

Peer Review File

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Review Comments A

Comment 1: One controversial drug in the causal relationship with cough is sitagliptin. Recent two papers suggested that it is unlikely to be a major cause of cough, at most in susceptible subgroups such as allergic patients. I suggest you discuss about possible relationships between cough and sitagliptin/DPP4 inhibitors.

1) Drug-Induced Cough. Shim JS, Song WJ, Morice AH. *Physiol Res.* 2020 Mar 27;69(Suppl 1):S81-S92.

2) Falsely Accused? Insufficient Evidence to Conclude that Sitagliptin is a Cause of Chronic Cough. Diczpinigaitis P, Satia I, Ferguson N. *Lung.* 2020 Apr;198(2):271-273.

Reply 1: Thank you for your suggestion. These newly published papers do suggest that there may be possible relationships between cough and sitagliptin/DPP4 inhibitors. The possible mechanisms have been added to the article.

Changes in the text: page 12, line 257

Comment 2: The clinical practice guidelines of ERS and ACCP cited should be

replaced with the most recent ones. The ERS guidelines had a section for drug-induced cough, addressing ACEI, ARB and some other drugs. The ACCP guidelines suggested that sitagliptin should be considered as a cause of cough, in addition to ACEI.

1) Classification of Cough as a Symptom in Adults and Management Algorithms: CHEST Guideline and Expert Panel Report. Irwin RS, French CL, Chang AB, Altman KW; CHEST Expert Cough Panel*. Chest. 2018 Jan;153(1):196-209.

2) ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. Morice AH, Millqvist E, Bieksiene K, Birring SS, Diczpinigaitis P, Domingo Ribas C, Hilton Boon M, Kantar A, Lai K, McGarvey L, Rigau D, Satia I, Smith J, Song WJ, Tonia T, van den Berg JWK, van Manen MJG, Zacharasiewicz A. Eur Respir J. 2020 Jan 2;55(1):1901136.

Reply 2: Thank you for your suggestion. The cited clinical practice guidelines of ERS, ACCP and Korea have already been replaced with the most recent guidelines.

Changes in the text: page 16, line 332 to page 16, line 338

Comment 3: It is unclear that all opioids have tussigenic potentials, otherwise specific opioids like fentanyl.

Reply 3: Thank you for this comment. It is true that not all opioids have tussigenic potential. Opioids are a selective antitussive agent, and a review about drugs for cough stated that the opioid agonists codeine and hydrocodone were effective in suppressing

cough (*Med Lett Drugs Ther. 2018 Dec 17;60(1562):206-208*). However, other opioids, such as Remifentanyl and Sufentanyl (but not Fentanyl), could also cause cough (*Shuying L, Ping L, Juan N, et al. Different interventions in preventing opioid-induced cough: a meta-analysis. J Clin Anesth 2016;34:440-7*).

Comment 4. I wonder if ACEI-Ach pathway is clinically relevant to humans. If it is, then the risk of cough with ACEI would be higher in patients with airway hyper-responsiveness, such as asthma or COPD.

Reply 4: Thank you for this comment. In current studies, the ACEI-Ach pathway was only confirmed in animal studies. For humans, a study about bronchial hyperreactivity and cough due to ACEIs indicated that ACEI-associated cough in asthmatic patients might be correlated with bronchial hyperreactivity. A study evaluated seventeen patients using ACEIs for hypertension based on baseline spirometry followed by a bronchial reactivity analysis by challenge with methacholine. Nine coughers and eight non-coughers were included in the study. Among the nine coughers, eight demonstrated bronchial hyperreactivity. Conversely, none of the non-coughers disclosed bronchial hyperreactivity. Eight of the nine coughers were re-challenged two to six months following cessation of ACEI therapy. Six of these eight patients showed persistent bronchial hyperreactivity. (*Kaufman J, Casanova JE, Riendl P, Schlueter DP. Bronchial hyperreactivity and cough due to angiotensin-converting enzyme inhibitors. Chest. 1989;95(3):544-548*). No large, randomized, controlled studies have been published

showing that patients with asthma or COPD have an increased risk of ACEI-associated cough or bronchospasm. A review on the incidence of cough and bronchial responsiveness associated with ACEI therapy in patients with asthma and chronic obstructive pulmonary disease (COPD) suggested that bronchial responsiveness as a result of ACEI use in patients with asthma or COPD is not higher than that in the general population (*Packard KA, Wurdeman RL, Arouni AJ. ACE inhibitor-induced bronchial reactivity in patients with respiratory dysfunction. Ann Pharmacother. 2002;36(6):1058-1067*). Relevant contents have been added into the paper.

Changes in the text: page 6, line 117

Review Comments B

Comment 1: About the definition of chronic cough .

Reply 1: Thank you for this comment. First, we agree that the definition of chronic cough is time based. In the broad sense, chronic cough is defined as a cough lasting for ≥ 8 weeks regardless of whether there is any abnormality in chest X-ray, while in the narrow sense, chronic cough is defined as a cough lasting for ≥ 8 weeks with a normal chest X-ray. The chronic cough in this article refers to the latter. Second, according to the guidelines of the ACCP, we have confirmed again that the cough duration of chronic cough is ≥ 8 weeks. (*Dicpinigaitis PV. Angiotensin-converting enzyme inhibitor-induced cough: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):169S-173S; Irwin RS, French CL, Chang AB, Altman KW; CHEST Expert*

Cough Panel. Classification of Cough as a Symptom in Adults and Management Algorithms: CHEST Guideline and Expert Panel Report. Chest. 2018;153(1):196-209*

Comment 2: How to distinguish allergic cough from NAEB and asthma?

Reply 2: Thank you for this comment. There is still controversy about the distinction and connection between AC and NAEB. Although both China and Japan define AC as a common cause of chronic cough and AC is also included in the guidelines on the diagnosis and treatment of chronic cough, there are some differences on the definition of AC. The most important point is that the diagnosis of AC in China has to meet the criterion of negative induced sputum eosinophilia, while the diagnosis of EB has to meet the criterion of greater than 2.5% eosinophils in the induced sputum (*Lai K. Chinese National Guidelines on Diagnosis and Management of Cough: consensus and controversy. J Thorac Dis. 2014;6(Suppl 7):S683-S688*). However, the diagnosis of AC in Japan must meet 8 criteria, including positive induced sputum eosinophilia (*Kohno S, Ishida T, Uchida Y, et al. The Japanese Respiratory Society guidelines for management of cough. Respirology 2006;11 Suppl 4:S135-S186*). In addition, the diagnostic criteria of AC in our study as well as the Chinese guidelines for chronic cough (except for negative airway hyperresponsiveness) should include allergic reaction, such as a history of allergic disease and/or previous anaphylaxis or allergic reaction; positive allergen skin prick test; or increased serum total IgE or positive allergen-specific IgE (*Lai K. Chinese National Guidelines on Diagnosis and*

Management of Cough: consensus and controversy. J Thorac Dis. 2014;6(Suppl 7):S683-S688).

Comment 3: Expand on how long it takes for cough resolves on its own after the withdrawal of the relevant drugs?

Reply 3: Thank you for your suggestion. According to ACCP Evidence-Based Clinical Practice Guidelines, ACEI-induced cough resolution typically occurs within 1 to 4 weeks after the cessation of therapy but may linger for up to 3 months. (*Dicpinigaitis PV. Angiotensin-converting enzyme inhibitor-induced cough: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):169S-173S).*

Changes in the text: page 2, line 36

Comment 4: about nomenclature of ACEIs.

Reply 4: Angiotensin-converting enzyme (ACE) is a member of the renin-angiotensin-aldosterone system (RAAS), which is an important regulator of blood pressure and salt-water homeostasis (*Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med. 1992;327(10):669-677).* With ACE inhibition, the renin-angiotensin-aldosterone cascade is blocked. Generally, renin is produced and released

in response to a decreased in blood flow to the juxtaglomerular apparatus of the kidney or in response to a decreased in the filtration of the sodium chloride concentration. It makes the degradation of hepatic angiotensinogen to its inactive peptide, angiotensin I. Then, angiotensin I is converted to active angiotensin II by ACE produced by the capillaries in the alveoli. ACE II is a competitive inhibitor of ACE and prevents conversion of angiotensin I to angiotensin II. ACE is also responsible for the degradation of bradykinin. Active bradykinin is produced by its precursor kininogen, and kininogen is decomposed by kallikrein. Bradykinin has a short half-life because it is rapidly degraded by ACE (*Packard KA, Wurdeman RL, Arouni AJ. ACE inhibitor-induced bronchial reactivity in patients with respiratory dysfunction. Ann Pharmacother.2002;36:1058–67*). Thus, the half-life of bradykinin can be prolonged by ACEI with ACE inhibition, and its activity and concentration can increase, which is thought to be associated with side effects of ACEI-inducing cough.

Comment 5: A diagram to explain where the bradykinin comes in.

Reply 5: Thank you for your suggestion. The diagram to explain where the bradykinin comes in has been added in the article.

Changes in the text: page 5, line 94

Comment 6: About morphine also promotes histamine release in some people.

Reply 6: I agree with the comment of this reviewer. Findings suggest that morphine could release histamine from mast cells rather than basophils (*Withington DE, Patrick JA, Reynolds F. Histamine release by morphine and diamorphine in man. Anaesthesia. 1993;48(1):26-29*).

Changes in the text: page 7, line 169

Comment 7: About abbreviation GERC.

Reply 7: Thank you for this comment. In the present study, GERC was used as the GERD-associated cough. The abbreviation GERC is used widely in our country, and it is also used in the Chinese Guidance of Chronic Cough referring to GERD-associated cough. It has been used in some scientific journals, including CHEST (*Lai K, Chen R, Lin J, et al. A prospective, multicenter survey on causes of chronic cough in China. Chest. 2013;143(3):613-620*; *Xu X, Chen Q, Liang S, Lv H, Qiu Z. Comparison of gastroesophageal reflux disease questionnaire and multichannel intraluminal impedance pH monitoring in identifying patients with chronic cough responsive to antireflux therapy. Chest. 2014;145(6):1264-1270*) and JTD (*Lai K, Shen H, Zhou X, et al. Clinical Practice Guidelines for Diagnosis and Management of Cough-Chinese Thoracic Society (CTS) Asthma Consortium. J Thorac Dis. 2018;10(11):6314-6351*).

Comment 8: About the relationships between cough and sitagliptin.

Reply 8: Thank you for your suggestion. Possible relationships between cough and sitagliptin/DPP4 inhibitors have been added to the article.

Changes in the text: page 12, line 257

Comment 9: Need to expand how to approach possible drug induced cough, how to stop meds, how long to wait to decide if it is a drug effect. In addition, red flags should be reviewed prior to looking at drugs as the cause, as assuming it is a medication side effect could lead to harm if they are ignored.

Reply 9: Thank you for your suggestion. The corresponding changes have been refined in the text.

Changes in the text: page 13, line 287 to page 13, line 296