Chapter 7. Pharmacological management of cough

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Abstract

The pharmacological management of chronic cough as a largely stagnated for the past 40 years. Drug development in acute cough has also been hampered because, despite the burgeoning market in over-the-counter remedies the drugs used are generic and so any claims of efficacy made can be utilised by competitor products. Thus there has been a paucity of high-quality trials due to lack of investment. Small trials of centrally acting neuromodulators such as low-dose opiates and gabapentin have demonstrated some efficacy. Drugs acting on the aetiological factors for chronic cough such as montelukast for eosinophilic bronchitis and azithromycin for oesophageal dysmotility have also demonstrated some efficacy in these phenotypes of chronic cough. However there is still no licensed meditation for the indication of refractory chronic cough.

It is only with the realisation that chronic cough is a separate disease characterised by hypersensitivity of the afferent vagus that investment in high-quality studies has been made. The finding that antagonism of the purinergic receptor P2X3 reduced cough counts has established chronic cough as a therapeutic opportunity. Gefapixant, the first in class P2X3 antagonist, has now successfully completed phase 3 studies. On the back of this success three other new chemical entities are in late stage development. The central role of substance P in the cough reflex has been confirmed by positive clinical studies of orvepitant an NK1 receptor blocker. Other potential therapeutic pathways include sodium channel blockade and TRPM8 agonists.

It is thus a very exciting time in the therapeutics of chronic cough. Treatment of this chronic, common and disabling condition is advancing in parallel with our understanding of the complex neural pathways relaying the aberrant noxious sensation provoking cough.

Introduction

The drug treatment of chronic cough (cough with a duration of >8 weeks) remains a challenge to many medical professionals. This is despite dramatic advances over the last decade in our understanding of the pathophysiology of cough hypersensitivity and its aetiology. This is, in part, due to the recent realization that chronic cough is a separate, distinct, clinical entity (Morice et al., 2014). The historically poor understanding of the aetiological mechanisms underlying chronic cough have resulted in poor treatment decisions, based on therapy for other diseases such as asthma which have led to a significant healthcare burden (Morice & Bush, 2003).

The recent publication of international guidelines on the diagnosis and treatment of chronic cough provides healthcare professionals with evidence-based guidance on current pharmacological treatments (Morice et al., 2020). Substantial advances are on the horizon with several new, effective, and novel therapies in phase 2 and 3 clinical trials which will see the first effective drugs to treat this cohort of patients in over 40 years

Historically the research into the pharmacological treatment of chronic cough has produced little in the way of effective therapies. (McGavery et al., 2019). This is despite the clear signal on need, in that OTC remedies are a multi-billion pound industry (Footitt & Johnson, 2009). These therapies, such as codeine, dextromethorphan and diphenhydramine may provide some benefits in acute cough (Birring et al., 2017) but have little or no clinical evidence in chronic cough. This lack of robust evidence alongside the compounds' prominent side effects such as sedation and the risk of addiction has resulted in such therapy being no longer recommended for long term use in cough. (Footitt & Johnson, 2009). To a greater extent this can be applied to codeine which, is still one of the most widely used antitussives even though many well-controlled studies show its lack of efficacy in reducing cough in man (Dicpinigaitis et al., 2014).

The first challenge healthcare professionals face when deciding on suitable pharmacological therapies for chronic cough lies in the correct diagnosis of any underlying cause. Previously the paradigm of the three causes of cough – the so-called

cough triad which consisted of asthma, GERD/GORD and postnasal drip was adopted as the underlying cause (Palombini et al., 1999). However many patients with classic asthma do not have a prominent cough and patients with an asthmatic phenotype i.e. those with eosinophilic bronchitis do not respond well to conventional asthma treatments. Similarly GERD, when diagnosed as acid reflux, does not respond in terms of cough to high-dose acid suppression (Faruqi et al., 2011). Finally postnasal drip is a sensation rather than a disease (Morice, 2014) and was adopted as a cause of cough because patients sometimes respond to 1st generation antihistamines. Thus each diagnostic box did not reflect the totality of the population presenting to specialist cough clinics.

Observational studies have shown that there is a unique phenotype of patients with chronic cough who are predominantly middle-aged women (Morice et al., 2014). Their main complaint being a hypersensitivity to external stimuli such as a change in temperature, strong smells, bleaches and perfumes. The concept thus arose that patients have an underlying neurological abnormality characterised by hypersensitivity of vagal afferents. (Mazzone, Chung & McGarvey, 2018). This resulted in a unifying diagnosis of cough hypersensitivity syndrome. This is defined as “a clinical syndrome characterised by troublesome coughing often triggered by low levels of thermal, mechanical or chemical exposure” (Morice et al., 2014).

It is, however, imperative that differentiation is made between those presenting with an eosinophilic or neutrophilic inflammation by first looking into a patient's eosinophilic biomarkers e.g. blood eosinophils, exhaled nitric oxide, or sputum eosinophilia. This is in order to prescribe the correct treatment to target the specific pathology of this treatable trait (Sadhegi et al., 2018).

Pharmacological Managements

Targeting Eosinophilic Airway Inflammation

Patients presenting with evidence of eosinophilic airway inflammation, which has a variety of different labels such as late onset asthma, cough variant asthma, or eosinophilic bronchitis, should be treated with a specific anti-inflammatory pathway. Although this subset of patients (perhaps 20%) presenting with chronic cough was first recognised by Gibson et al., in 1989, it is often overlooked or misdiagnosed as classic asthma despite the lack of airway obstruction or hyperresponsiveness.

The presence of eosinophil inflammation must be recognised before commencing other treatments as not only is it a treatable cause of chronic cough, but the treatment used is significantly different from that advocated in classic asthma. Since there is little or no bronchoconstriction, bronchodilator therapy is ineffective. It is this subset of patients who respond to inhaled corticosteroids (ICS) (Brightling et al.,1999). A short 2-4 week trial of ICS is recommended after which, if no clinical benefit is seen treatment should be stopped (Morice et al., 2019). The evidence of the efficacy of inhaled corticosteroids in this cohort of patients is varied, Chadhuri et al., 2004 report significant decrease in cough severity compared to placebo when patients were prescribed a 2-week high dose of ICS whereas Boulet et al. (1994) and Pizzchini et al., (1999) saw lack of clinical significance in improving cough outcomes compared to placebo when using ICS. As expected the reported adverse events (AE's) in all three trials were low. Due to the possible clinical benefit and the low risk of adverse events the recommendation of ICS prescribed at high doses is advocated as a treatment trial in recent ERS guidance (Morice et al., 2020). It is likely that because of the different distribution of eosinophilic inflammation between classic asthma and cough related eosinophilic bronchitis that topical therapy such as ICS may be less effective (Birightling et al., 1999). A short course of oral prednisolone is advocated by some as a therapeutic trial to confirm the diagnosis. Even then some patients do not respond to systemic therapy by corticosteroids.

In eosinophilic patients a recommendation for an oral leukotriene antagonist such as Montelukast may be warranted. A therapeutic trial of 2-4 weeks is based on results from placebo-controlled RCTs on the use of the leukotriene receptor antagonist zafirlukast (Dicpinigaitis, Dobkin & Reichel, 2002) and the effectiveness of montelukast (Spector & Tan, 2004).

Cough Neuromodulators

Currently there are few treatment options directed at cough hypersensitivity itself. The hypothesis that hyperexcitability of afferent sensory neurons plays a role in the aetiology of chronic cough is supported by evidence of increased sensitivity to challenge agents such as capsaicin and citric acid (Rai et al., 2018). There is a large overlap of sensitivity in the normal population with some individuals not coughing at all, even at high concentrations. It is thus impossible to have a “normal range” with cough patients uniformly being excessively sensitive. The location of this hypersensitivity depends on the individual patient. There is clearly a major element of peripheral nerve hypersensitivity since inhalational challenge with rapidly metabolised agents such as ATP and distilled water have been shown to be decreased by blockade of the P2 X3 receptors (Morice at al., 2019). Interestingly capsaicin and citric acid are not diminished by blocking this pathway inferring that there is much diversity and redundancy within the afferent neural pathways.

While peripheral neuronal blockade does demonstrate clinically meaningful reduction in cough hypersensitivity, central activity is also clearly important. Recent studies using fMRI have demonstrated descending cortical pathways which inhibit cough sensitivity and when absent, for whatever reason, excessively coughing results (Ando et al., 2016).Replacement of these inhibitory pathways with agents such as opiates and first-generation antihistamines allow treatment for patients with cough hypersensitivity who have reduced cortical inhibition of the cough reflex.

Opiates have long been advocated as an anti-tussives with their use first discussed in literature by Mudge in 1778. However, randomised controlled data was only provided more recently. This study provided evidence of significant benefit of slow-release morphine (MST) vs placebo in reducing cough (by 40%) and improving cough specific quality of life (Morice et al., 2007). In clinical practice it seems that this benefit is restricted to some patients and not others. Patients either respond to opiates or not. A short-term trial of one weeks therapy should suffice to determine whether the patient is

a responder or not. There is no point in increasing the dose if the patient does not respond because, unlike pain, higher doses do not seem to be increasingly efficacious. Concerns have been raised regarding the side effect profile of MST including constipation and drowsiness but in that study it was found to be well tolerated (Morice, et al. 2007). The effectiveness of MST has recently been supported by a study by Al-Shekllly et al., 2017 This double blind RCT of low dose MST was performed in patients known to be opiate responders. It showed that MST provides clinically significant reductions in objective cough and cough specific quality of life vs placebo. Morphine continues to be the neuromodulator of choice in treating chronic cough and its use is recommended in the ERS guidelines (Morice, et al. 2020). Uptake may be limited by the anxieties of patients willing to take it and medical professionals willing to prescribe it. In certain countries this has led to limited use outside specialist clinics because of its status as a controlled drug (Dicpinigaitis et al., 2014).

Other neuromodulators used in cough treatment pathways include gabapentin and pregablin. The similarities between the proposed mechanisms of chronic pain and chronic cough led to the research into these compounds for this indication (Dicpinigaitis, 2014). Caution must be taken however, when using gabapentin or pregabalin due to the paucity of RCTs using these compounds. A single RCT comparing 1800mg of Gabapentin versus placebo highlighted small but statistically significant improvements in quality of life outcomes, cough frequency, and cough visual analogue scales (Ryan et al., 2012). A further study from the same group of pregabalin (maximum dose 300mg daily) combined with Speech Therapy showed significant improvement in quality of life outcomes, however, this trial has major limitations due to the low subject numbers and the fact the control group also received speech therapy with pregabalin having no statistically significant effect in lowering cough frequency in comparison to speech therapy only. (Vertigan et al., 2016). There was a high incidence of AE'S shown in both of these studies including cognitive changes, drowsiness and blurred vision (Ryan et al., 2012). This raises questions as to how well these compounds are tolerated in the long term.

Promotility Agents

Patients with chronic cough can present with elevated markers of neutrophilic inflammation including in induced sputum. The use of the macrolide therapy such as azithromycin is therefore advocated based on the benefits seen in a number of airway diseases such as COPD (Albert et al., 2011), asthma (Gibson et al., 2017), cystic fibrosis (Kabra et al., 2010) and bronchiectasis (Wong et al., 2012). It has been suggested that this broad spectrum of activity is due to hypothesised properties as an anti-inflammatory and anti-neutrophil alongside its broad spectrum antimicrobial activity (Hodgson et al. 2016). However, azithromycin is a potent agonist of the hormone motilin (Broad & Sanger, 2013) and has been shown to improve oesophageal motility (Mertens et al., 2009) and we believe that this underlies its therapeutic effects in this diverse collection of airway diseases. A reduction in exacerbation events is the main outcome in the studies and this infers that reflux and aspiration are major precipitants of deterioration in these conditions.

We have shown that patients with chronic cough have a greater than 80% incidence of oesophageal dysmotility (Burke, Jackson & Morice, 2018). However the use of azithromycin has yet to be conclusively shown to be of benefit in such patients. The best evidence is from studies in chronic cough in COPD with azithromycin resulting in a clinically significant reduction in cough related quality-of-life versus placebo in a controlled RCT (Berkhof et al., 2013). In an 8 weeks study using low dose azithromycin three times a week in patients with isolated chronic cough a placebo controlled RCT showed clinical important reduction in cough quality-of-life but did not produce a clinically significant reduction ($p=0.12$) in objective cough counting (Hodgson et al., 2016). The lack of significance in this study may be explained by lack of power (only 22 patients in azithromycin arm) and the use of a low dose, that is, azithromycin 250mg three times a week. Clinical experience has shown many patients report improvement in chronic cough with azithromycin 250mg daily. There is therefore an area that clearly warrants further investigation. Currently, however, the ERS Task Force only recommend routine use of macrolide therapy in a chronic cough in patients with a productive cough, refractory to other treatments (Morice et al., 2020).

Novel Treatments

ATP Story

The serendipitous finding that P2X3 inhibitors decrease cough counts in patients with severe chronic cough could be the biggest breakthrough in the pharmacological treatment of this condition. ATP is released in response to tissue injury and acts on afferent sensory nerves leading to a state of cough hypersensitivity (Bonvini et al., 2016).

The role of ATP in chronic cough has now been explored in numerous clinical studies. The direct role of ATP in chronic cough is supported by the work of Fowles et al., 2017, who demonstrated that inhalation of exogeneous ATP evokes cough in both healthy volunteers and chronic cough patients. These findings support the hypothesis that the hyperexcitability of sensory nerves in chronic cough is caused by the increased release of ATP into the extracellular space during airway inflammation.

Early clinical trials in the use of the prototypic P2X3 antagonist, gefapixant showed a reduction of cough by up to 75% vs placebo in patients with chronic cough (Abdulqawi et al., 2015) and was the foundation for the concept that ATP was a major mediator of hypersensitivity in chronic cough. The success of gefapixant has since been strengthened by phase 2 clinical trials (figure 1). A placebo controlled study looking at ATP evoked cough demonstrated that a single dose of Gefapixant 100mg inhibited ATP induced cough resulting in statistically significant reductions in cough challenge sensitivity in both healthy volunteers and chronic cough patients when compared to placebo (Morice at el., 2019). Interesting, this study found no effect of gefapixant on citric acid and capsaicin challenge inferring that there are at least two different pathways in man. One is an irritant pathway sensitive to acid and TRPV 1 stimulation by capsaicin and another pathway responsible for the pathophysiology of cough hypersensitivity. This finding infers that P2X3 antagonist may be safer than conventional antitussives since they target only the pathophysiological pathway and preserve the vital irritant

pathway which protects the airway from aspiration. In this study up to 75% of healthy volunteers and 67% of chronic cough patients report dysgeusia (Morice et al,. 2019).

Further studies have taken place exploring the efficacy and tolerability of various doses of gefapixant over a longer duration. Smith et al., 2020 report the use of gefapixant in a two double blind placebo controlled, two period crossover, dose escalation studies with dosage ranging from 7.5 mg to 200mg over 16 days in both arms. Clinical significance was seen across both studies in reducing awake cough as well as cough over a 24hour period but only with doses of 30mg and above. A statistical improvement was also seen in cough related quality of life and patient reported outcomes.

A phase 2b double blind, parallel group, placebo-controlled trial exploring the tolerability and efficacy of gefapixant over 12 weeks supports its use as an antitussive with significant improvements shown in cough frequency and patient reported outcomes in the 50mg dose vs placebo. It also demonstrated a positive safety profile although again, this dose saw 48% of patients reporting dysgeusia resulting in some patient discontinuation (Smith et al., 2020). The results of 2 phase 3 studies of this compound have been recently published an abstract form and confirm the efficacy of gefapixant at 45 mg. These are the first large-scale chronic cough studies with a positive outcome.

Although gefapixant appears to be at the forefront of chronic cough therapeutics some doubt may be cast over the patients' tolerability of dysgeusia over the long term. The results of follow-on studies investigating the tolerability of gefapixant in these phase 3 trials is awaited. The AE of taste disturbance can be explained through ATP serving as the key neurotransmitter for the peripheral taste system requiring the heterotrimer of the P2X2/3 receptor for the sensory transmission within this system (Finger et al., 2005). It is for this reason several new agents, deemed to be more selective for the P2X3 homotrimer rather than the P2X2/3 receptor, are currently being evaluated in phase 2 clinical trials.

Bayer: The lead compound currently in phase 2 studies is BAY1817080. Results from a recently completed double blind, placebo controlled, randomised crossover study comparing BAY1817080 at doses of 10mg, 50mg, 200mg, and 750mg BD versus placebo show a dose related inhibition of cough (figure 2). As a potent P2X3 receptor antagonist this compound has been well tolerated with a low number of taste disturbances whilst reducing 24hr cough count against placebo and significantly reducing patient-reported cough severity with dosing of 50mg and above (Morice et al., 2020). This compound is currently being studied in phase 2b RCTs to test its efficacy in a larger population over a more prolonged period.

Bellus: BLU-5937 is a selective P2X3 antagonist which has recently completed an initial phase 2 study. This small molecule has been shown to be a potent, selective, and noncompetitive P2X3 homotrimeric receptor antagonist which in preclinical and animal studies has shown to have a low incidence of taste disturbances likely due to its higher selectivity (Garceau & Chauret, 2019). Although the phase 2 study did not reach a statistically significant reduction in its primary endpoint of awake cough counts, this was mainly due to the early termination of the study because of the onset of Covid 19 restrictions. When the study was terminated a number of patients had only completed a single arm of this crossover study. If the per protocol population is considered then the results on cough counting and other parameters are significant. It is only the intention-to-treat population in which these metrics do not reach significance.

Shionogi: Recruitment into a large phase 2 RCT of S-600918 is currently ongoing. Results from a small phase 2 trial in 33 Japanese patients show promise for S-600918 an oral P2X3 receptor antagonist as an effective antitussive. Again, due to its high selectivity for the P2X3 homotrimer early indications show a low incidence of taste disturbance with this compound at 150mg although the ongoing study is exploring the efficacy of 50mg, 150mg, and 300mg daily vs placebo (Niimi et al., 2019).

Neurokin Story

It was first suggested in 1987 that substance P may have a role in cough reflex sensitivity since it is broken down by angiotensin-converting enzyme and accumulation may occur with ACE inhibition (Morice at al., 1987). Substance P acts on the NK-1 receptor and overpitant, a NK-1 antagonist has been developed as a possible antitussive. It has been assessed in both phase 1 and phase 2 clinical trials. Results from an open label pilot study using 30mg daily for 4 weeks showed that not only was the drug safe and well-tolerated within this small cohort of patients but significant improvement was seen in cough frequency as well as patient-reported outcomes (Smith et al., 2019). Further exploration of this compound in a phase 2b double blind, placebo controlled trial using doses of 10mg, 20mg and 30mg showed statistically significant results in patient-reported outcomes but unfortunately significance was not seen in the reduction of awake cough due to a high placebo response (Smith et al., 2020). In a subgroup analysis significant benefit was seen in those patients whose baseline cough counts were greater than the median. Because it has a different, presumably central, mode of action it is likely that a different profile of cough responses will be seen with NK-1 antagonists. In many ways it is similar to the response of opiates where patient reported outcomes predominate in the beneficial effects. There was no effect on cough challenge in either of the two studies for morphine.

ACE inhibitor

Whilst the focus seems to be on adding in therapy to treat chronic cough a review of existing therapy should be the first line of management. Experience working in a specialist cough clinic has shown that approximately 10% of patients will present with a long history of chronic cough that correlates with the commencement of an ACE inhibitor. It is over 35 years since ACE inhibitor cough was first described by Sesoko & Keneko in 1985. Discontinuation of the therapy will result in cessation of the persistent cough in as little as a few days although because ACE inhibitors cause cough by resetting the sensitivity of the cough reflex (figure 3) it can take many months for this hypersensitivity to return to normal.(Robinson, Celermajer & Bye, 1997).

Conclusion

The future of the pharmacological treatment of chronic cough is an area with a huge amount of promise with compounds such as M8 agonists and sodium channel blockers being explored for their antitussive properties. With the novel therapies described within this chapter programmed to finish phase 3 studies in the coming years this nascent field of medicine will have specific licensed therapies to treat a neglected patient population. Collaborations such as NEUROCOUGH (McGavery et al., 2019) will also promote future multinational and multidisciplinary collaborations to ensure that further research is geared towards improving the care of chronic cough patients with the overall aim of addressing their currently unmet needs.

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Figure 1

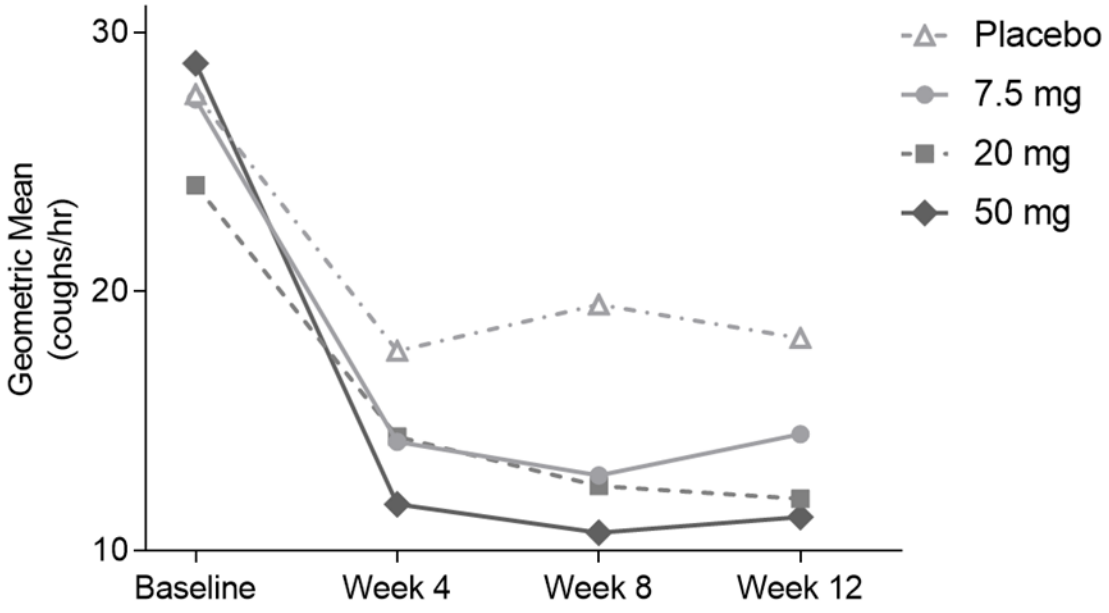

30
20
10
Geometric Mean
(coughs/hr)
Baseline
Week 4
Week 8
Week 12
Placebo
7.5 mg
20 mg
50 mg

Figure 2

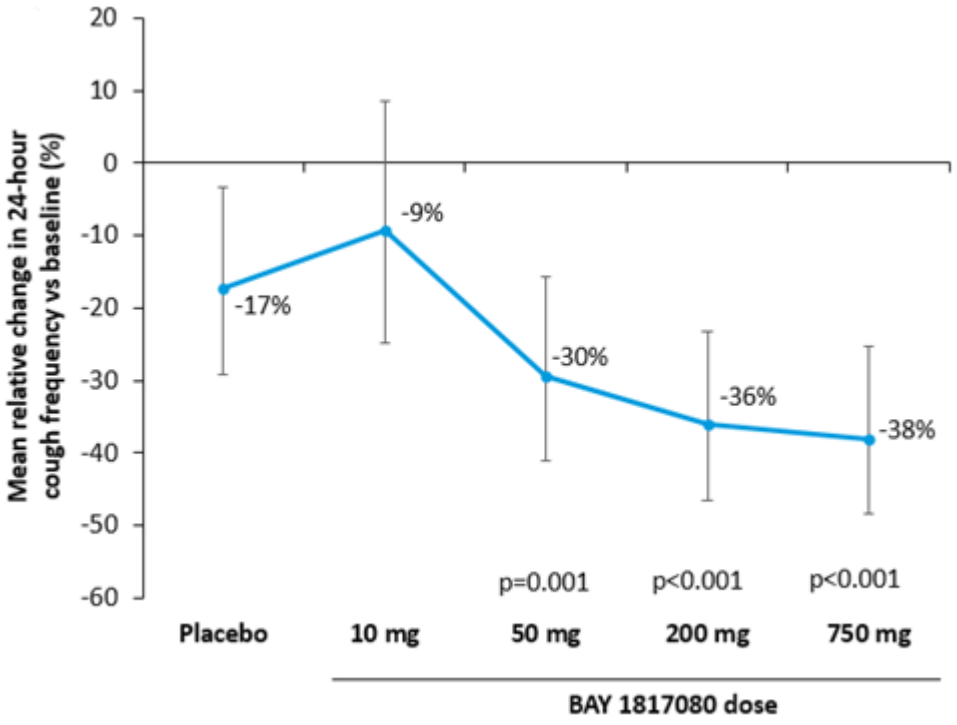
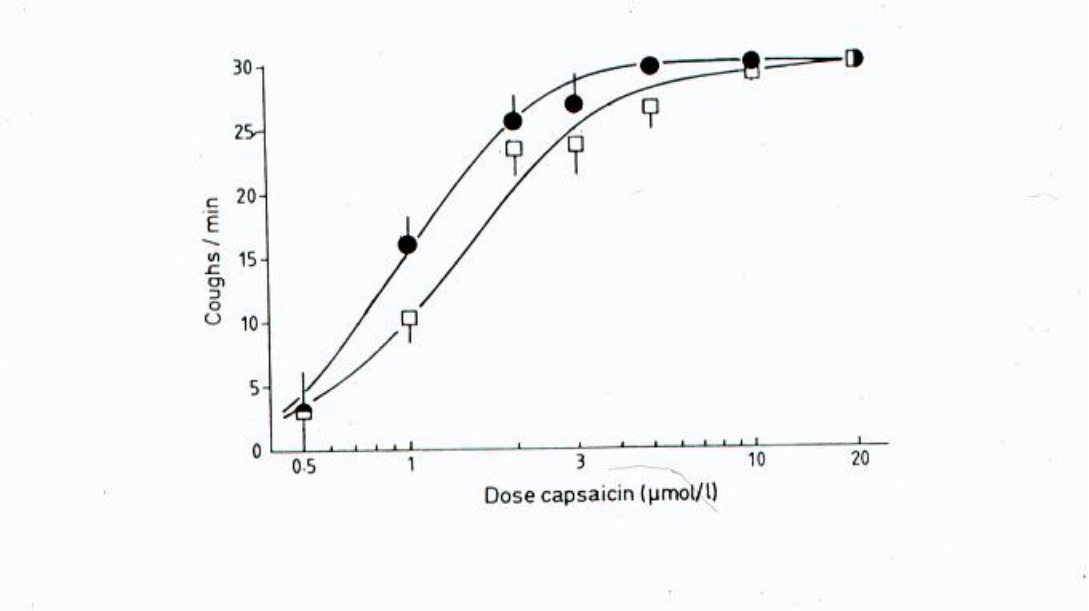

Mean relative change in 24-hour cough frequency vs baseline (%)
20
10
0
-10
-20
-30
-40
-50
-60
-17%
-9%
-30%
-36%
-38%
p=0.001
p<0.001
p<0.001
Placebo
10 mg
50 mg
200 mg
750 mg
BAY 1817080 dose

Figure 3



legends to figures

Figure 1

The P2X3 antagonist gefapixant. Effect on awake cough frequency (Primary Endpoint) in Phase 2b study

Figure 2

The effect of1817080 on cough frequency in a phase 2 study. Mean relative change in 24-hour cough frequency vs. baseline. Duration of treatment was 1 week with each dose of BAY 1817080

Figure 3

The effect of the ACE inhibitor captopril on cough reflex sensitivity as demonstrated by inhalational challenge with capsaicin. Open squares placebo, closed circles captopril