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LEADING ARTICLE

Drugs Targeting Cough Receptors: New Therapeutic Options in Refractory or Unexplained Chronic Cough

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Abstract

Refractory chronic cough is a disabling disease with very limited therapeutic options. A better understanding of cough pathophysiology has led to the development of emerging drugs targeting cough receptors. Recent strides have illuminated novel therapeutic avenues, notably centred on modulating transient receptor potential (TRP) channels, purinergic receptors, and neurokinin receptors. By modulating these receptors, the goal is to intervene in the sensory pathways that trigger cough reflexes, thereby providing relief without compromising vital protective mechanisms. These innovative pharmacotherapies hold promise for improvement of refractory chronic cough by offering improved efficacy and potentially mitigating adverse effects associated with current recommended treatments. A deeper comprehension of their precise mechanisms of action and clinical viability is imperative for optimising therapeutic interventions and elevating patient care standards in respiratory health. This review delineates the evolving landscape of drug development in this domain, emphasising the significance of these advancements in reshaping the paradigm of cough management.

Key Points

Recent strides have illuminated novel therapeutic avenues, notably centred on modulating transient receptor potential (TRP) channels, purinergic receptors, and neurokinin receptors.

Innovative pharmacotherapies that target cough receptors hold promise for improvement of refractory chronic cough by offering improved efficacy and potentially mitigating adverse effects associated with current recommended treatments.

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1 Introduction

Cough is defined as a sudden and noisy expulsion of air from the lungs. It is a physiological reflex that protects the airways from aspiration or compounds that could damage the bronchi or the lungs. However, when cough reflex is exacerbated by infections (mostly virus) or diseases, cough is perceived as a symptom by patients. When patients suffer from cough that lasts for longer than 8 weeks, it is now widely admitted that they are affected by chronic cough [1]. This entity is a common reason for medical consultation given the estimated worldwide prevalence of 9.6% [2]. According to more recent data, the prevalence of chronic cough in westernised countries is close to 5% of the general population. For example, the prevalence of chronic cough was estimated at 5.0% in the USA [3], 5.5% in Spain [4] and 4.8% in France [5]. Unlike cough, which is a symptom, many experts consider that chronic cough should be seen as a disease [6]. Although for many patients chronic cough improves once the underlying causes are treated, some patients present unexplained or refractory chronic cough with no obvious aetiology or persistent cough despite optimal management. Refractory chronic cough is estimated to account for approximately 15% of cases among chronic cough patients [7]. However, there is a lack of robust data. One of the main complication of

chronic cough is its psycho-social impact [8]. Indeed, quality of life is altered because of the difficulties encountered in performing routine activities of daily living by individuals whose medical condition is audibly noticeable [9]. Patients with refractory chronic cough no longer attend public places or meet up with family and friends, etc. They also suffer from physical complications of chronic cough with cough syncope, abdominal wall hernias, incontinence urinary, etc. However, despite progress in understanding neurological dysfunction in refractory chronic cough, the underlying mechanism of this entity has not been fully elucidated to date. Over the past decade, the concept of cough hypersensitivity syndrome has emerged in a bid to explain that cough reflex sensitivity increases in some patients [10]. Although this concept is not fully understood in humans, it is useful in managing patients with chronic cough and refractory chronic cough. Indeed, it has now been established that neuromodulators should be used in a refractory chronic cough context [1, 11]. Amitriptyline, pregabalin/gabapentin and morphine have proven efficacy in managing cough severity or frequency in studies with a small sample size [12–15]. Although these drugs have been found to be helpful in some patients in clinical practice, their benefit/risk balance needs to be considered given the side effects of these neuromodulators (mainly drowsiness). New therapeutic options are urgently needed. Recent data on the role of cough receptors provided an opportunity to develop new effective treatments in refractory chronic cough. The effects of drugs targeting cough receptors will be discussed in this paper.

2 Cough Hypersensitivity

Patients with chronic cough present with a hypersensitivity disorder in which they cough readily to low-level stimuli which normally do not cause coughing in healthy individuals [10, 16, 17]. It is now well established that hypertussia and allotussia are considered common characteristics of cough hypersensitivity. Hypertussia and allotussia refer to abnormal excessive coughing in response to airway irritation and coughing in response to stimuli not normally provoking cough, respectively. Clinically, the urge-to-cough, usually seen in cough hypersensitivity, presents as laryngeal irritation, often described as a persistent tickle, itch or globus sensation located in the throat and because of the unpleasantness of this sensation, and the hypersensitivity of the neural pathways involved, the urge-to-cough proves to be an important contributing component to the overall morbidity burden of chronic cough. Indeed, patients frequently perform volitional coughing or throat clearing manoeuvres in an attempt to relieve their urge-to-cough, in much the same way that scratching is performed in an attempt to satiate an itch [10]. As such, the presentation of chronic cough hypersensitivity can be a mixture of troublesome reflex and volitional coughing or throat clearing, accompanied by comorbid anxiety or depression due to the cognitive impacts of the persistent urge-to-cough and unabating nature of the problem. Clinical management is further complicated because recent studies have identified problems with behavioural suppression of cough in patients with chronic cough [18–20], suggesting that therapies that simply target the cough sensory nerves in the airways may not be sufficient to adequately control chronic cough. This complexity is reflected in the combinatorial pharmacological and behavioural therapeutic approaches now commonly used in chronic cough management programmes, and the renewed interest in centrally acting cough suppressants.

3 Cough Receptors: The Start of the Troubles

The neurobiology of cough has been reviewed in detail elsewhere [10, 21]. The airways receive dense sensory nerve fibre innervation from the vagus nerves. Subsets of these sensory nerve fibres are equipped with receptors and ion channels that allow for the detection of a range of potentially irritating stimuli, which can be present in the airways in the form of either physical (particulates, mucus, or other stimuli that distort the airway wall), chemical (inhaled, aspirated or locally produced chemicals, including inflammatory mediators or changes in local tissue osmolarity) or thermal (typically cold) irritants. Two complimentary vagal sensory nerve pathways monitor the airways for these stimuli (Fig. 1). One type (termed C-fibres) is more specialised in responding to chemical and thermal stimuli and these are distributed extensively in the mucosa at all airway levels and in the lung parenchyma. The other type (termed the A-delta [δ] fibres) is more specialised for responding to physical stimuli and these are mostly restricted to the large airways (larynx, trachea and main bronchi) [22, 23]. When activated, both vagal cough fibre subtypes can trigger reflex coughing via inputs to the brainstem respiratory centres, temporarily reconfiguring normal breathing patterns into a cough respiratory pattern [24]. In addition, cough-related vagal sensory inputs to the brainstem can ascend to the higher brain where they encode for conscious perceptions of airway irritation, often referred to as the urge-to-cough [25–27]. Higher brain processing also produces cognitive and affective (emotional) dimensions of coughing [14, 28].

The molecular basis for cough sensory neuron activation in the airways has been studied extensively, mostly using in vivo or in vitro preclinical animal systems [29]. The conversion of an airway stimulus into sensory nerve activation and signal propagation involves two steps: stimulus transduction and action potential conduction (Fig. 1). The transduction of a stimulus into electrochemical activity in

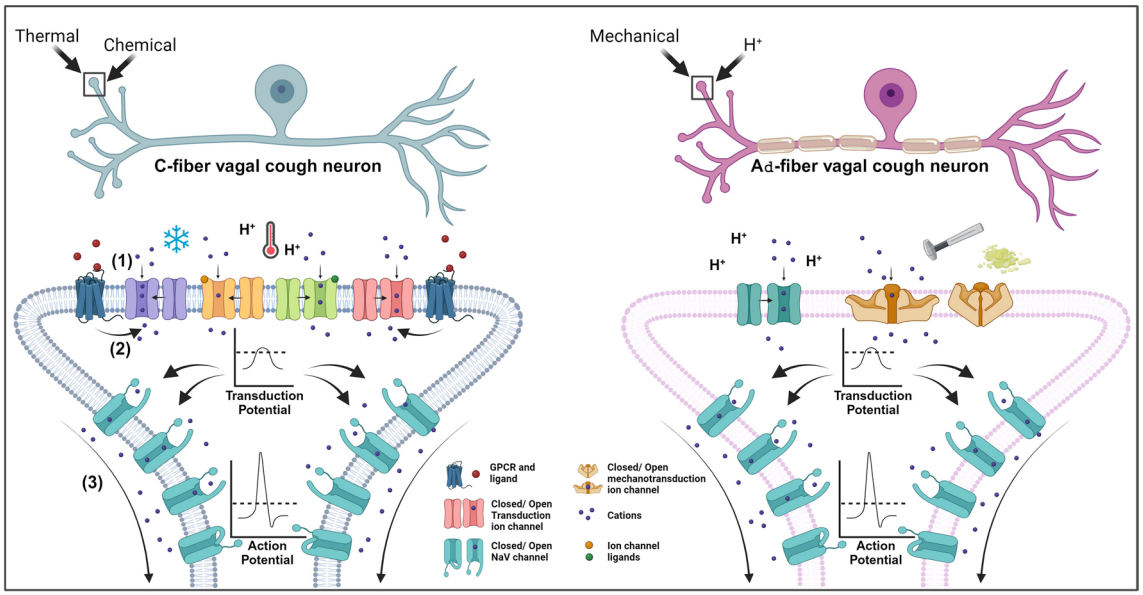

Fig. 1 Two classes of vagal cough-evoking sensory neurons. C-fibres are responsive to a wide range of chemical and thermal stimuli, whereas Aδ-fibres have a more restricted sensitivity to mechanical (e.g., mucus or particulate matter) and acidic stimuli. Modality responsivity is dependent on the expression of stimulus-specific G protein-coupled receptors (GPCRs) and ion channels by sensory nerve terminals in the airway wall. Activation of these receptors and channels leads to ionic influx into the nerve terminal and the generation of a transduction potential (graphs). If the transduction potential reaches threshold (dotted lines) then voltage gated sodium channels (NaVs) open and action potential waves propagate centrally to evoke coughing. Strategies for preventing cough sensory neuron activity include: (1) directly blocking transduction receptor/channel activation; (2) blocking intracellular signalling coupling GPCRs with ion channel activation; or (3) blocking NaV-dependent action potential firing

cough sensory nerve terminals relies on the sensory nerve expression of a wide variety of G-protein-coupled receptors (GPCRs) and ion channels that are specific for different stimulus modalities (physical, chemical and thermal) (Table 1). Stimulus induced activation of these receptors and channels leads to localised ionic currents across the sensory nerve terminal membrane. For example, C-fibre cough nerve terminals express Transient Receptor Potential Vanilloid 1 (TRPV1) ion channels, sensitive to the irritant chemical capsaicin, low threshold noxious thermal (40–50 °C) heat and acidic stimuli (protons), and when activated, the opening of the channel allows for sodium and calcium ion entry into the nerve terminal and the generation of a localised transduction current [30, 31]. If transduction currents are of sufficient magnitude to subsequently open nerve terminal voltage gated sodium channels, then sensory nerve action potential conduction may be achieved [32]. As action potential initiation is an 'all or nothing' phenomenon, when elicited, a wave of voltage gated sodium channel activation along the sensory axon propagates the action potential centrally. G-protein-coupled receptor activation does not directly result in transduction currents as GPCRs themselves cannot directly facilitate ion movement across the membrane. Instead, GPCRs gate a range of local ion channels through intracellular second messenger signalling, which in turn allow for the ionic events to occur [33, 34]. Thus, a number of potential sensory nerve fibre targets for therapeutic intervention exist, including drugs that prevent GPCR binding or intracellular signalling, transduction channel activation, or action potential propagation [30] (Fig. 1).

Because cough is a vital protective reflex that serves to clear and protect the airways, it may be undesirable to therapeutically target mechanisms that render cough sensory nerve fibres unresponsive to natural stimuli. Instead, targeting the underlying causes of cough hypersensitivity may be more desirable. However, the molecular mechanisms that lead to chronic cough hypersensitivity have not been fully elucidated. Studies in animals highlight the potential for vagal sensory nerve fibres to become hypersensitive on the background or airway inflammation [10, 29]. Vagal sensory nerve fibres express a range of receptors for prostaglandins, cytokines and inflammatory alarmins. If activated by their cognate inflammatory ligand, signalling via these receptors can lead to the direct activation of sensory nerve fibres or render them more sensitive to concomitant stimuli through alternate signalling mechanisms. A stereotypical example of this is the prostaglandin PGE2, which via binding to C-fibre sensory nerve EP GPCRs, lowers the threshold for stimuli to then activate alternate ion channels, including TRPV1 [35]. Furthermore, TRPV1 expression was shown to be increased in airway biopsy samples from chronic cough patients [36]. This can manifest as a shift in the thermal sensitivity of

Table 1 Common receptors and ion channels expressed by vagal C and Aδ-fibres involved in cough

Receptor/channel	Ligand/stimulus	Fibre type
Adenosine A2 receptors (A2a/A2b)	Adenosine	C
Acid sensing ion channel (ASICs)	Protons	C and Ad
Bradykinin 2 receptor (B2)	Bradykinin	C
Cysteinyl leukotriene 1 receptor (Cys-LT1R)	Leukotriene D4/C4	C
Interferon receptor (IFNAR1, IFGR2)	Alpha, beta and gamma interferons	C
Nicotinic acetylcholine receptor (a3b4 nAChR)	Nicotine, acetylcholine	C
Prostaglandin D2 receptor (DP1R)	Prostaglandin D2	C
Prostaglandin E2 receptor (EP3R)	Prostaglandin E2	C
Purinergic 2X3 homotrimeric channel (P2X3)	ATP	C
Purinergic 2X2/3 heterotrimeric channel (P2X2/3)	ATP	C
Tumour necrosis factor receptor (TNFRs)	Tumour necrosis factor alpha (TNFα)	C
Transient Receptor Potential A1 channel (TRPA1)	Mustard oil, acrolein, gingerol cinnamaldehyde, cold	C
Transient Receptor Potential V1 channel (TRPV1)	Capsaicin, protons, heat	C
Transient Receptor Potential M8 channel (TRPM8)	Menthol, cooling	C
Voltage-gated sodium channel 1.7 (NaV1.7)	Voltage	C and Ad
Voltage-gated sodium channel 1.8 (NaV1.8)	Voltage	C
Voltage-gated sodium channel 1.9 (NaV1.9)	Voltage	C and Ad
Unknown	Mechanical	Ad

TRPV1, rendering the channel responsive to non-noxious heat and increasing the likelihood of channel opening, even at physiological temperatures [37]. However, whether TRPV1 signalling is a major components of chronic cough hypersensitivity in humans is questionable [38].

Instead, clinical studies in humans have identified one potential mechanism of chronic cough hypersensitivity involving the purine adenosine triphosphate (ATP), which is proving therapeutically promising [39, 40]. The mechanisms underpinning ATP release have not yet been fully defined in chronic cough. However, ATP is believed to serve as an inflammatory alarmin, released from injured or activated airway epithelia, and airway C-fibres are responsive to extracellular ATP via their expression of P2X2/3 heterotrimeric or P2X3 homotrimeric purinergic receptors. Accordingly, as discussed below, Phase 2 and 3 trials with P2X3 receptor antagonists have proved clinically beneficial in some patients with refractory chronic cough. The extent to which ATP is involved in chronic cough associated with common diseases, such as gastroesophageal reflux disease (GERD), asthma or rhinosinusitis is not known. Nevertheless, as treatment dedicated to these diseases may not completely assuage cough hypersensitivity, there is a rationale to consider a trial of drugs that act on the ATP pathway in these patients.

Increased cough receptor input to the central nervous system is believed to underlie chronic cough. Although the central neural circuits mediating cough and related sensations have been described in reasonable detail, knowledge of the pharmacology of transmission along these circuits is rudimentary as are the specific processes that contribute altered central neural transmission. Neuropeptides, (e.g., substance P, glutamate, gamma aminobutyric acid (GABA), opioids and other neurotransmitters are likely involved at different central locations, and this has formed the rationale for clinical trials of drugs targeting their receptors.

4 Targeted Therapies in Refractory Chronic Cough: Pharmacological Data

Recent research in the treatment of chronic cough has highlighted a surge in drug development, featuring molecules displaying activity in both the central and/or peripheral nervous systems [41]. The presumed benefit of historical drugs, such as opioids (morphine, codeine), neuromodulators (pregabalin, gabapentin) or antidepressants (amitriptyline), has been observed in small sample size cohort studies, casting doubt on the real-world benefit/risk balance and highlighting the need for new pharmacological targets. The latest drugs under development fall into two broad categories of ligands—those influencing peptidergic neurotransmission and those targeting ion channels.

4.1 Molecular Targets of New Antitussive Drugs

4.1.1 Peptidergic Neurotransmission

Attempts have been made to repurpose existing licensed medicines using octreotide, a synthetic octapeptide agonist

of somatostatin receptors. Octreotide can assist in restoring normal gastrointestinal activity, which may be impaired in patients with refractory chronic cough. Oesophageal dysmotility is common in patients with chronic cough [42]. This is an oesophageal smooth-muscle disorder leading to peristaltic dysfunction. It has been shown that long breaks in oesophageal peristaltic integrity are associated with cough and lead to suboptimal benefit from anti-reflux therapy [43].

Octreotide has to be administered via subcutaneous injections and is frequently responsible for gastrointestinal adverse events [44]. Another pathway under investigation is the tachykinin system, which involves a group of neuropeptides including substance P, neurokinin A and neurokinin B, which play crucial roles in neurotransmission. These peptides interact with specific G protein-coupled receptors known as tachykinin receptors. There are three main types of tachykinin receptors, namely NK_1, NK_2 and NK_3, which selectively bind to different tachykinins. NK_1 receptor activation is involved in cough. Aprepitant, a NK_1 receptor antagonist currently approved for chemotherapy-induced nausea and vomiting, showed interesting results in cancer-related cough [45]. Other NK_1 receptor antagonists have been under investigation for the treatment of refractory chronic cough in Phase II clinical trials. Orvepitant, a centrally acting NK1 antagonist developed as an antidepressant (Nerre Therapeutics Ltd.), showed promising results in 13 patients taking part in the VOLCANO-1 study [46]. In this study, a statistically and clinically significant improvement in objective daytime cough frequency was observed at Week 4 with orvepitant compared to placebo. A statistical and clinical improvement in cough severity was also documented based on the visual analogue scale (VAS) score. Interestingly, the effect was sustained at 8 weeks despite treatment discontinuation at Week 4. Serlopitant (Vyne Therapeutics Inc.) has failed to demonstrate any benefit (NCT03282591) [47].

4.1.2 Ion Channels

The family of ion channels is extensive, encompassing both voltage-gated (e.g. voltage-gated sodium channels) and ligand-gated (e.g., nicotinic, transient receptor potential receptors, or purinergic P2X receptors) ion channels.

Voltage-dependent sodium channels Voltage-dependent sodium channels play a crucial role in the generation and propagation of electrical signals in excitable cells and may be implicated in sensory nerves excitability associated with chronic cough. There are nine known subtypes of voltage-gated sodium channels in mammals, classified as Nav1.1 to Nav1.9. Ongoing research aims to unravel the specific mechanisms linking voltage-gated sodium channels to chronic cough, as with lidocaine, a non-selective inhibitor used as a local anaesthetic agent. The beneficial effects of lidocaine on 10-h cough frequency, when applied as a buccal spray, suggest a role in inhibiting voltage-gated sodium channels in sensory oropharyngeal fibres for refractory chronic cough [48]. GSK2339345, a voltage-gated sodium channels inhibitor, had no anti-tussive effect in patients with refractory chronic cough [49]. Other sodium channel inhibitors are currently undergoing Phase II clinical trials in refractory chronic cough, such as NTX-1175 (Nocion Therapeutics, NCT05628740), delivered as a dry powder to the airways.

Nicotinic α_7 acetylcholine receptors While nicotinic receptors are primarily associated with synaptic transmission in the central nervous system, their role in chronic cough involves a combination of central effects and the modulation of sensory nerve excitability in the respiratory tract through α7 nAChRs expressed on sensory nerve fibres in the airways. Modulating the activity of these receptors was explored as a strategy to alleviate chronic cough symptoms using the agonist bradanicline, but no significant response was obtained [50].

Transient receptor potential (TRP) channels Transient receptor potential (TRP) channels are a diverse family of ion channels found in cell membranes, playing a crucial role in sensory perception and cellular signalling. The main subtypes include TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPA (ankyrin) and TRPML (mucolipin), each with distinct functions and sensitivities to various stimuli such as temperature, pressure and chemicals. Given that high TRPV1 expression was found in the bronchial mucosa of patients with refractory chronic cough, antagonists of TRPV1 were developed in those patients [36]. However, the results of clinical studies with inhibitors of TRPV1 channels (SB-705498, GlaxoSmithKline; XEN-D0501, Pila Pharma); TRPA1 (GRC-17536, Glenmark Pharmaceuticals Ltd); or TRPV4 (GSK2798745, GlaxoSmithKline) have not corroborated the findings of preclinical studies [51]. They failed to demonstrate a benefit in Phase II trials showing either adverse effects or lack of efficacy (Table 2). Although no improvement in 24-h objective cough frequency was observed with the TRPV1 antagonist (SB-705498) (600 mg) compared to placebo, a significant improvement in cough reflex sensitivity to capsaicin was noted 2 h and 24 h after a single dose of this compound [51]. XEN-D0501, another TRPV1 antagonist, is 1000-fold more potent than SB-705498 at inhibiting capsaicin-induced depolarisation of guinea pig and human isolated vagus nerve [38]. Despite this and although XEN-D0501 significantly reduced maximal cough responses to capsaicin, no effect on spontaneous awake cough frequency was observed [38]. These data demonstrate that TRPV1 cannot be considered as a potential

Table 2 Summary of clinical trial with compounds targeting cough receptors in patients with refractory chronic cough

Study	Number of patients	Inclusion criteria	Product	Design	Duration	Results
P2X3 antagonists						
Gefapixant						
Abdulqawi et al. [66]	$n = 34$	Chronic cough (≥8 weeks)	Gefapixant/AF-219 600 mg bid or placebo	Phase 2a	2 weeks	Compared to placebo: cough frequency was reduced by 75%
Smith et al. [67]	$n = 59$	Chronic cough (≥1 year), exclusion of potential underlying causes, VAS ≥40 mm	Gefapixant: ascending doses (7.5–200 mg) or placebo	Phase 2a	16 days	Gefapixant doses ≥30 mg produced maximal improvements in cough frequency compared with placebo
Smith et al. [68]	$n = 253$	Refractory or unexplained chronic cough lasting 1 year or longer, VAS 40 mm or higher	Gefapixant (7.5 mg, 20 mg or 50 mg) bid or placebo	Phase 2b	12 weeks	Gefapixant 50 mg (significant relative change −37.0%) Gefapixant 7.5 mg and 20 mg (non-significant relative change −22.0% and −22.2%)
Morice et al. [69]	$n = 36$	Refractory or unexplained chronic cough lasting 1 year or longer or healthy volunteer	Gefapixant (100 mg/day) or placebo	Phase 2	1 day	C2 and C5 increase in the concentration of ATP and distilled water with gefapixant.
Mc Gravey et al. [70]	$n = 732$ in COUGH-1 and 1317 in COUGH-2	Refractory or unexplained chronic cough lasting 1 year or longer, VAS 40 mm or higher	Gefapixant 15 mg or 45 mg bid or placebo	Phase 3	12 weeks and 24 weeks	Only gefapixant 45 mg bid showed significant reductions in 24-h cough frequency compared with placebo
Mc Gravey et al. [73]	$n = 415$	Refractory or unexplained chronic cough with cough onset less than 1 year, VAS 40 mm or higher	Gefapixant 45 mg bid or placebo	Phase 3	12 weeks	Significant improvement of LCQ score with gefapixant compared with placebo
Sivopixant						
Niimi et al. [77]	$n = 31$	RCC for ≥6 months, VAS ≥40 mm and an average subjective cough frequency while awake of ≥10 h−1 during the previous 24 h for ≥70% of the days during the screening period	Sivopixant 150 mg qd	Phase 2a	2 weeks	Sivopixant 150 mg qd decreased cough frequency during daytime (primary end-point) and over 24 h (secondary end-point) by −31.6% ($p = 0.0546$) and −30.9% ($p = 0.0386$)
Mc Garvey et al. [78]	$n = 400$	RCC/UCC for ≥ 1 year, VAS score ≥ 40 mm and ≥ 10 coughs/h on the 24-h cough count recording	Sivopixant 50, 150, or 300 mg or placebo qd	Phase 2b	4 weeks	No statistical differences in terms of 24-h cough frequency change between baseline and 4-week visit
Eliapixant						
Morice et al. [83]	$n = 37$	RCC for ≥ 1 year, VAS ≥ 40 mm	Eliapixant 50, 200 and 750 mg bid 1 week each or placebo	Phase 2a	3 weeks	Eliapixant significantly reduced cough frequency and cough severity at doses ≥50 mg
Dicpinigaitis et al. [84]	$n = 310$	RCC for ≥ 1 year, VAS ≥ 40 mm	Eliapixant 25, 75 and 150 mg bid or placebo	Phase 2b	12 weeks	A statistically significant dose–response signal was detected with eliapixant for change from baseline in 24-h cough count at Week 12

Table 2 (continued)

Study	Number of patients	Inclusion criteria	Product	Design	Duration	Results
Camlipixant						
Birring et al. [75]	$n = 249$	RCC for ≥ 1 year, VAS ≥ 40 mm and a baseline awake cough frequency ≥ 25 coughs/h	Camlipixant (12.5, 50 and 200 mg bid) or placebo	Phase 2b	4 weeks	Reductions in 24-h cough frequency over placebo at 28 days of − 21.1%, $p = 0.098$, − 34.4%, $p = 0.003$ and − 34.2%, $p = 0.005$, at 12.5, 50, and 200 mg bid, respectively
Filapixant						
Friedrich et al. [86]	$n = 23$	24-h cough frequency on Day 4	Ascending doses of filapixant (20, 80, 150, and 250 mg, bid, 4-days-on/3-days-off) or placebo (cross-over)	Phase 2b	4 days each group	Reductions in 24-h cough frequency over placebo ranged from 17% (80 mg dose) to 37% (250 mg dose)
Transient receptor potential vanilloid 1 (TRPV1)						
Khlaid et al. [51]	$n = 21$	RCC for ≥ 8 weeks and C5>250 mM after capsaicin challenge test	SB-705498 600 mg or placebo	Phase 2a	24 h	No improvement of 24-h objective cough frequency compared with placebo
Belvisi et al. [38]	$n = 20$	RCC with an awake cough frequency of more than 1.5 coughs/h and a maximal capsaicin cough response over four inhalations (E_{max}) of more than 10 coughs	XEN-D0501 or placebo	Phase 2a	2 weeks	No effect on spontaneous awake cough frequency
TRPM8						
Birring et al. [53]	$n = 51$	RCC/UCC diagnosis ≥ 1year, cough severity VAS score ≥ 40 mm and 24-h cough frequency ≥ 10 coughs/h	AX-8 40 mg 2 doses or placebo	Phase 2a	8 h	Reduction of cough frequency within 15 min, and more than placebo over 2 h and 4 h
Neurokinin 1						
Smith et al. [46]	$n = 13$	RCC with daytime cough frequency >3 to <250 coughs/h	Orvepitant 30 mg/d for 4 weeks	Phase 2a	4 weeks	Statistically and clinically significant improvement in objective daytime cough frequency at Week 4
$GABA_B$ receptor agonist						
Badri et al. [87]	$n = 22$	RCC	Lesogaberan 120 mg bid or placebo	Phase 2a	2 weeks	Improvement of cough hypersensitivity and the number of bouts of coughing with lesogaberan, but not coughs per/h
Voltage-dependent sodium channel antagonists						
Abdulqawi et al. [48]	$n = 26$	RCC	Nebulised lidocaine or lidocaine delivered by a throat spray and matched placebo	Phase 2a		Lidocaine throat spray was effective in reducing cough frequency in patients with RCC but not nebulized lidocaine

Table 2 (continued)

Study	Number of patients	Inclusion criteria	Product	Design	Duration	Results
Smith et al. [49]	$n = 16$	RCC	GSK2339345 or placebo 2 inhaled doses 4-h apart	Phase 2a	4 h	8-h cough counts increased following GSK2339345 treatment compared with placebo

C5 concentration of capsaicin inducing at least 5 coughs, *RCC* refractory chronic cough, *VAS* visual analogue scale

target for the treatment of chronic cough. Hence, although promising in preclinical studies, the clinical development of TRPV1 and TRPA1 channel antagonists has been unsuccessful due to lack of efficacy and the occurrence of adverse effects in both cases, thus demonstrating that TRPV1 cannot be considered a potential target for the treatment of chronic cough. This is probably due to distinct physiological and pathological cough reflex pathways [52] as well as more complex pathophysiological mechanisms of chemically induced cough (with capsaicin or citric acid) in humans than those observed in animal models. Moreover, TRP channels are involved in multiple physiological processes, such as thermoregulation and sensory perception, and targeting them may lead to off-target effects, including thermohypoesthesia, dysgeusia and changes in body temperature sensation observed in patients from Phase II studies [38]. Nonetheless, a recent, orally administered TRPA1 inhibitor, GDC-6599 (Genentech, Inc.), is currently at the Phase II clinical trial stage for chronic cough (NCT05660850). Preclinical studies and a Phase I trial have indicated that it is well tolerated, marking a departure from previous molecules in this regard. Similarly, AX-8, a TRPM8 receptor inhibitor (primarily known for their role in sensing cold temperatures and responding to cooling agents, such as menthol) has shown promising results in a Phase II trial [53]. In this study, two doses of AX-8 (40 mg orally dispersible tablet) or placebo were administered 8 h apart. Although the primary endpoint (8-h cough frequency on Day 1) was not met, AX-8 reduced cough frequency within 15 min, and more than placebo over 2 h and 4 h.

ATP-dependent purinergic receptors Purinergic receptors are membrane proteins with the ability to recognise extracellular nucleotides. Two distinct families of purinergic receptors have been identified, namely the ligand-gated P2X receptor ion channels and the G protein-coupled P2Y receptors. There are seven subtypes of P2X receptors, P_2X_1–P_2X_7, which are all non-selective cation channels, allowing the passage of Na^+ and Ca^{2+}, and are triggered by ATP. P2X receptors are expressed in a wide range of cells where they play a role in regulating processes such as platelet activation, smooth-muscle contraction, synaptic transmission, nociception, inflammation, hearing, taste and cough [54]. Given their involvement in these diverse physiological functions, P2X receptors have become significant targets for pharmacological interventions. These drugs act on cough hypersensitivity with no impact on the protective property of the cough reflex. In addition to the primary orthosteric binding site for ATP, these receptors possess supplementary allosteric sites where the effects of the agonist can be influenced or modulated by other agents, known as allosteric modulators [55]. The P_2X_3 receptor has thus emerged as a potential therapeutic target for refractory chronic cough and numerous P2X3 inhibitors have been recently developed (Table 3).

Their international non-proprietary name ends with the suffix-pixant, and they include gefapixant, sivopixant, eliapixant, filapixant and camlipixant, some of which are described as negative allosteric modulators [55–57]. However, their binding affinity to heterotrimer P2X3/3, mainly expressed in gustatory tissue, drive the onset of adverse events related to taste disturbance. Drugs demonstrating high affinity for the P2X3 homotrimer and lower affinity for the P2X2/3 heterotrimer show potential, making the relative affinity for receptor subtypes a key determinant in their action. Results of Phase II or Phase III trials are presented below. Other new P2X3 antagonists are being developed and are currently at the preclinical or early clinical study stage. These include the allosteric modulator, PSFL2915 [58], the water-soluble small molecule, DT-0111, a simple ATP analogue but without P2X3/P2X2/3 receptor selectivity [59], or HRS-2261 (Guangdong Hengrui Pharmaceutical Co., Ltd.), now being trialled in a Phase II study (NCT05733533) in the wake of encouraging results in the Phase I study [60].

Gefapixant Pharmacokinetic data: Gefapixant is a first-in-class oral P2X3 receptor antagonist. The formulation of gefapixant has evolved during different clinical trial phases and the results of available studies show improvements in pharmacokinetic properties following formulation changes. In early-phase studies, the free base form used exhibited significantly altered absorption in the presence of food and variations in gastric pH, with exposure increasing twofold in the fed state and decreasing by a factor of 2–7 when administered concomitantly with omeprazole. For Phase II trials, anhydrous citric acid was added during the formulation to neutralise the effect of food or proton pump inhibitor (PPI) administration (exposure variations < 1.5-fold). Gefapixant citrate salt therefore replaced the free base as the pharmaceutical active substance in subsequent formulations, i.e., those used in Phase III trials and for the commercial forms of the drug, with minor changes in excipients between these last two stages. Ultimately, the commercial form exhibits no food- or PPI-related effects on drug absorption, with peak concentrations being reached within 1.8–2.0 h with oral bioavailability of at least 78% [61, 62]. Gefapixant demonstrates low plasma protein binding (55%) and limited central nervous system penetration. It undergoes minimal hepatic metabolism (< 14%), resulting in unchanged gefapixant being the predominant circulating form in plasma. The primary pathway for the elimination of gefapixant is via renal excretion, which encompasses both passive renal filtration and active transport mechanisms [62, 63]. Population pharmacokinetic studies conducted with this molecule, primarily using data from Phase III trials, show the effects of body weight, age, and sex on distribution and elimination parameters, as well as the impact of renal function on drug elimination [64], which was confirmed in a dedicated study [65]. Thus, the elimination half-life of 8.4 h in patients with normal renal function increases to 15.1 h in those with severe renal impairment, justifying dose adjustment with daily doses being halved in this patient population (once-daily instead of twice-daily dosing) [64].

Clinical trial data: In a Phase 2a trial, oral gefapixant was administered at a twice-daily dose of 600 mg [66]. At Week 2, the mean daytime cough frequency was reduced by 75% (95% CI 50–88) in the primary analysis ($p = 0.0003$) and 84% (60–94) in the per-protocol analysis ($p = 0.0005$), both being adjusted for placebo. Daytime and night-time cough severity VAS scores also improved with gefapixant compared to placebo. Six patients of 12 discontinued gefapixant due to taste disturbances (hypogeusia or dysgeusia). A dose-escalation study was also performed in order to better characterise the efficacy/safety profile [67]. In 2 cross-over double-blind controlled trials, gefapixant was administered orally in ascending doses (study 1: 50–200 mg, study 2: 7.5–50 mg) for 16 days. Awake cough frequency was significantly reduced with a dose of 50-mg twice daily (bid) or higher and 15-mg bid or higher compared to placebo, in studies 1 and 2, respectively. A maximal effect on awake

Table 3 P2X3 antagonists in development (clinical development was stopped for some of them)

Drug	Assay	IC_{50} P_2X_3 (nM)	IC_{50} $P_2X_{2/3}$ (nM)	References
Gefapixant	Rat & human P2X3 & P2X2/3 receptors, calcium flux & voltage-clamp assays Receptors expressed in 1321N1 cells, inhibition of α,β-methylene ATP-evoked currents	30 153	100–250 220	[56, 89–91]
Sivopixant	Receptors expressed in C6BU-1 cells, inhibition of ATP-induced (P2X3) or α,β-methylene ATP-induced (P2X2/3) calcium flux	4.2	1100	[92]
Eliapixant	Receptors expressed in 1321N1 cell lines, α,β-meATP-induced calcium flux Whole cell patch-clamp electrophysiological assay, α,β-meATP	8 10	163 129	[93]
Filapixant	Human receptors, inhibition of α,β-methylene ATP-induced calcium flux	7	760	[94, 95]
Camlipixant	Human receptors expressed in HEK293 cells, inhibition of α,β-methylene ATP-induced calcium flux	25	> 24,000	[96]
PSFL2915	Receptors expressed in HEK293T cells, voltage-clamp fluorometry	319	261	[58]

ATP adenosine triphosphate, *IC_{50}* half-maximal inhibitory concentration

cough frequency was observed with a dose of 30 mg or 50 mg bid or higher compared to placebo, in studies 1 and 2, respectively. Similar results were documented for 24-h cough frequency. Interestingly, the cough severity VAS score improved significantly compared to placebo at a dose level of 100 mg bid in study 1. However, an improvement in the cough severity VAS score was observed with a dose of 30 mg bid in study 2. Taste disturbances were dose related, occurring at the highest doses (150 and 200 mg) in the majority of patients, and substantially reducing in study 2. A higher incidence of albeit insignificant antitussive effects was documented in patients with taste disturbances.

In a Phase 2b trial, the efficacy of placebo or gefapixant (7.5 mg, 20 mg or 50 mg twice daily) on wake cough frequency was analysed after 12 weeks [68]. Only gefapixant 50 mg showed a significant reduction in objective awake cough frequency after 12 weeks compared to placebo (relative change—37.0%). The percentage reductions from baseline in objective awake cough frequency after 12 weeks for the 7.5-mg and 20-mg doses of gefapixant were greater than those noted with placebo but the difference was not significant (− 22.0% and − 22.2% compared to placebo, respectively). Adverse events involving taste were dose related and observed in up to 81% of patients receiving the 50-mg dose. However, this adverse event rarely led to treatment discontinuation in this study. Interestingly, the effect of gefapixant on cough sensitivity was assessed using different challenge tests [69]. Healthy volunteers or refractory chronic cough patients were treated with 100 mg/day of gefapixant or placebo. Challenge tests with ATP, citric acid, capsaicin and distilled water were performed 1, 3 and 5 h post-dose. The primary endpoint was the lowest concentration of inhaled solution required to trigger ≥ 2 coughs (C2) or ≥ 5 coughs (C5). Gefapixant was associated with an increase in the concentration of ATP and distilled water required to induce C2 and C5 in both healthy volunteers and refractory chronic cough patients compared to placebo. Capsaicin and citric acid concentrations did not increase with gefapixant for C2 and C5 in either healthy volunteers or refractory chronic cough patients. These results are not fully understood. However, it is speculated that the TRPV4/ATP pathway, which is responsible for cough hypersensitivity, could be targeted by gefapixant. The usefulness of the ATP or distilled water test as a gefapixant response marker requires further investigation.

Following these promising results, two large, randomised controlled trials (COUGH 1 and COUGH 2) were conducted in refractory chronic cough patients with cough lasting for more than 1 year [70]. In total, 732 patients were enrolled in the COUGH-1 study and 1317 for COUGH-2. Patients were randomised to receive placebo, gefapixant 15 mg bid, or gefapixant 45 mg bid. The primary efficacy outcomes were 24-h cough frequency assessed by the cough monitor, Vitalojak, through Week 12 in COUGH 1 and Week 24 in COUGH 2. Gefapixant 45 mg bid showed significant reductions in 24-h cough frequency compared to placebo at Week 12 in COUGH-1 (18.5% [95% CI 32.9–0.9]) and at Week 24 in COUGH-2 (14.6% [26.1–1.4]). A significant improvement in quality of life (LCQ score) was also observed with gefapixant 45 mg compared to placebo. Taste-related adverse events were observed in 59.3% and 68.9% of cases in COUGH-1 and COUGH-2 trials, respectively. It is interesting to note that taste-related adverse events were mild to moderate in most cases and treatment discontinuation in a small proportion of patients led to taste improvement within several days. Interestingly, in a post hoc analysis, gefapixant was significantly effective only in North America and Europe [70]. A better effectiveness of gefapixant in a specific genetic pattern has never been studied. However, a recent study showed that repeat expansion of the RFC1 gene is particularly common in refractory chronic cough [71], but the world-wide distribution of this genetic disorder is still unknown. Specific data on the effectiveness of gefapixant in patients with repeat expansion of the RFC1 gene are needed.

In a post hoc analysis, highest cough frequency (≥ 20/h), a more severe cough (VAS score ≥ 60 mm) and longer cough duration (≥ 10 years) were associated with a greater response to gefapixant [72]. Gefapixant was also studied in recent-onset chronic cough [73]. A statistically significant treatment difference of 0.75 point (MCID 1.3) in favour of gefapixant versus placebo was observed in terms of change from baseline LCQ to total score at Week 12. A recent study showed that gefapixant had no effect on cough in patients with idiopathic pulmonary fibrosis (IPF) [74]. In 2022, gefapixant was approved under the brand name, Lyfnua, in Japan and Switzerland for the treatment of adults with refractory or unexplained chronic cough. More recently, it was approved by European Medical Agency (EMA) for Europe. The US Food and Drug Administration (FDA) Commission in charge of gefapixant approval deemed that the available data were inadequate to establish the efficacy of gefapixant—hence the application for gefapixant approval was rejected by the FDA. The FDA expressed concerns about the clinical benefit of the drug. Following a validation study of the cough monitor, VitaloJAK, cough frequency was recounted in two pivotal trials. A significant decrease in cough frequency with gefapixant versus placebo was found in only one trial. Concerns were also raised regarding the clinically meaningful improvement with gefapixant. Indeed, gefapixant reduced the number of coughs by one to two per hour in the two trials versus placebo. However, the FDA did not consider this to be a clinically meaningful improvement. Moreover, a large placebo effect was observed in both trials. Compared to a treatment effect that is not deemed clinically meaningful, this large placebo effect was another argument against the approval of gefapixant.

Camlipixant: Camlipixant is still under development. In the Phase 2b trial conducted in 249 refractory chronic cough patients with a baseline awake cough frequency ≥ 25 coughs/h, camlipixant (BLU-5937) reduced 24-h cough frequency after 28 days by −21.1%, $p = 0.098$, −34.4%, $p = 0.003$ and −34.2%, $p = 0.005$, at doses of 12.5, 50, and 200 mg bid, respectively, versus placebo [75]. Similar improvements in awake cough frequency were recorded on Day 28. The efficacy of camlipixant did not depend on taste disturbance [76]. A Phase III trial is ongoing (NCT05599191).

Other P2X3 antagonists Sivopixant: In a Phase 2a trial involving 31 patients with refractory chronic cough, sivopixant 150 mg, administered once daily for 2 weeks, decreased cough frequency by − 31.6% ($p = 0.0546$) and − 30.9% ($p = 0.0386$), during the daytime (primary endpoint) and over 24 h (secondary endpoint), respectively [77]. Mild taste disturbance occurred in two patients (6.5%). In a Phase 2b study, no statistical differences were observed between sivopixant 50, 150, or 300 mg compared to placebo in terms of change in 24-h cough frequency from baseline to the Week 4 visit [78]. Placebo-adjusted changes in hourly cough count over 24 h were 13.17% ($p = 0.3532$), − 1.77% ($p = 0.8935$), and − 12.47% ($p = 0.3241$). Single daily dosing with sivopixant 300 mg significantly reduced cough severity (VAS) compared to placebo (− 6.55 mm). Moreover, 61.3%, 78.3%, 86.8% and 71.4% of patients receiving sivopixant 50, 150, 300 mg, and placebo, respectively, noted an improvement in their cough based on the Patient Global Impression of Change. The percentage of patients reporting an improvement in terms of cough was 14.2% higher with sivopixant 300 mg compared to placebo. Post hoc analysis did not reveal any subgroup effect. SHIONOGI decided not to launch a Phase III trial based on the previous data.

Eliapixant: Pharmacokinetic data are much sparser for other P2X3 antagonists and are limited to eliapixant. Following administration of the oral solution, the peak plasma concentration is reached in 2 h in healthy volunteers with 50% bioavailability unaffected by food [79, 80]. The unchanged form is mainly found in the plasma (73%), and eliapixant is excreted primarily via the faeces (86%) after oxidative metabolism with predominant involvement of CY3A4—a source of potential drug interactions. Urinary excretion of metabolites accounted for 12% with a plasma elimination half-life of 48.3 h [79]. In Phase I and II trials with immediate-release tablets, it took longer to reach peak plasma concentrations (3–4 h) with increased eliapixant exposure if administered concomitantly with food (particularly with a high fat content), or with itraconazole, a known CYP 3A4 inhibitor [81, 82]. Elimination half-lives of 62.7 and 51.8 h were recorded following doses of 200 and 750 mg, respectively, allowing for receptor occupancy > 80% associated with drug efficacy [82].

In a Phase 2a trial, patients with refractory chronic cough for at least 1 year received placebo for 2 weeks followed by eliapixant 10 mg for 1 week or eliapixant 50, 200 and 750 mg twice daily for 1 week per dose level [83]. Eliapixant significantly reduced cough frequency and cough severity at doses ≥ 50 mg. In a Phase 2b trial comparing eliapixant 25, 75 and 150 mg bid with placebo, a statistically significant dose-response signal was detected with eliapixant for change in 24-h cough count between baseline and Week 12 [84]. Changes of 12-, 27- and 18-in terms of 24-h cough count were recorded with eliapixant 25, 75 and 150 mg, respectively, versus placebo at Week 12. Alanine aminotransferase levels exceeded the threefold upper limit of normal in 2 participants receiving eliapixant (75 mg, $n = 1$; 150 mg, $n = 1$). A moderate drug-induced liver injury of hepatocellular origin was diagnosed in the patient receiving eliapixant 150 mg. Bayer discontinued development of eliapixant in February 2022 after concluding that the benefits of the drug did not outweigh the risks in refractory chronic cough [85].

Filapixant: A novel selective P2X3 receptor antagonist, filapixant (BAY1902607) was recently studied in patients with refractory chronic cough [86]. In a double-blind, randomised, placebo-controlled study with a cross-over design, 23 patients were treated with ascending doses of filapixant in one period (20, 80, 150 and 250 mg, bid, 4-days-on/3-days-off) and placebo in the other. The primary efficacy endpoint was the 24-h cough frequency on Day 4 of each dosing step. Reductions in 24-h cough frequency over placebo ranged from 17% (80 mg dose) to 37% (250 mg dose). No further studies are currently scheduled in clinicaltrials.gov.

Other pathways Gamma-aminobutyric acid type B receptors ($GABA_b$ receptors): Gamma-aminobutyric acid type B ($GABA_b$) receptors are G protein-coupled receptors that respond to the neurotransmitter gamma-aminobutyric acid (GABA). Gamma-aminobutyric acid type B receptor activation typically leads to inhibitory effects on neurotransmitter release, including the release of excitatory neurotransmitters. Lesogaberan is a peripherally acting $GABA_b$ agonist featured in a Phase II clinical trial [87]. However, the effect on cough frequency did not differ statistically from placebo.

4.1.3 Others

Other molecular targets of interest are currently being explored in the treatment of refractory chronic cough, and Phase II trial outcomes are expected in the coming months. For example, acloproxalap (ADX-629, Aldeyra Therapeutics), an oral inhibitor of Reactive Aldehydes Species-Pro-inflammatory (RASP), is undergoing evaluation (NCT05392192). Acloproxalap lowers RASP levels, which may be increased in patients with chronic cough

and contribute to inflammation. Glutamate is an excitatory neuromediator gating ionotropic N-Methyl-D-Aspartate (NMDA) channels, which were shown to be involved in the mediation of cough evoked by mechanical stimulation in animal models [88]. Studies with the NMDA antagonists V3381 (Vernalis (R&D) Ltd., NCT01401673) and ifenprodil (Algernon Pharmaceuticals) are currently ongoing. The role of opioid receptors in cough was extensively reported, and recent developments on this pathway include oral nalbuphine (Trevi Therapeutics), which acts as both a kappa opioid receptor agonist and mu opioid receptor antagonist, and may have some pharmacokinetic advantage due to an extended release formulation.

5 Conclusion

The concept of cough hypersensitivity syndrome and greater understanding of chronic cough pathophysiology leads to the development of new drugs in refractory chronic cough. The emerging drugs targeting cough receptors look very promising for the treatment of refractory chronic cough. Effective strategies are urgently needed in this condition since no drugs are currently marketed apart from Japan. Although much work remains to be done in terms of patient selection in order to deliver the right drug to the right patient, the future looks very promising given the number of compounds under development and targeting cough receptors.

Declarations

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Conflict of interest Prof. Guilleminault reports personal fees from Bayer and MSD. He has participated in clinical trials from Bayer and MSD. He also reports grants, personal fees, and non-financial support from AstraZeneca, personal fees and non-financial support from GSK, personal fees and non-financial support from Novartis, personal fees from Chiesi, and personal fees and non-financial support from Sanofi, outside the submitted work. Prof Grassin-Delyle declares personal fees from MSD and grant support from AstraZeneca and Air Liquide, outside of the submitted work. Prof. Mazzone declares honoraria from Merck, NeRRe Therapeutics, Reckitt Benckiser, Chiesi and Bellus Health and grant support from Merck, Reckitt Benkiser and Bellus Health, outside of the submitted work.

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Author contributions Laurent Guilleminault was in charge of manuscript design. Laurent Guilleminault has written the introduction and conclusion. Stuart Mazzone has written the section on cough receptors. Stanislas Grassin-Delyle and Laurent Guilleminault has written the section on drugs. All the authors have validated the final version of the manuscript.

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