REVIEW

Drug-Induced Cough

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Summary

Since the recognition of angiotensin-converting enzyme inhibitors (ACEIs)-induced cough, drug has been considered as a potential cause of chronic cough. This review presents recent knowledge on drug-induced coughs in patients with chronic cough. The focus is placed on ACEIs, for which there are a multitude of studies documenting their associations with cough. Additional drugs are discussed for which there are reports of cough as a side effect of treatment, and the potential mechanisms of these effects are discussed.

Key words

Cough • Drug • Medication • Angiotensin-converting enzyme inhibitors

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Introduction

Chronic cough is a multi-factorial disease with a neurological basis in adults (Morice *et al.* 2014a, Song and Morice 2017). The recognition of angiotensin-converting enzyme inhibitors (ACEIs)-induced coughs (Sesoko and Kaneko 1985, Semple and Herd 1986, Morice *et al.* 1987) has not only led to the clinical recommendation that drug should be considered as a potential cause of cough (Irwin *et al.* 2018, Song *et al.* 2018, Morice *et al.* 2019), but also has provided an important clue to the notion that cough reflex hypersensitivity commonly underlies chronic cough in adults (Morice *et al.* 2014a) (Fig. 1). Left-shift in dose-response curve in capsaicin inhalation challenge was a proof for cough reflex hypersensitivity induced by ACEIs (Morice *et al.* 1987). Also, given the fact that ACEI-induced cough occurs in only about 10 % of patients taking the medicine (Matchar *et al.* 2008), the drug is likely to be a trigger in susceptible individuals, rather than be a direct cause of cough.

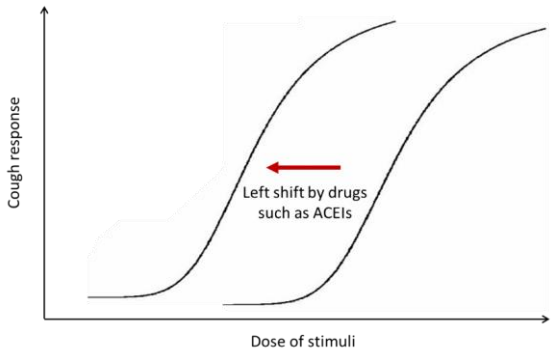

Fig. 1. Schematic presentation of drug-induced cough reflex hypersensitivity

While causative potential of ACEIs in the pathogenesis of cough was consistently demonstrated in clinical trials (Dicpinigaitis 2006), it is unclear if any

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drugs other than ACEIs warrant further clinical attention in patients presenting with cough. In the literature, several drugs such as sitagliptin, topiramate, or methotrexate were reported to have pro-tussive potentials in some patients. Given rapid global population ageing (Song *et al.* 2019), it is supposed to be increasingly important to consider drug-induced cough in the clinics. This review aims to summarize recent knowledge on coughs induced by systemic medications, including the epidemiology and potential mechanisms.

Angiotensin-converting enzyme inhibitors

Since the first introduction of captopril in the late 1970s, ACEIs have been widely utilized for patients with hypertension, coronary diseases, heart failure, or chronic kidney diseases (Edwards and Padfield 1985, Li *et al.* 2014, Bertrand 2004, Jafar *et al.* 2001). They are usually well tolerated, but may cause side effects; cough is one of the common adverse reactions potentially leading to the drug discontinuation or more anti-tussive uses (Dicpinigaitis 2006, Matchar *et al.* 2008, Vegter *et al.* 2013).

Clinical manifestation of ACEI-induced cough

ACEI-induced cough is typically a persistent dry cough, combined with a tickle in the throat (Dicpinigaitis 2006). ACEI-induced cough may occur within a few hours of the first dose as well as weeks or months later, and is more frequent in female patients and nonsmokers (Os *et al.* 1994, Yilmaz 2019). In the observational study of Japanese patients with hypertension, cough frequently occurred within the first month and mostly within 6 months since the drug initiation (Sato and Fukuda 2015). In the French pharmacovigilance database analysis, the mean duration of onset was 156.8 days (95 % confidence interval [95 % CI]: 84.9 to 241.7 days) (Humbert *et al.* 2017). Patients who develop ACEI-induced cough or angioedema cannot usually tolerate another medication in the same class, which would act via a similar mechanism. The only effective management of ACEI-induced cough is discontinuation of the ACEI, with improvement typically observed within 1 to 4 weeks, but some cases have been reported to last up to 3 months (Dicpinigaitis 2006).

Epidemiology of ACEI-induced cough

The incidence of coughing related to ACEIs was reported to vary widely among studies of patients taking an ACEI, ranging from 0 % to 37 % (mean, 10 %) (Yusuf *et al.* 1991, Bart *et al.* 1999, Matchar *et al.* 2008, Brugts *et al.* 2014, Sato and Fukuda 2015). These variations may originate from heterogeneity in study population and design, duration of observation, or measurement of cough. However, importantly, patients taking placebos in randomized controlled trials (RCTs) may also experience coughing, and thus the relative risk (RR), rather than absolute risk, would be more appropriate in understanding the epidemiology of ACEI-induced cough. In a recent meta-analysis of RCTs reporting cough (as a side effect) in patients taking ACEI or placebo due to cardiovascular diseases, only a portion (37 %) of the incidences comprising an overall rate of ACEI-induced cough (13.5 %) were caused by the ACEI after correcting for cases of cough in the placebo groups (Vukadinovic *et al.* 2019). The findings suggested that a substantial proportion of cough in patients taking ACEIs may be potentially unrelated to the drug intake. Indeed, there have been cases of spontaneous resolution of cough while maintaining ACEI treatment as well as nonrecurrence of cough after the ACEI is re-administered (Reisin and Schneeweiss 1992, Sato and Fukuda 2015). These findings remind us that re-exposure to ACEI should be considered before complete withdrawal, particularly in patients likely to benefit from the therapy. Meanwhile, interestingly, the proportion of cough caused by the ACEIs (after correction for placebos) varied substantially among patients with different underlying conditions, showing the highest rate in patients with hypertension (85 %) but lower rates in those with coronary disease (42 %) or heart failure (29 %) (Vukadinovic *et al.* 2019). These findings suggest that host factors are likely to be important in the pathogenesis of ACEI-induced cough.

The frequency of cough on ACEI is consistently higher in female patients (Os *et al.* 1994, Visser *et al.* 1995, Kim *et al.* 2000, Morimoto *et al.* 2004, Brugts *et al.* 2014, Sato and Fukuda 2015, Alharbi *et al.* 2017). In a pooled analysis of three RCTs comparing perindopril and placebo in 27,492 patients with vascular diseases, older age (≥65 years) and female gender were positively associated with risk of ACEI-induced cough, with adjusted odds ratio (OR) of 1.53 (95 % CI: 1.35 to 1.73) and 1.92 (95 % CI: 1.68 to 2.18), respectively (Brugts *et al.* 2014). In a prospective observational study of 176 outpatients taking perindopril or imidapril for hypertension in Japan (average observation period: 18 months), the incidence of cough was 19.9 % and two thirds of them were females (Sato and Fukuda 2015).

Among the 446 ACEI-induced cough cases registered in the French pharmacovigilance database, the incidence in women (mean age, 64 years) was twice that in men, and the mean duration of onset was 156.8 days (Humbert *et al.* 2017). Meanwhile, in a pooled of analysis of individual patient data from 6 placebo-controlled trials of children with hypertension on ACEIs, the risk of cough in ACEI treatment group was not different with that in placebo group (3.2 % vs. 2.5 %), and the female predominance in the ACEI group was not statistically significant (4.8 % vs. 2.2 %, p=0.13) (Baker-Smith *et al.* 2010). The age and sex characteristics seen in patients with ACEI-induced cough are in line with those seen in most patients attending specialist clinics with chronic cough (Morice *et al.* 2014b). These similarities support the notion that ACEI is a trigger factor to enhance cough reflex and thus provoke cough in susceptible individuals.

The risk of ACEI-induced cough is reported to be higher in East Asian patients (McDowell *et al.* 2006). In a meta-analysis of possible ethnic differences in risks of adverse reactions to cardiovascular drugs, the RR of cough from ACEI was 2.7 (95 % CI: 1.6 to 4.5) in East Asians than in whites, whereas it did not differ between black and non-black patients (RR: 1.1, 95 % CI: 0.54 to 2.27) (McDowell *et al.* 2006). However, the ethnic difference was not confirmed in a pooled analysis of individual patient data from 3 RCTs comparing perindopril and placebo (Brugts *et al.* 2014).

Mechanisms of ACEI-induced cough

ACEI-induced cough appears only to occur in susceptible individuals, regardless of the dose of drug, though the individual susceptibility is not yet fully understood. However, the development of cough may be attributable to the accumulation of bradykinin or substance P, which are degraded by ACE in the upper and lower respiratory tracts (Dykewicz 2004, Morice *et al.* 1987) (Fig. 2). Bradykinin, converted from kininogen by kallikrein, has a short half-life as a result of rapid degradation by ACE (Packard *et al.* 2002). ACEIs suppress this degradation, resulting in an increase in bradykinin concentrations (Packard *et al.* 2002, Dykewicz 2004). In guinea pigs, inhaled bradykinin sensitizes cough reflex (El-Hashim and Amine 2005) and also triggers cough responses (Hewitt *et al.* 2016). Bradykinin also activates phospholipase A2, which leads to the generation of arachidonic acid derivatives such as leukotrienes, histamines, and prostaglandin I2 and E2, which may cause cough, bronchospasm, and nasal discharge (Trifilieff *et al.* 1993, Packard *et al.* 2002, Dykewicz 2004). Substance P pathways involving neurokinin-1 receptor may have important implications in the pathogenesis of ACEI-induced cough. Substance P is degraded by ACE, and has the potential to mediate cough induced by cigarette smoke or allergen challenge (Ujiie *et al.* 1993, Sekizawa *et al.* 1995). In a recent pilot study, a neurokinin-1 receptor antagonist, orvepitant, significantly improved cough outcomes in patients with chronic refractory cough (Smith *et al.* 2019).

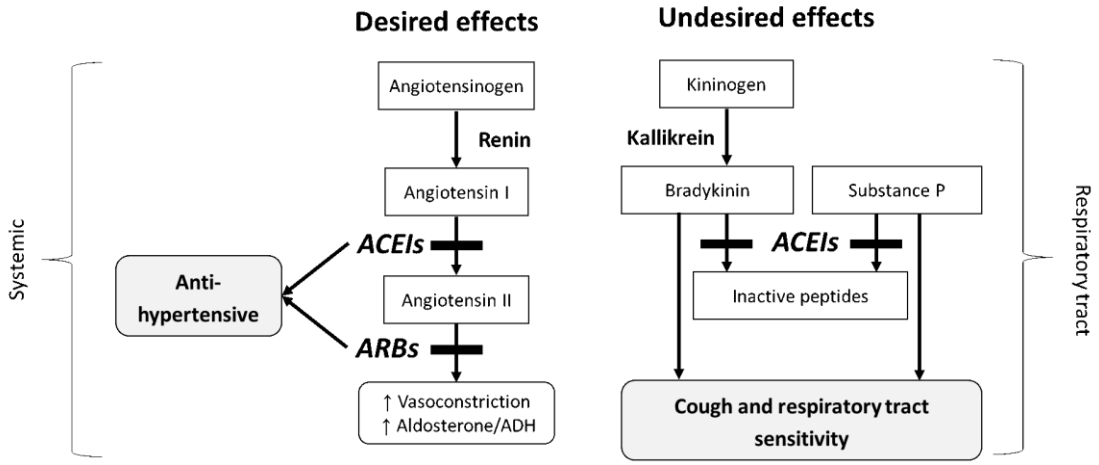

Fig. 2. Effects of angiotensin converting enzyme inhibitors on blood pressure and cough. Angiotensin-converting enzyme (ACE) mediates the conversion of angiotensin I to angiotensin II, but also it is involved in the degradation of bradykinin and substance P; thus, the inhibition of ACE may lead to undesired respiratory tract sensitivity including cough.

Studies have reported there is likely individual genetic susceptibility to ACEI-induced cough, including polymorphisms in genes encoding the bradykinin receptor, ACE (insertion/deletion), and aminopeptidase P, which is involved in bradykinin degradation (Kaufman *et al.* 1989, Kaufman *et al.* 1992, O'Connell *et al.* 1994, Ravid *et al.* 1994, Mukae *et al.* 2000, Lee and Tsai 2001, Ignjatovic *et al.* 2002, Nikpoor *et al.* 2005, Dicpinigaitis 2006), suggesting the pathophysiologic mechanisms are likely involve ACE-bradykinin pathways. Studies identified a genetic variant of the bradykinin B2 receptor promoter in patients with ACEI-induced cough, suggesting that the transcription of this receptor contributes to ACEI-induced cough (Mukae *et al.* 2000, Mukae *et al.* 2002). However, relationships between ACEI-induced cough and genetic polymorphisms in ACE or bradykinin receptors were controversial (Woo *et al.* 2009). In patients with non-productive chronic cough, neurokinin-2 receptor polymorphisms were significantly associated with enhanced capsaicin sensitivity (Park *et al.* 2006). Meta-analyses indicated that ACEI-induced cough is associated with the insertion/deletion polymorphisms of the ACE gene (Li *et al.* 2012) and single-nucleotide polymorphisms in *RBFOX3*, *GABRG2*, *SH2B1*, and *MBOAT1*, for which the functional roles were not identified (Mahmoudpour *et al.* 2017). A genome-wide association study of a Swedish population found near-significant associations between genes outside the bradykinin pathway and ACEI-induced cough, indicating that additional pathways might also contribute (Hallberg *et al.* 2017).

As some ACEIs may cross the blood-brain barrier (Fazal *et al.* 2017), it would be interesting to see whether the cough is related to central or peripheral activity of the drugs. However, in our recent systematic reviews of RCTs of patients with cardiovascular disease (unpublished data), the RRs of ACEI-induced cough (vs. placebo) did not appear to differ by the blood-brain barrier permeability of ACEIs (centrally acting ACEIs, RR: 2.56, 95 % CI: 1.78-3.68, vs. peripherally acting ACEIs, RR: 2.18, 95 % CI: 1.78-2.68), implying that the site of drug action on the cough reflex is likely to in the periphery.

Angiotensin II receptor blockers

Patients in whom ACEIs are discontinued because of cough may be given an angiotensin II receptor blockers (ARBs). In patients with hypertension, the incidence of withdrawal due to adverse effects was lower for ARBs compared with ACEIs (RR: 0.83, 95 % CI: 0.74 to 0.93), which was largely attributable to cough (Li *et al.* 2014). In patients with intolerance to ACEIs, ARBs were well tolerated with a significantly fewer risk of cough (RR: 0.37, 95 % CI: 0.28 to 0.48), and the incidence of cough on ARBs was comparable to that of placebos (RR: 1.01, 95 % CI: 0.74 to 1.39) (Caldeira *et al.* 2012). These findings confirmed that the risk of cough is not elevated in most patients taking ARBs. However, there is a case report that cough occurred 3 days after initiating an ARB and disappeared 1 week after the drug was changed to an ACEI (Dashti-Khavidaki *et al.* 2008).

Sitagliptin

Sitagliptin is a highly selective oral dipeptidyl peptidase-4 (DPP IV) inhibitor that inhibits the breakdown of incretins such as glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide (Kim *et al.* 2014). In a placebo-controlled trial assessing the efficacy and tolerability of sitagliptin in patients with type 2 diabetes mellitus who were inadequately controlled on metformin alone, the incidence of cough as a side effect was reported to be higher in the sitagliptin group compared with the placebo group (14/464 vs. 4/237) (Charbonnel *et al.* 2006). A case series described 15 patients intolerant to sitagliptin, where 13 of them reported cough with other respiratory symptoms such as rhinorrhea or dyspnea/wheeze. All of them had underlying allergic rhinitis, and the frequency was significantly higher than that in sitagliptin-tolerant patients (6 of 18, $p<0.001$). Sitagliptin was re-administered to 5 intolerant patients, and cough recurred in 4 of them (Baraniuk and Jamieson 2010). However, the risk of cough was not evident in any other RCTs or pooled analyses comparing sitagliptin and placebo (Williams-Herman *et al.* 2010, Engel *et al.* 2013, Arjona Ferreira *et al.* 2013, Ahren *et al.* 2014). Placebo-controlled trials with other DPP IV inhibitors, including linagliptin, saxagliptin and vildagliptin, also did not report any increased risk of cough (Cai *et al.* 2012, Lehrke *et al.* 2014, Doucet *et al.* 2011). Mechanistically, inhibition of DPP IV pathways may aggravate allergic inflammation (Yan *et al.* 2012). DPP IV is expressed in bronchial epithelial cells, which is up-regulated by interleukin-13 stimulation (Shiobara *et al.* 2016). These findings collectively suggest the risk of sitagliptin-induced cough is not clear, but might be potentially

attributed to host-drug interactions, such as allergic comorbidity, which warrants further investigation for clinical impact.

Calcium channel blockers

Calcium channel blockers may not have direct pro-tussive effects, but potentially trigger cough in certain individuals, possibly by attenuating the lower esophageal sphincter and reducing esophageal clearance (Medford 2012). Cough in these patients may represent a symptom of reflux, even without dyspepsia, and this reflux cough may be aggravated after meals and when in a stooping posture (Morice *et al.* 2006). In an observational study of 371 patients receiving calcium channel blockers for hypertension, 45.4 % of 130 patients with pre-existing gastrointestinal symptoms reported a worsening of reflux symptoms (Hughes *et al.* 2007). When reflux cough is suspected, it is recommended that the calcium channel blocker should be discontinued for up to 3 months to determine if the cough improves (Morice *et al.* 2006, Medford 2012).

Fentanyl

Fentanyl-induced cough is a common problem encountered in perioperative settings. Fentanyl is widely used to achieve analgesia and reduce anxiety with general anesthesia because it has a rapid onset and short duration, induces less histamine release, and has no negative inotropic effects (Tsou *et al.* 2002, Saleh *et al.* 2014). However, when administered intravenously as a bolus, 18-65 % of patients reportedly exhibit cough (Saleh *et al.* 2014). Several patho-mechanisms have been proposed to explain this. For example, fentanyl inhibits central sympathetic outflow to induce vagal predominance, which may lead to bronchoconstriction and cough (Agarwal *et al.* 2003, Kamei *et al.* 2013). In addition, fentanyl may induce a pulmonary chemoreflex, possibly by constricting tracheal smooth muscles and stimulating vagal C-fibers, irritant receptors, or pulmonary vessels of the upper airway mucosa (Bohrer *et al.* 1990). Intravenous fentanyl may also induce the release of histamine and neuropeptides by acting on prejunctional μ-opioid receptors (Ai *et al.* 2010).

A meta-analysis of 34 trials showed that lidocaine, ketamine, dexmedetomidine, a priming dose of fentanyl, propofol, dezocine, dexamethasone, dextromethorphan, and magnesium sulfate may help to reduce fentanyl-induced cough, whereas salbutamol, tramadol, midazolam, and atropine are likely to be ineffective (Shuying *et al.* 2016). There are no reports that transdermal administration of fentanyl via a patch causes coughing, although it has been reported to aggravate respiratory symptoms in asthmatics, which resolved 72 h after the patch was removed (Parmar 2009).

Latanoprost

Latanoprost is a prostaglandin F2-α analog ophthalmic solution, which is commonly used for the management of glaucoma (Klimko and Sharif 2019). In humans, prostaglandin F2-α receptors are present in the respiratory tracts and inhalation of prostaglandin F2-α significantly induced left-shifts in dose response curves in capsaicin cough challenge tests (Nichol *et al.* 1990, Stone, Barnes, and Fuller 1992). In a case report of 51-year-old woman, it was also demonstrated that even ophthalmic drops of latanoprost may up-regulate cough reflex and cause clinically troublesome cough (Fahim and Morice 2009). The prevalence of latanoprost-induced cough is unclear, but this case report highlights the importance of recognizing topical drug exposure as a potential cause of cough.

Miscellaneous

Topiramate

Topiramate is a new-generation antiepileptic drug widely used for migraine prophylaxis that increases the main inhibitory neurotransmitter in the brain, gamma aminobutyric acid (Tosun *et al.* 2012, Silberstein 2017). Since topiramate was approved by the United States Food and Drug Administration in 2004 for the prevention of migraines (Lainez *et al.* 2007), only two case reports on four patients so far have documented cough caused by topiramate (Maggioni *et al.* 2010, Tosun *et al.* 2012). To our knowledge, cough was not reported as a common issue in RCTs with topiramate. A case in one of the reports involved a dry cough that did not improve with antitussives, an inhaled glucocorticoid, or bronchodilators but only disappeared once topiramate was discontinued because of its sedative effect; however, the cough returned one day after the patient began retaking topiramate, but again disappeared over 3 weeks after the drug was discontinued (Tosun *et al.* 2012). In another report, 3 cases of topiramate-induced intractable coughing was described (Maggioni *et al.* 2010). In all

these cases, cough developed soon after topiramate initiation, and resolved rapidly (within 1 week) after the drug discontinuation (Maggioni *et al.* 2010, Tosun *et al.* 2012).

Phenytoin

A case was reported of an immediate occurrence of nocturnal dry cough after oral phenytoin administration (Nascimento *et al.* 2016). In this case, the symptom lasted for 6 months and disappeared after phenytoin was discontinued. In another case report, intravenous administration of phenytoin immediately produced bronchospasm and cough, which have involved central sympathetic inhibition with vagal predominance (Dube and Rath 2012).

Methotrexate

Although pneumonitis is a well-known side effect of methotrexate, a case series documented ten patients who developed sustained nonproductive cough while receiving methotrexate, in the absence of dyspnea, impaired lung function, or evidence of lung parenchymal diseases in chest radiograph or lung biopsies (Schnabel *et al.* 1996). All ten patients were being treated with methotrexate for rheumatoid arthritis, and the coughs improved with symptomatic care with or without the discontinuation of methotrexate (Schnabel *et al.* 1996).

Mycophenolate mofetil

There is a report of five kidney transplant patients who developed cough after taking mycophenolate mofetil (Elli *et al.* 1998). Despite normal chest radiography, nonproductive cough occurred 36 to 84 days after these patients were administered the drug, and only discontinuation of mycophenolate mofetil reduced the cough symptoms (Elli *et al.* 1998).

Table 1. Drug-induced cough and possible mechanisms reported in the literature

Drug	Route of administration	Clinical manifestation	Possible mechanisms
ACEI	Oral	Dry cough	Impaired degradation of bradykinin and substance P which mediated by ACE, causing enhanced cough reflex, accumulation of AA derivatives, nitric oxide production
Sitagliptin	Oral	Cough, rhinorrhea, dyspnea, wheeze	May aggravate underlying allergic conditions
Calcium channel blocker	Usually oral	Cough with or without reflux symptoms	May aggravate underlying reflux conditions
Fentanyl	IV	Cough, bronchoconstriction (usually in perioperative settings)	May inhibit central sympathetic tone and increase vagal tone
Latanoprost	Ophthalmic	Dry cough	Absorption of PGF2-α may enhance cough reflex in central nerve systems
Miscellaneous:			
Topiramate	Oral	Dry cough	Unknown
Phenytoin	Oral, IV	Nocturnal dry cough	Unknown
Methotrexate	Oral	Dry cough	Unknown
Mycophenolate mofetil	Oral	Dry cough	Unknown
Omeprazole	Oral	Dry cough, worsened at night	Unknown

Omeprazole

Omeprazole is one of widely used proton pump inhibitors to relieve peptic symptoms in patients with gastroesophageal acidic reflux diseases (Kahrilas *et al.* 2013). Omeprazole-induced cough is very rare, but two case reported has been documented so far (Howaizi and Delafosse 2003, Reiche *et al.* 2010).

Conclusions

In this review, we summarized drug-induced coughs and their potential mechanisms reported in the literature so far (Table 1). Cases of ACEI-induced cough have suggested that drug may act as a trigger for cough reflex up-regulation and have drawn attention to the thinking that cough hypersensitivity underlies chronic cough. Except for ACEIs, however most clinical evidence for other drugs is still limited to case reports and the mechanisms of associations are unclear. Some drugs including calcium channel blockers, sitagliptin, or latanoprost showed the potential to provoke clinical coughs in susceptible individuals with certain cough-related comorbidities, such as allergic inflammation or reflux, however, the prevalence and clinical impact is still unclear. A few case reports described patients with cough possibly related to topiramate, phenytoin, methotrexate, mycophenolate mofetil, or omeprazole. Recognition of drug-induced cough is clinically important, as its identification will help the resolution of cough without further needs for diagnostic or therapeutic efforts. Further attention should be given to any unexplained cough cases, particularly when patients are taking drugs with potentials to influence cough.

Conflict of Interest

There is no conflict of interest.

Abbreviations

ACEI, angiotensin-converting enzyme inhibitor; ARB, Angiotensin II receptor blockers; DPP IV, dipeptidyl peptidase-4; AA, arachidonic acid; PGF2-α, prostaglandin F2-α.

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