



The Honorable Seema Verma
Administrator
U.S. Centers for Medicare & Medicaid Services
200 Independence Avenue, SW
Washington, DC 20201

September 11, 2020

Dear Administrator Verma,

On (1/11/19), the Alliance for Headache Disorders Advocacy (AHDA) submitted a formal request for reconsideration (the “appeal”) of the CMS Decision Memo for National Coverage Determination (NCD) [CAG-00296R] of (1/4/11). This NCD denies coverage of home use of durable medical equipment for oxygen therapy for the acute treatment of cluster headache attacks for Medicare and Medicaid beneficiaries.

This letter is a response to the opening of the analysis of the NCD on (8/17/20), and the period for submission of public comments on reconsideration of the NCD.

We hereby provide further evidence and data for overturning the NCD that were not included in the original request for reconsideration of (1/11/19).

Effectiveness of oxygen for cluster headache therapy:

Cluster headache attacks are excruciatingly painful individual events, typically of approximately one hour duration, that occur between 1 and 8 times per day, on a daily basis while in-cycle (weeks to months) for patients with episodic cluster headache, or every day without remission for patients with chronic cluster headache (approx. 15% of all cluster headache patients)¹.

As noted in the appeal, for over 25 years the use of high-flow oxygen has been established as the international standard of care for the acute treatment of cluster headache attacks in adults. Per consensus treatment protocols, 95% to 100% normobaric (0.1 MPa) oxygen is typically delivered at 12 to 15 L/min via a non-rebreathing mask for 15 to 20 minute periods at the outset of individual cluster headache attacks ².

¹ <https://ichd-3.org/3-trigeminal-autonomic-cephalalgias/3-1-cluster-headache/>

² Cohen A, Burns B, Goadsby P. High flow oxygen for treatment of cluster headache. *JAMA* 2009;302:2451–2457.

This standard of care is based upon cumulative Class 1 evidence from four randomized controlled clinical trials ^{2,3,4,5}.

The central role for oxygen in the treatment of cluster headache is affirmed in all twenty-one available clinical practice guidelines issued by authoritative agencies worldwide:

American Academy of Neurology⁶, American Headache Society⁷, British Association for the Study of Headaches⁸, Bulgarian Headache and Pain Society⁹, Cochrane Database of Systematic Reviews¹⁰, Czech Headache Society¹¹, European Federation of Neurological Societies¹², European Headache Federation¹³, French Headache Society¹⁴, German Migraine and Headache Society¹⁵, German Society for Neurology¹⁶, Hungarian Headache Society¹⁷, Italian Society for the Study of Headaches¹⁸, Netherlands Society of Neurology¹⁹, Portuguese Neurological Society²⁰,

³ Kudrow L. Response of cluster headache attacks to oxygen inhalation. *Headache*. 1981;21:1–4.

⁴ Fogan L. Treatment of cluster headache: a double blind comparison of oxygen v. air inhalation. *Arch Neurol* 1985;42:362–363.

⁵ Dirks, H.T., et al., Oxygen treatment for cluster headache attacks at different flow rates: a double-blind, randomized, crossover study. *J Headache Pain* 2018;19:94.

⁶ Francis GF, Becker WJ, Pringsheim TM. Acute and preventive pharmacologic treatment of cluster headache. *Neurology*. 2010 Aug 3;75(5):463-73. *Headache*. 2016;56:1093-1106.

⁷ Robbins MS, Starling AJ, Pringsheim TM, Becker WJ, Schwedt T. Treatment of Cluster Headache: The American Headache Society Evidence-Based Guidelines. *Headache*. 2016;56:1093-106.

⁸ http://www.bash.org.uk/wp-content/uploads/2012/07/10102-BASH-Guidelines-update-2_v5-1-indd.pdf

⁹ http://www.glavobolie.org/articles_lechenie-na-klastarno-glavobolie

¹⁰ Bennett MH, French C, Schnabel A, Wasiaik J, Kranke P, Weibel S. Normobaric and hyperbaric oxygen therapy for the treatment and prevention of migraine and cluster headache. *Cochrane Database Syst Rev*. 2015 Dec 28;(12):CD005219.

¹¹ <http://www.czech-hs.cz/odborna-verejnost/lecba-cluster-headache/>

¹² A May 1, M Leone, J Afra, et. al. EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. *Eur J Neurol*. 2006 Oct;13(10):1066-77.

¹³ Steiner TJ, Jensen R, Katsarava Z, et al. Aids to management of headache disorders in primary care (2nd edition). *J Headache Pain*. 2019;20:57.

¹⁴ Donnet A, Demarquay G, Ducros A, et al. French guidelines for diagnosis and treatment of cluster headache (French Headache Society). *Rev Neurol (Paris)*. 2014;170:653-70.

¹⁵ May A, Evers S, Straube A, Pfaffenrath, et al. Treatment and prophylaxis for cluster headaches and other trigeminal autonomic headaches. Revised recommendations of the German Migraine and Headache Society. *Schmerz*. 2005;19:225-41.

¹⁶ <https://dgn.org/leitlinien/3051-II-54-II-clusterkopfschmerz-und-trigeminoautonome-kopfschmerzen>

¹⁷ http://www.fejfajas-tarsasag.hu/upload/fejfajas/document/cephalalgia_hungarica19_29_70.pdf?web_id=

¹⁸ Sarchielli P, Granella F, Prudenzano MP, et al. Italian guidelines for primary headaches: 2012 revised version. *J Headache Pain*. 2012;13 Suppl 2(Suppl 2):S31-70.

¹⁹ Koehler PJ. Chronic recurrent headache without neurological abnormalities. Practice guidelines of the Netherlands Society of Neurology. *Ned Tijdschr Geneeskd*. 1999;143:295-300.

²⁰ <http://www.cefaleias-spc.com/wp-content/uploads/2019/01/sinapse-vol-9-n-2-suplemento-1-1.pdf>

Romanian Neurological Society²¹, Spanish Headache Society²², Swiss Headache Society²³, Taiwan Headache Society²⁴, United Kingdom, National Institute for Health and Care Excellence (NICE)²⁵, and United States Veterans Administration / Department of Defense²⁶.

The NCD defined a CMS requirement for positive findings from a prospective clinical trial performed under Coverage with Evidence Development (CED) for the safety and efficacy of oxygen for cluster headache attacks among Medicare beneficiaries, aged ≥ 65 years. This requirement is predicated on the assumption that the safety and efficacy of oxygen varies on the basis of the age of cluster headache patients, and that this therapy would therefore be unsafe and/or ineffective when used at home by Medicare beneficiaries.

However, in none of the twenty-one above-referenced practice guidelines is a distinction drawn with respect to the safety, tolerability, or effectiveness of oxygen therapy for cluster headache attacks for adults aged < 65 years vs. aged ≥ 65 years.

On the contrary, survey studies have found no difference in the safety, tolerability, or effectiveness of oxygen therapy on the basis of the age of adult cluster headache patients, apart from patients 61 years or older reporting more rapid onset of relief (see below).^{27,28}

Risk of oxygen toxicity with oxygen therapy for cluster headache for Medicare beneficiaries:

In a large survey study (n = 1344)²⁹, the mode cluster attack frequency was two attacks per day (24%) with 80% of respondents reporting four or fewer attacks per day (figure below).

²¹ http://www.neurology.ro/components/com_rsform/uploads/5581115d6d653-Ghiduri_de_diagnostic_si_tratament_in_neurologie.pdf

²² http://cefaleas.sen.es/pdf/GUIA_NEURO_2015.pdf

²³ https://www.headache.ch/download/Content_attachments/FileBaseDoc/SKG_Therapieempfehlungen_2018_DE_15_WEB.pdf

²⁴ Chen P-K, Chen H-M, Chen W-H, et. al. Treatment guidelines for acute and preventive treatment of cluster headache. *Acta Neurol Taiwan*. 2011;20:213-27.

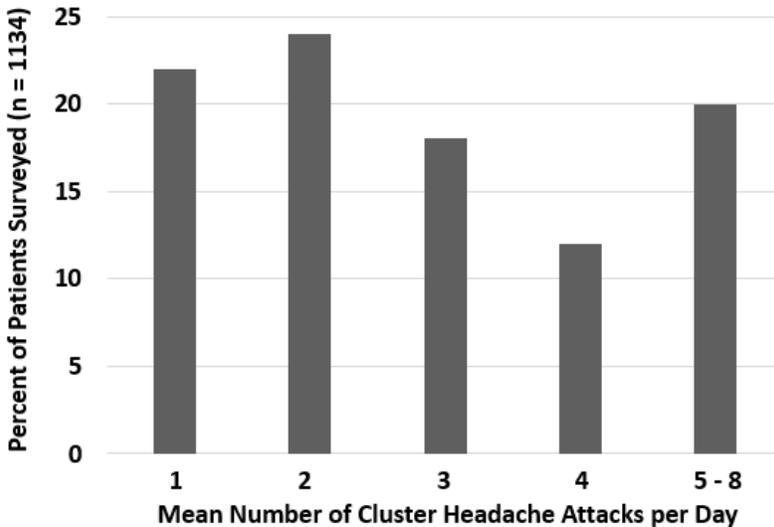
²⁵ National Institute for Health and Care Excellence (NICE) Headaches in Over 12s: Diagnosis and Management. Manchester: NICE; 25 November 2015.

²⁶ VA/DoD Clinical Practice Guidelines for the Primary Care Management of Headache, Version 1.0 – 2020. <https://www.healthquality.va.gov/guidelines/Pain/headache/>

²⁷ Rozen TD, Fishman RS, Inhaled Oxygen and Cluster Headache Sufferers in the United States: Use, Efficacy and Economics: Results From the United States Cluster Headache Survey. *Headache*. 2011;51:191-200.

²⁸ Pearson SM, Burish MJ, Shapiro RE, Yan Y, Schor LI. Effectiveness of oxygen and other acute treatments for cluster headache: Results from the Cluster Headache Questionnaire, an international survey. *Headache*. 2019;59:235-249.

²⁹ Rozen TD, Fishman RS, Cluster headache in the United States of America: demographics, clinical characteristics, triggers, suicidality, and personal burden. *Headache*. 2012 Jan;52(1):99-113.



Using oxygen therapy at various flow rates and delivery methods (many suboptimal), more than half of all surveyed cluster patients reported complete pain relief within 20 minutes, whereas patients 61 years or older typically achieved complete pain cessation within 10 minutes ²⁷.

Based on these estimates, Medicare beneficiaries (≥ 65 years) with cluster headache would be expected to rarely experience more than 4 attacks per day or require oxygen therapy for more than 15 minute exposures per attack. For such patients, oxygen exposure would total no more than 60 minutes per day, distributed across four 15 minute periods, each separated by at least one hour. For the very rare patient who may have 8 attacks per day, this would amount to a total of two hours of highly discontinuous oxygen exposure.

The earliest clinical manifestation of oxygen toxicity is pulmonary (acute tracheobronchitis) ³⁰. While sub-clinical decreases in tracheobronchial cilia activity may be detected after 3 hours of continuous 90% to 95% normobaric oxygen exposure in otherwise healthy humans, acute tracheobronchitis is not clinically apparent until 4 to 22 hours have elapsed of continuous exposure to $>95\%$ normobaric oxygen. Upon stopping oxygen, symptoms subside within a few hours, and resolve within a few days.

Based on these data, the risk of pulmonary oxygen toxicity is remote with use of oxygen for cluster headache attacks, as clinically indicated. Further, central nervous system toxicity does not occur with normobaric oxygen exposures at all ³⁰.

³⁰ Thomson, L. Oxygen Toxicity. *Paediatr Respir Rev.* 2014;15:120-123.

Notably, no cases of oxygen toxicity of any kind have ever been reported in the published clinical literature for cluster headache, and surveyed cluster headache patients have not reported oxygen toxicity either ^{27,28}.

Risk of excruciating pain with denial of home use of oxygen therapy for cluster headache attacks by Medicare beneficiaries:

Burish and colleagues have recently published further data from the international clinical survey study of cluster headache patients, as previously cited in the appeal. ²⁸

Respondents of this survey were identified as carrying the diagnosis of cluster headache if they stated that they had received the diagnosis from a health care provider, as well as met the current International Classification of Headache Disorders (ICHD, 3rd Edition) criteria for the diagnosis of cluster headache or probable cluster headache, as determined by their responses to on-line survey questions.

Burish et al. now report ³¹ direct validation of the diagnosis of cluster headache in a random sample of 5% (81 of 1604) of respondents by interview of an investigator. They confirmed the diagnosis of cluster headache in 97.5% (79/81) of the respondents that were interviewed.

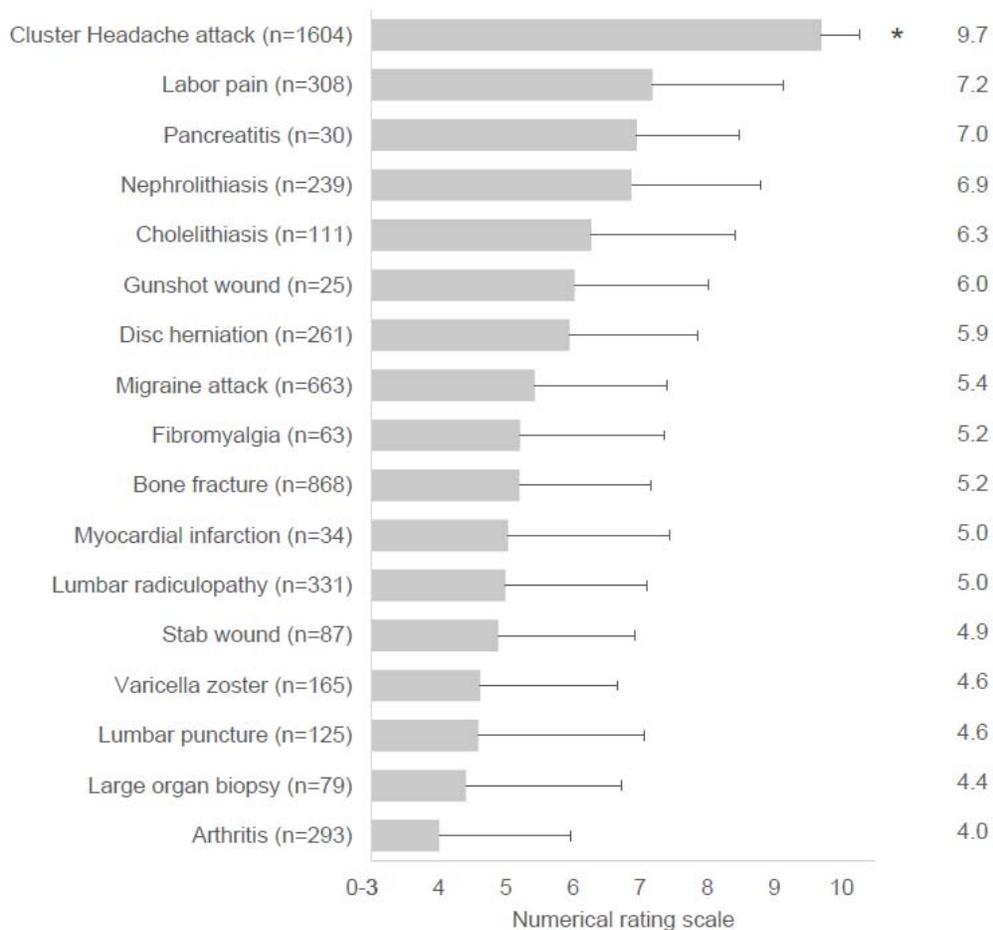
Further, Burish et al. have now published data ³² from this survey population with respect to the relative severity of cluster headache pain, compared to other sources of pain experienced by these survey respondents.

Cluster headache was the most severe pain, by far, with a mean of 9.7 (out of 10), followed by labor pain at 7.2, pancreatitis at 7.0, and nephrolithiasis at 6.9 (figure below). There was a notable gap between cluster headache 9.7 and labor pain 7.2, while the rest of the disorders fell in a more continuous spectrum between 4.0 and 7.2. Cluster headache was significantly more painful than every other disorder examined ($p < 0.001$).

The majority of cluster headache respondents (72.1%, 1157/1604) rated the pain of cluster headache as the worst imaginable, 10/10. Pain intensity was rated between 9.0-9.9 in 18.3% (294/1605), between 8.0-8.9 in 8.5% (136/1604), and between 7.0-7.9 in only 1.1% (12/1604).

³¹ Burish, M.J., Pearson, S.M., R.E. Shapiro, W. Zhang, L.I. Schor. Oxygen as the optimal acute medication for cluster headache: a comment and additional validation step from the Cluster Headache Questionnaire. *Headache. In press*, 2020.

³² Burish, M.J., Pearson, S.M., R.E. Shapiro, W. Zhang, L.I. Schor. Cluster Headache Is One of the Most Intensely Painful Human Conditions: Results From the International Cluster Headache Questionnaire. *Headache. In press*. 2020.



Risk of suicidality with denial of home use of oxygen therapy for cluster headache attacks by Medicare beneficiaries:

The pain severity of cluster headache attacks is associated with heightened suicidality. In a 2008 web-based US survey (1133 respondents)²⁹, 55% of cluster headache respondents reported suicidal ideation and 2% had attempted suicide. In a smaller Korean clinic-based survey, 2.3% of respondents reported suicide attempts during attacks³³. In our international web-based survey (1604 total respondents), 70% reported suicidal ideation during an attack, and 12% had attempted suicide (data not yet published). These rates of suicidality are approximately 20 times those of baseline US population estimates³⁴.

³³ Ji Lee M, Cho SJ, Wook Park J, et al. Increased suicidality in patients with cluster headache. *Cephalalgia*. 2019;39:1249-1256.

³⁴ <https://www.nimh.nih.gov/health/statistics/suicide.shtml>

Further relevant recently published reports:

Since our submission of the appeal, multiple further studies have been published that support the role of oxygen in the treatment of cluster headache.

1. Brandt RB, Doesborg PGG, Haan J, Ferrari MD, Fronczek R. Pharmacotherapy for Cluster Headache. *CNS Drugs*. 2020;34:171-184.
2. Douglas VP, Douglas KAA, Rizzo JF 3rd, Chwalisz BK. Case report: Orbital myositis triggering oxygen-responsive cluster headache. *Cephalalgia*. 2020;40:313-316.
3. Guo XN, Lu JJ, Ni JQ, Lu HF, Zhao HR, Chen G. The role of oxygen in cluster headache. *Med Gas Res*. 2019;9:229-231.
4. Hernandez Fustes OJ. Cluster headache by orbital myositis. Comment: Orbital myositis triggering oxygen-responsive cluster headache. *Cephalalgia*. 2020 Jul 28:333102420944860. Online ahead of print.
5. Magis D. Emerging treatments for cluster headache: hopes and disappointments. *Curr Opin Neurol*. 2019;32:432-437.
6. Perez DJ. Empiric use of oxygen for acute atraumatic, unilateral, retro-orbital headaches. *JAAPA*. 2020;33:25-27.
7. Popescu C. Cluster-Like Headache Revealing Polycythemia Vera: A Case Report. *Case Rep Neurol*. 2020;12:184-188.
8. Rossi P, De La Torre ER, Mitsikostas D, Di Lorenzo C, Palmaro A. Availability of Effective Evidence-Based Symptomatic Treatments for Cluster Headache in the EU Countries-A Survey of the European Headache Alliance and European Headache Federation. *J Oral Facial Pain Headache*. 2020;34:7-12.
9. Saeedi M, Shahvaran SM, Ramezani M, Rafiemanesh H, Karimialavijeh E. Comparing the effects of 3 oxygen delivery methods plus intravenous ketorolac on primary headaches: A randomized clinical trial. *Am J Emerg Med*. 2020;38:55-59.
10. Seav SM, Schuster NM. Cluster-status migrainosus with a weekly periodicity responsive to high-flow oxygen: A case report. *Cephalalgia*. 2019;39:157-160.

Conclusions:

In summary, oxygen therapy is established and accepted internationally as safe and effective in the home setting for the treatment of adults ≥ 65 years with cluster headache.

The withholding of this therapy continues to place Medicare beneficiaries at serious risk for excruciating pain and life-threatening harms.

We strongly urge you to reconsider and overturn the injurious CMS Decision Memo for National Coverage Determination (NCD) [CAG-00296R] to permit coverage of home use of oxygen for the treatment of cluster headache attacks by Medicare and Medicaid beneficiaries.

Sincerely,



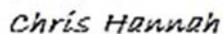
Christopher Gottschalk, MD
President
Alliance for Headache Disorders Advocacy



Josie Cooper
Executive Director
Alliance for Patient Access



Peter J. Goadsby, MD, PhD, FAHS
President
American Headache Society



Christopher Hannah
President
Cluster Headache Support Group



Thomas N. Ward, MD
President
Headache Cooperative of New England



James C. Stevens, MD, FAAN
President
American Academy of Neurology



Eileen Brewer
President
Clusterbusters



Kevin Lenaburg
Executive Director
Coalition for Headache and Migraine Patients



Susan Hutchinson, MD
President
Headache Cooperative of the Pacific



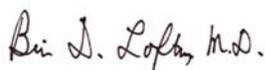
Cathy Glaser
Executive Director
Migraine Research Foundation



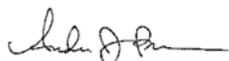
Shirley Kessel
Executive Director
Miles for Migraine



Timothy R. Smith, MD, RPh, FACP, AQH
Vice President
National Headache Foundation



Brian Loftus, MD
President
Southern Headache Society



Andrea Buchanan
Vice President & Secretary
Spinal CSF Leak Foundation