



**QUEEN'S
UNIVERSITY
BELFAST**

Reply to Weinberger

Birring, S. S., Morice, A. H., Diczpinigaitis, P. V., McGarvey, L. P., Pavord, I. D., Green, S. A., Philip, G., & Smith, J. A. (2023). Reply to Weinberger. *American Journal of Respiratory and Critical Care Medicine*, 207(12), 1650-1651. <https://doi.org/10.1164/rccm.202304-0709LE>

Published in:

American Journal of Respiratory and Critical Care Medicine

Document Version:

Publisher's PDF, also known as Version of record

Queen's University Belfast - Research Portal:

[Link to publication record in Queen's University Belfast Research Portal](#)

Publisher rights

Copyright 2023 the authors.

This is an open access article published under a Creative Commons Attribution-NonCommercial-NoDerivs License (<https://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits distribution and reproduction for non-commercial purposes, provided the author and source are cited.

General rights

Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.

Open Access

This research has been made openly available by Queen's academics and its Open Research team. We would love to hear how access to this research benefits you. – Share your feedback with us: <http://go.qub.ac.uk/oa-feedback>

Author disclosures are available with the text of this letter at www.atsjournals.org.

Correspondence and requests for reprints should be addressed to Miles Weinberger, M.D., 450 Sandalwood Ct., Encinitas, CA 92024.
Email: miles-weinberger@uiowa.edu.

References

- Gibson PG. Management of cough. *J Allergy Clin Immunol Pract* 2019;7:1724–1729.
- Birring SS, Dicipinigitis PV, Smith JA, Morice AH, McGarvey LP, Pavord ID, *et al.* Efficacy and safety of gefapixant for refractory or unexplained chronic cough over 52 weeks. *Am J Respir Crit Care Med* 2023;207:1539–1542.
- McGarvey LP, Birring SS, Morice AH, Dicipinigitis PV, Pavord ID, Schellhout J, *et al.*; COUGH-1 and COUGH-2 Investigators. Efficacy and safety of gefapixant, a P2X₃ receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-2): results from two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials. *Lancet* 2022;399:909–923.
- Weinberger M, Buettner D, Anbar RD. A review, update, and commentary for the cough without a cause: facts and factoids of the habit cough. *J Clin Med* 2023;12:1970.
- Weinberger M, Buettner D. Habit cough is a cause of chronic cough in adults. *Ann Allergy Asthma Immunol* [online ahead of print] 25 Mar 2023; DOI: 10.1016/j.anai.2023.03.018.
- Wikipedia. Ted Kaptchuk. [accessed 2023 Apr 23]. Available from: https://en.wikipedia.org/wiki/Ted_Kaptchuk.

Copyright © 2023 by the American Thoracic Society



Reply to Weinberger

Surinder S. Birring¹, Alyn H. Morice², Peter V. Dicipinigitis³, Lorcan P. McGarvey⁴, Ian D. Pavord⁵, Stuart A. Green⁶, George Philip⁶, and Jaclyn A. Smith⁷

¹Centre for Human & Applied Physiological Sciences, Faculty of Life Sciences & Medicine, King's College London, London, United Kingdom; ²Hull York Medical School, Cottingham, United Kingdom; ³Albert Einstein College of Medicine & Montefiore Medical Center, Bronx, New York; ⁴Wolfson Institute for Experimental Medicine, Queen's University Belfast, Belfast, United Kingdom; ⁵National Institute for Health Research Respiratory Biomedical Research Centre, University of Oxford, Oxford, United Kingdom; ⁶Merck & Co., Inc., Rahway, New Jersey; and ⁷Division of Immunology, Immunity to Infection & Respiratory Medicine, University of Manchester & Manchester University NHS Trust, Manchester, United Kingdom

ORCID IDs: 0000-0003-2525-6291 (S.S.B.); 0000-0002-6135-9610 (A.H.M.); 0000-0002-3906-7232 (G.P.); 0000-0001-8837-4928 (J.A.S.).

Ⓓ This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0. For commercial usage and reprints, please e-mail Diane Gern (dgern@thoracic.org).

Originally Published in Press as DOI: 10.1164/rccm.202304-0709LE on April 27, 2023

From the Authors:

We thank Dr. Weinberger for his interest in our studies and for articulating the important burden of chronic cough. Dr. Weinberger has described his anecdotal experience of suggestion therapy, a type of psychotherapy for patients with habit cough (other terms that have been used for coughing without a discernable cough trigger are “tic cough” or “psychogenic cough”), which is a distinct condition that predominantly afflicts adolescent boys (1). In contrast, refractory chronic cough (RCC) is a common disorder resulting from apparent dysregulation of the cough reflex arc leading to cough hypersensitivity, in which coughing is caused by various innocuous triggers that should not stimulate cough. RCC occurs with a peak incidence in the fifth and sixth decades and twice as frequently in women (2).

Dr. Weinberger points out the high placebo response in our trials of gefapixant, a P2X₃ receptor antagonist, published in a recent issue of the *Journal* (3). The placebo response seen in cough trials is similar to that seen in other conditions thought to arise from neuronal dysfunction such as chronic pain, irritable bowel syndrome, and migraine. It is interesting to note that the sizes of the placebo responses in the trials of gefapixant have increased from the phase IIB trial to the phase III trials. This finding contrasts with the reductions in cough frequency from baseline in gefapixant-treated patients, which have remained remarkably consistent (4, 5).

Although the mechanism of the placebo response is poorly understood in RCC, it is likely to be multifactorial. Participants' previous experiences and memories and their expectations of receiving an effective therapy may all contribute. Dr. Weinberger proposes that, like suggestion therapy, placebo treatment acts by suggesting to the patient that the cough will decrease simply by using medication, as if medications had not been tried by these patients before they entered the gefapixant trials. In fact, the medical history in these patients (whose mean duration of cough history was >11 years in the phase III trials) shows that many medications had been used by these patients without relief of their cough. In addition, specifically in the approximately 60% of patients whose chronic cough was related to potential underlying conditions (such as asthma), all of these patients were required to show that their cough was refractory to at least 2 months of stable guideline-suggested therapy before assessment of their eligibility to enter the phase III trials (4).

Nonpharmacological approaches have been shown to have a role in treating RCC; for example, there is randomized controlled trial evidence to support the efficacy of cough control therapy comprising a range of measures such as trigger identification, laryngeal hydration, treatment of breathing pattern disorders, cough suppression techniques, and lifestyle advice (6). Whether suggestion plays a role in altering patient expectations in chronic cough in trials remains to be determined. Although any disease has psychological elements, we caution against labeling RCC as a habit disorder that is entirely susceptible to suggestion therapy. Indeed, whether suggestion therapy has any effect in the treatment of cough has yet to be evaluated in a randomized controlled trial with validated endpoints. In contrast, in each randomized controlled phase II and phase III cough trial that has been performed to date, gefapixant has demonstrated statistically significant efficacy,

consistently outperforming placebo and, as shown in our recent contribution to the *Journal* (3), providing a durable treatment benefit. ■

Correspondence and requests for reprints should be addressed to Surinder S. Biring, M.D., Department of Respiratory Medicine, Chest Unit, Cheyne Wing, King's College Hospital, Denmark Hill, London SE5 9RS, UK. Email: surinder.biring@nhs.net.

References

- Ojoo JC, Kastelik JA, Morice AH. A boy with a disabling cough. *Lancet* 2003;361:674.
- Morice AH, Jakes AD, Faruqi S, Biring SS, McGarvey L, Canning B, *et al.*; Chronic Cough Registry. A worldwide survey of chronic cough: a manifestation of enhanced somatosensory response. *Eur Respir J* 2014; 44:1149–1155.
- Biring SS, Dicipinigaitis PV, Smith JA, Morice AH, McGarvey LP, Pavord ID, *et al.* Efficacy and safety of gefapixant for refractory or unexplained chronic cough over 52 weeks. *Am J Respir Crit Care Med* 2023;207:1539–1542.
- McGarvey LP, Biring SS, Morice AH, Dicipinigaitis PV, Pavord ID, Schelfhout J, *et al.*; COUGH-1 and COUGH-2 Investigators. Efficacy and safety of gefapixant, a P2X₃ receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-2): results from two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials. *Lancet* 2022;399: 909–923.
- Smith JA, Kitt MM, Morice AH, Biring SS, McGarvey LP, Sher MR, *et al.*; Protocol 012 Investigators. Gefapixant, a P2X₃ receptor antagonist, for the treatment of refractory or unexplained chronic cough: a randomised, double-blind, controlled, parallel-group, phase 2b trial. *Lancet Respir Med* 2020;8:775–785.
- Chamberlain Mitchell SA, Garrod R, Clark L, Douiri A, Parker SM, Ellis J, *et al.* Physiotherapy, and speech and language therapy intervention for patients with refractory chronic cough: a multicentre randomised control trial. *Thorax* 2017;72:129–136.

Copyright © 2023 by the American Thoracic Society