition for treating cough, these may not have been achieved. Based on this single negative study, a potential effect of TRPA1 antagonism on cough cannot be excluded. Although other companies have been developing drugs for this target (Hydra, Almirall), further studies treating cough are awaited.⁴⁷

TRPV4 antagonism. Recent preclinical studies have implicated the TRPV4 receptor in the release of ATP, and subsequent activation of P2X3 channels.⁴⁸ Thus, TRPV4 antagonism may provide an opportunity to block P2X3 activation upstream and avoid taste side effects. A GSK compound has recently been tested in a small proof-of-concept study, but was stopped after recruitment of 17 subjects, as an interim analysis suggested lack of efficacy on cough frequency.⁴⁹ As no measure of target engagement was included, the potential of this target cannot be ruled out at present.

TRPM8 antagonism. Menthol is a cooling agent found in many over-the-counter medicines, mainly to reduce throat irritation. Its cooling properties are mediated via the TRPM8 receptor and a single study has suggested inhaled menthol reduces cough evoked by citric acid,⁵⁰ but there are no data evaluating its effects on cough frequency. Recently a small

biotech has performed a pilot study of a novel TRPM8 agonist (AX-8) dispersible tablet in patients with RCC; however, the results are so far not in the public domain.⁵¹

GABA_B receptor agonists

Lesogaberan (AstraZeneca, Alderley Park, UK) is a peripherally acting gamma-aminobutyric acid B (GABA_B) receptor agonist, originally developed for the treatment of gastroesophageal reflux disease. This class of therapies has been shown to reduce reflux events, irrespective of acidity, by blocking relaxations of the lower esophageal sphincter.^{52,53} The development of lesogaberan was not progressed as in unselected patients with reflux disease its effect was only marginally superior to placebo for typical symptoms of reflux disease.⁵⁴ After the observation of reductions in citric acid evoked cough in a pre-clinical model,⁵⁵ a recent proof-of-concept study has provided some evidence of an antitussive effect in patients with RCC, with a nonsignificant reduction in awake cough frequency of 26% over placebo and a significant improvement of capsaicin-evoked cough. *Post hoc* analyses suggest the effect is more likely mediated via neuronal pathways controlling cough rather than by reducing gastroesophageal reflux.

Sodium cromoglycate

Small clinical studies using subjective endpoints have suggested a possible antitussive effect of inhaled sodium cromoglycate in patients with lung cancer⁵⁶ and angiotensin converting enzyme (ACE) inhibitor-induced cough,⁵⁷ although the possible mechanism of action was not clear. Recent preclinical data have implicated cromoglycate in the reduction of C-fiber activity via GPR35, an orphan G-protein-coupled receptor.⁵⁸

A recent proof-of-concept study of a high-dose nebulized cromoglycate (PA101, Patara) suggested that this therapy may have an antitussive effect in patients with IPF but not those with RCC.¹³ Notably, although a reduction of 31.1% in cough frequency was achieved, the improvement in PROs was not statistically significant and well below accepted minimally important differences (MIDs), questioning the value of this agent as a potential therapy. A possible explanation for this discordance in findings is that the endpoints chosen were developed for assessing patients with RCC and lack validation in IPF. Nonetheless, a larger phase IIb study is now recruiting, evaluating a range of doses versus placebo for cough in patients with IPF with 24-hour cough frequency as the primary endpoint.⁵⁹

Sodium channel blockade

Lidocaine primarily blocks voltage-gated sodium (NaV) channels, which play a key role in action potential generation and propagation. Nebulized lidocaine is used off license by some clinicians to treat RCC,⁶⁰ and a recent systematic review supports an effect of intravenous lidocaine to prevent cough associated with intubation, extubation, and opioid use in surgical patients.⁶¹ However, most studies suggesting an antitussive benefit from local anesthetics have used poorly validated endpoints. One study evaluated the effect of a single dose (600 mg) of nebulized lidocaine, versus a lidocaine throat spray (100 mg) and matched placebos through objective cough monitoring. Only lidocaine throat spray significantly reduced cough frequency over placebo (50.8% reduction over 3 hours after dose, 20% reduction over 10 hours after dose).⁶² The main liability of indiscriminate systemic blockade of sodium channels is cardiac toxicity. Topical delivery to the throat/upper airway and selective

blockade of the channel subtypes (NaV 1.7 or NaV 1.8) thought to be expressed by airway nerves but not cardiac/striated muscle may provide strategies for mitigating systemic toxicities.⁶³ Topical delivery may still cause issues with compromise of airway protection by altering sensations in the throat, affecting swallowing and loss of cough reflex responses to mechanical stimuli in the larynx. Also any irritancy of drugs may especially provoke coughing during inhalation in patients with chronic cough sensitized to such stimuli.

A couple of novel sodium channel blocking drugs have been evaluated for the treatment of chronic cough in recent years. GlaxoSmithKline developed a nonselective inhaled sodium channel blocker, but the proof-of-concept study was stopped for futility after an interim analysis of the first 11 patients.⁶⁴ No beneficial effect of the drug was seen on cough frequency, cough challenge or PROs, and administration of the drug-induced coughing.

Similarly, Verona Pharma evaluated nebulized carcanium chloride, also a nonselective NaV blocker, in a pilot study (n = 8) in patients with cough associated with IPF.⁶⁵ Although this study suggested a beneficial effect, a subsequent powered follow-up study using validated endpoints was unable to replicate these findings; the drug evoked coughing for 3 to 4 hours after administration.⁶⁶

CENTRAL NEURONAL TARGETS FOR PHARMACOTHERAPY

Numerous peripheral receptors are involved in the activation of the neuronal pathways evoking cough, some of which have already been shown to be redundant in disease for example, TRPV1 in RCC.⁴¹ Therefore, targeting the CNS has the potential advantage of modulating numerous pathways where they converge and synapse in the brainstem nuclei or higher centers (Figures 2 and 3).

Neurokinin receptor 1 antagonism

Preclinical experiments have suggested that neurokinin 1 (NK-1) receptors and their main ligand substance P have importance in the CNS in evoking cough. The nTS is known to be enriched with substance P immunoreactive nerve terminals and microinjection of substance P into this region enhances cough responses, via the NK-1 receptor.⁶⁷ Moreover, environmental exposures such as cigarette smoke enhance nTS synaptic transmission and cough responses, blocked by NK-1 receptor antagonism.⁸

Licensed NK-1 antagonists are available for the treatment of chemotherapy-induced nausea and vomiting, and recently a small proof-of-concept study evaluated 3 days of treatment with 1 such therapy (aprepitant) in patients with cough associated with lung cancer.⁶⁸ Cough frequency was reduced by 23% during waking hours and 30% over 24 hours (over placebo), accompanied by improvements in PROs. Based on this work, 2 phase 2b studies of novel NK-1 antagonists commenced, orvepitant (NeRR Therapeutics Ltd⁶⁹) and serlopitant (Menlo Therapeutics Inc.⁷⁰) in patients with RCC, that is, a different patient group. For orvepitant, an open-label pilot study (n = 13) performed in patients with RCC, to inform the design of the phase 2b study, suggested reductions in cough from baseline of 28% at week 1 to 26% at week 4.⁷¹ The effect was sustained after discontinuation of therapy (29% reduction at week 8), suggesting that a parallel group placebo-controlled study would be required to evaluate against placebo. The phase 2b study is

evaluating several doses and has completed recruitment; results are awaited.⁶⁹ For serlopitant, no data to suggest efficacy in refractory cough were collected before undertaking the phase 2b study. This study has recently been completed, and brief data suggesting that the study was negative have been press-released;⁷² further details are awaited.

$\alpha 7$ acetylcholine receptor agonism

Bradanicline (Attenua Inc.) is a selective agonist of the $\alpha 7$ subtype of ACh receptors. This drug was previously developed for schizophrenia, targeting sensory gating mechanisms in the CNS.^{73,74} The concept of an antitussive effect of this therapy is based on the observation that nicotine inhibits capsaicin-evoked cough in humans.^{75,76} Preclinical data suggest that this inhibitory effect is mediated by activation of the $\alpha 7$ receptor.⁷⁷ As effects on experimentally evoked cough responses have been found poorly predictive of effects on spontaneous cough,^{16,18,40,41} the effects on cough frequency in a phase 2a dose ranging study are awaited for proof of concept.⁷⁸

CONCLUSIONS

In conclusion, there has been a very significant growth in the development of therapeutic agents to treat cough, especially RCC. A broad range of receptors are being targeted with most in the peripheral nervous system. As the most of these therapies exhibit specific mechanisms of action, they are likely to improve our knowledge of the pathophysiology of chronic cough, in addition to providing the possibility of new therapies for patients. The P2X3 antagonist, Gefapixant currently holds the most promise to be the first therapy licensed for the treatment of RCC, but as further programs yield data, other new therapies may emerge. Such therapies have the potential to change the way refractory cough is managed and reduce the prolonged suffering patients with this condition currently withstand. However, a significant amount of further work is still needed to better evaluate chronic coughing, both in refractory patients and in cough associated with common respiratory conditions. Unraveling of the underlying mechanisms and the identification of markers of these will ultimately be needed to characterize patients and match them to the most appropriate treatments.

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