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Formal Request for National Coverage Determination Reconsideration

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

January 11, 2019

Dear Administrator Verma,

In accordance with the "Medicare Program; Revised Process for Making National Coverage Determinations" [https://www.govinfo.gov/content/pkg/FR-2013-08-07/pdf/2013-19060.pdf, CMS–3284–N], we hereby submit a complete, formal request for reconsideration of the CMS Decision Memo for National Coverage Determination [CAG-00296R] of (1/4/11), that 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.

Home oxygen therapy provides highly significant, relevant, useful, medical benefits to Medicare and Medicaid beneficiaries who experience cluster headache attacks.

On (3/22/18), Representative Andy Harris, MD, wrote to you to strongly urge your prompt reconsideration of CAG-00296R. We refer you to his letter (attached) for details regarding home oxygen for cluster headache attacks, the medical and ethical justifications for CMS coverage for home oxygen use, and the significant risks and hazards of denial of access to this therapy for Medicare and Medicaid beneficiaries.

On (8/23/18), you responded to Representative Harris, and stated (letter attached):

"*In order to move forward on this topic, published studies demonstrating that the use of high dose oxygen for CH in the home setting leads to improved health outcomes needs to be provided to CMS… In our previous conversations with relevant stakeholders, we've encouraged them to submit any new evidence specific for the home use of oxygen prescribed under the durable medical equipment benefit for the treatment of CH. Your letter mentions not-yet published retrospective survey data. We would gladly review this information either in advance of publication or following publication, as well as any other newly published data available in the public domain*."

In accordance with CMS–3284–N, we now submit "*additional scientific evidence that was not considered during the most recent review along with a sound premise that new evidence may change the NCD decision*".

Pearson, S.M., et al. Effectiveness of Oxygen and Other Acute Treatments for Cluster Headache: Results from the Cluster Headache Questionnaire, an International Survey, *Headache* 2019;0:1-15 (published on-line 1/11/19).

This study provides new evidence of the safety and effectiveness of oxygen therapy for the acute treatment of cluster headache attacks. We briefly summarize the key study findings below and have attached a PDF of the full publication.

This study is a retrospective single interaction survey that enrolled 2,193 subjects over 26 months (March 2016 to April 2018) from an international on-line catchment. 1,310 (60%) enrolled subjects were from the United States. To be eligible for enrollment, subjects had to declare that they had been diagnosed with cluster headache by a health care provider, as well as that they 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. 139 (8.7%) of enrolled subjects were 65 years or older (i.e., age of Medicare beneficiaries). 90 subjects 65 years or older had trialed oxygen therapy.

Effectiveness of acute oxygen therapy for cluster headache (Pearson et al., Figure 2)

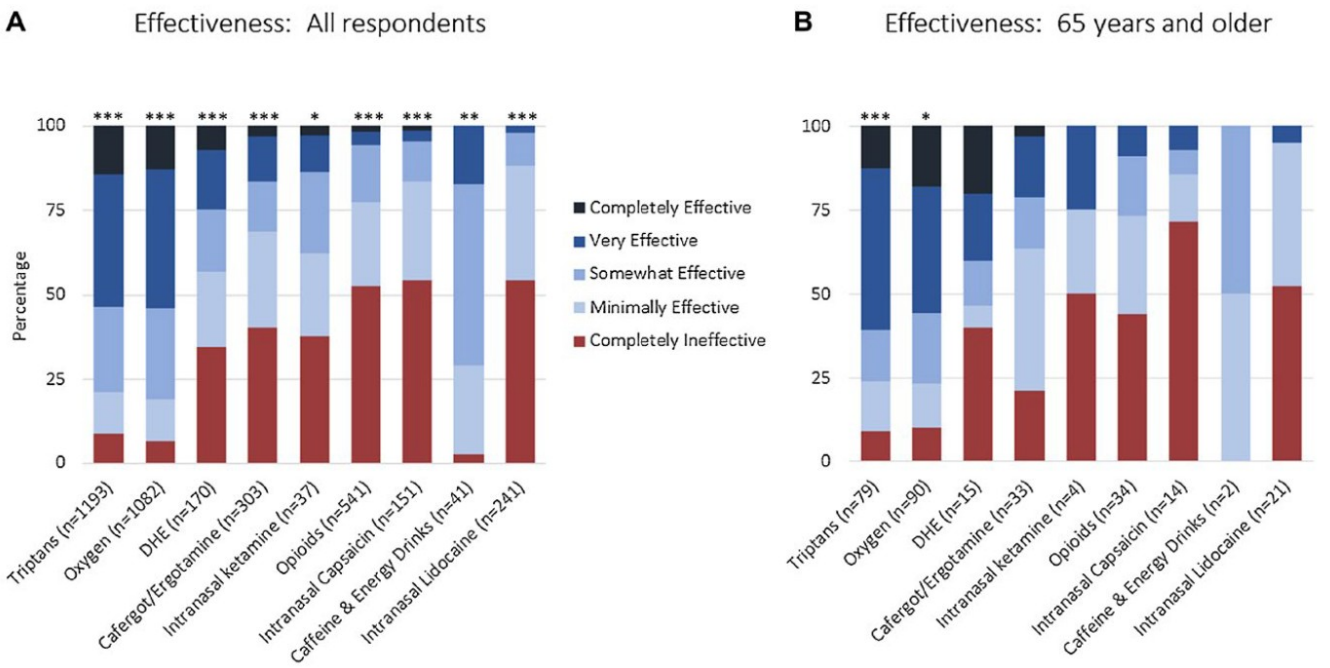

Fig. 2.—Effectiveness of acute medications in cluster headache based on an international survey. Figure shows all respondents (A) and respondents age 65 and older (B). Not all respondents trialed every medication, thus the number of responses for each medication is shown. Adjusted *P* values compare completely effective, very effective, somewhat effective, minimally effective, and completely ineffective for individual medications; asterisks denote adjusted *P* value <.05 (*), <.001 (**), and <.0001 (***). Values for this figure are listed in Supplemental Table 3.

Among the cluster headache subjects 65 years and older, 77% reported oxygen therapy to be effective (18% "*completely*", 38% "*very*", 21% "somewhat"). By comparison, 67% of subjects 65 years or older reported triptan therapy to be effective (11% "*completely*", 42% "*very*", 13% "*somewhat*").

Among respondents (irrespective of age) who had experienced trials each of oxygen, triptans, and opioids for acute treatment of cluster headache attacks, comparison of triptans and oxygen did not demonstrate a statistically significant difference in effectiveness (P value = .99), and oxygen was more likely to be effective than opioids (odds ratio: 19.94 (95% CI 16.32-24.38), P < .0001).

Safety and tolerability of acute oxygen therapy for cluster headache (Pearson et al., Figures 3 and 4)

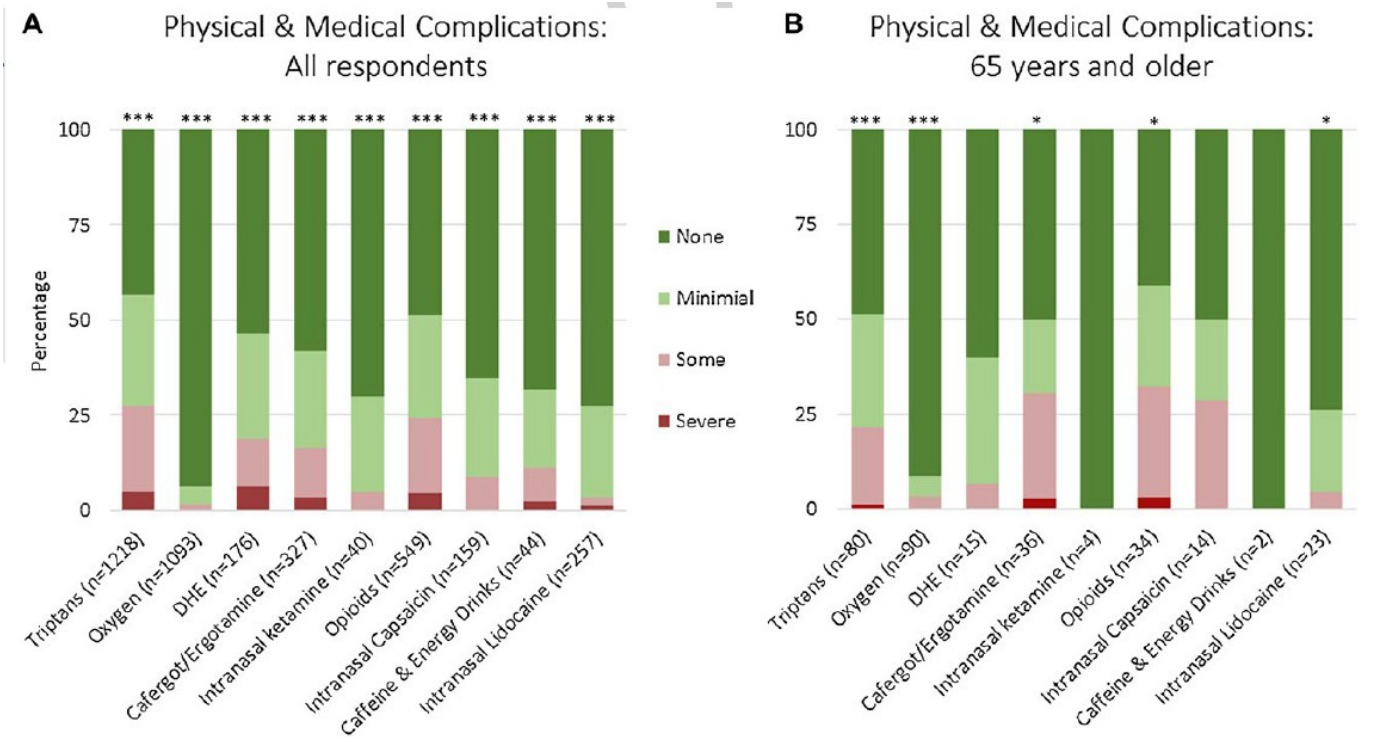

Fig. 3.—Physical and medical adverse effects of acute medications in cluster headache based on an international survey. Figure shows all respondents (A) and respondents age 65 and older (B). Not all respondents trialed every medication, thus the number of responses for each medication is shown. Adjusted *P* values compare no, mild, some, and severe adverse effects for individual medications; asterisks denote adjusted *P* value <.05 (*), <.001 (**), and <.0001 (***). Values for this figure are listed in Supplemental Table 3.

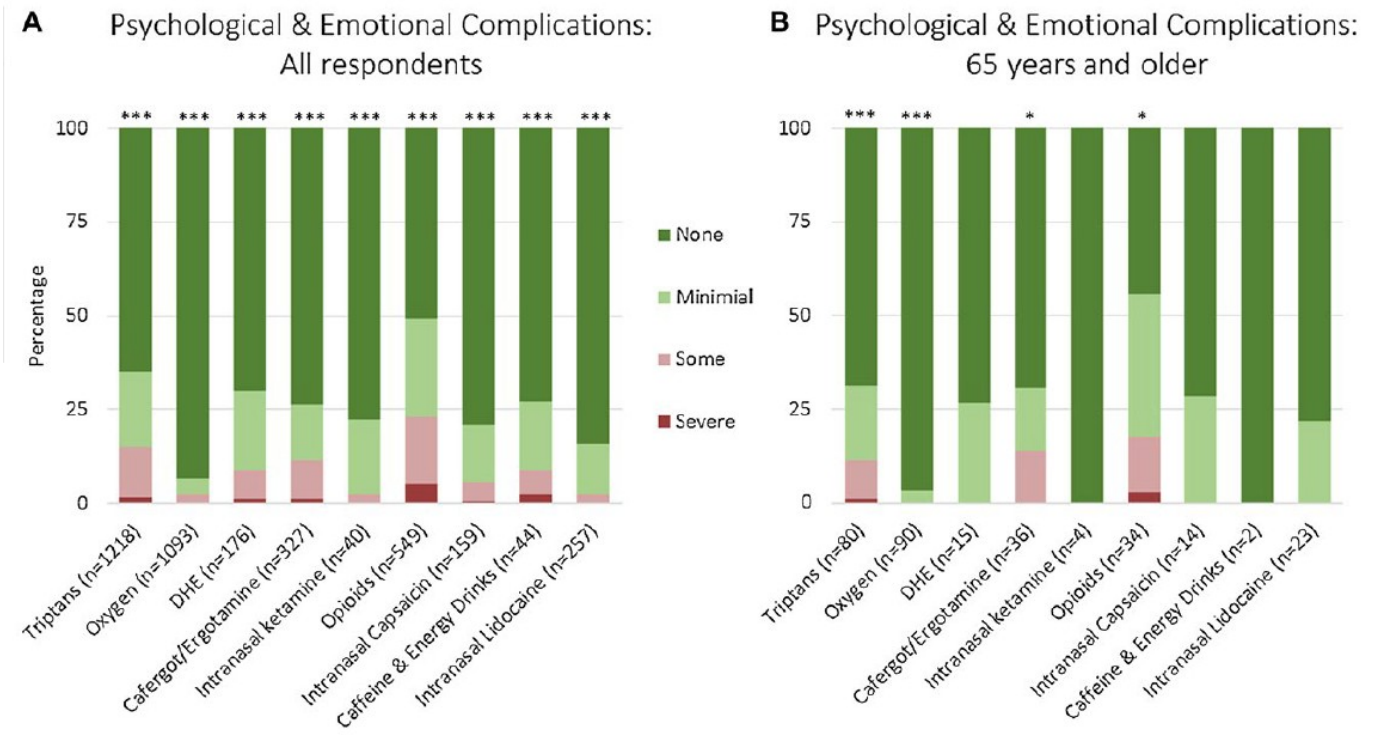

Fig. 4.—Psychological and emotional adverse effects of acute medications in cluster headache based on an international survey. Figure shows all respondents (A) and respondents age 65 and older (B). Not all respondents trialed every medication, thus the number of responses for each medication is shown. Adjusted *P* values compare no, mild, some, and severe adverse effects for individual medications; asterisks denote adjusted *P* value <.05 (*), <.001 (**), and <.0001 (***). Values for this figure are listed in Supplemental Table 3.

Among cluster headache subjects 65 years and older, reported complications of any kind from oxygen therapy were very uncommon. Specifically, 91% of such respondents reported "*no*", 6% reported "*minimal*", and 3% reported "*some*" physical and medical complications. While 97% of such respondents reported "*no*" and 3% reported "*minimal*" psychological and emotional complications. No respondents reported "*some*" or "*severe*" psychological and emotional complications.

Among respondents (irrespective of age) who had experienced trials each of oxygen, triptans, and opioids for acute treatment of cluster headache attacks, opioids (odds ratio 15.54, 95% CI 10.70-22.57, P < .0001), and triptans (odds ratio 6.71, 95% CI 4.67-9.65, P < .0001) were more likely than oxygen to be associated with physical or medical complications, and opioids (odds ratio 1628.18, 95% CI 981.78-2700.15, P < .0001), and triptans (odds ratio 464.43, 95% CI 300.94-716.73, P < .0001) were more likely than oxygen to be associated with psychological or emotional complications.

Other relevant, recently published, studies on acute oxygen therapy for cluster headache.

In addition to (Pearson et al. 2019), 13 peer-reviewed research studies or topic reviews (below) have been published since issuance of CAG-00296R that support the efficacy/effectiveness, tolerability, and safety of oxygen for the acute treatment of cluster headache attacks.

1. Dirkx, 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.
2. Evers, S., et al., The use of oxygen in cluster headache treatment worldwide - a survey of the International Headache Society (IHS). *Cephalalgia* 2017;37:396-398.
3. O'Brien, M., et al., Economics of Inhaled Oxygen Use as an Acute Therapy for Cluster Headache in the United States of America. *Headache* 2017;57:1416-1427.
4. Petersen, A.S., et al., Oxygen treatment of cluster headache: A review. *Cephalalgia* 2014;34:1079–1087.
5. Petersen, A.S., et al., Oxygen therapy for cluster headache. A mask comparison trial. A single-blinded, placebo-controlled, crossover study. *Cephalalgia*. 2017;37:214-224.
6. Robbins, M.S., et al., Treatment of Cluster Headache: The American Headache Society Evidence-Based Guidelines. *Headache* 2016;56:1093-106.
7. Rozen, T.D., R.S. Fishman, 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.
8. Rozen, T.D., Inhaled Oxygen for Cluster Headache: Efficacy, Mechanism of Action, Utilization, and Economics. *Curr Pain Headache Rep*. 2012;16:175-179.
9. Rozen, T.D., R.S. Fishman, Female cluster headache in the United States of America: what are the gender differences? Results from the United States Cluster Headache Survey. *J Neurol Sci*. 2012;317:17-28.
10. Rozen, T.D., R.S. Fishman, Demand valve oxygen: a promising new oxygen delivery system for the acute treatment of cluster headache. *Pain Med*. 2013;14:455-9.
11. Rozen, T.D., Cluster Headache Clinical Phenotypes: Tobacco Nonexposed (Never Smoker and No Parental Secondary Smoke Exposure as a Child) versus Tobacco-Exposed: Results from the United States Cluster Headache Survey. *Headache*. 2018;58:688-699.
12. Schindler, E.A.D., et al., Survey Analysis of the Use, Effectiveness, and Patient-Reported Tolerability of Inhaled Oxygen Compared With Injectable Sumatriptan for the Acute Treatment of Cluster Headache. *Headache* 2018;58:1568-1578.
13. Tepper, S.J., et al., Prescribing Oxygen for Cluster Headache: A Guide for the Provider. *Headache* 2017;57:1428-1430.

Three of these recent studies enrolled subjects that were 65 years or older (Dirkx, et al. 2018, Peterson, et al. 2017, Schindler, et al. 2018), and three further studies enrolled subjects that were 61 years or older (Rozen & Fishman. 2011, Rozen & Fishman. 2012, Rozen 2018).

In the (Rozen & Fishman 2011) on-line survey study, 1,134 cluster headache respondents were enrolled, of which 66% had tried oxygen therapy. These authors reported: "*Oxygen effectiveness did not vary by age class: ages 21-30 years (70% stated effective), ages 31-40 years (73% stated effective), ages 41-50 years (70% stated effective), ages 51-60 years (69% stated effective), and ages 61 plus years (67% stated effective).*"

Including the 2009 study of Cohen et al. (*JAMA*. 2009;302:2451-7), there are now three published prospective randomized controlled trials that report efficacy, tolerability, and safety of acute oxygen treatment for cluster headache attacks, and that included subjects 65 years or older. Though these studies were not powered to report subgroup analyses limited only to such older subjects, none of these studies reported serious adverse events for oxygen therapy for subjects of any age.

The CMS requirement for a prospective clinical trial under Coverage with Evidence Development (CED).

CMS stated in CAG-00296R that additional clinical research was required under a CED before coverage would be reconsidered for home oxygen for cluster headache:

"*The clinical study must address one or more aspect of the following questions*

1. *Prospectively, compared to individuals with cluster headache who do not receive NBOT, do Medicare beneficiaries with CH who receive NBOT have improved outcomes as indicated by:*
    a. *Pain relief*
    b. *Time to pain relief*
    c. *Durability of pain relief*
2. *Prospectively, among Medicare beneficiaries with cluster headache, which method of oxygen delivery provides the most benefit as indicated by:*
    a. *Pain relief*
    b. *Time to pain relief*
    c. *Durability of pain relief*
3. *Prospectively, among Medicare beneficiaries with cluster headache, what other factors, if any, predict patient's response to 100% oxygen therapy as indicated by:*
    a. *Pain relief*
    b. *Time to pain relief*
    c. *Durability of pain relief"*

…The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations the protocol must discuss why these criteria are necessary. Address the following:

- *Inclusion and exclusion criteria and how they will affect enrollment.*
- *Inclusion of women and minorities.*
- *Inclusion of Medicare enrollees.*

…There is insufficient evidence in the medical literature indicating that oxygen use is safe in Medicare patients with CH and other co-morbidities. Large studies are needed to confirm its safety in this group."

Necessity of a prospective clinical trial under Coverage with Evidence Development (CED).

We believe that the CMS requirement to develop and execute a prospective efficacy and safety clinical trial of oxygen for cluster headache attacks in patients 65 years or older is unnecessary.

The evidence from published studies (cited above) reveals no significant difference in the efficacy/effectiveness, tolerability, or safety of oxygen for cluster headache patients aged 65 years or older, relative to younger patients.

The premise that oxygen therapy for cluster headache is either significantly less effective, or incurs significantly higher risks of adverse events, among individuals aged 65 years or older is unsupported by published clinical trials or case reports which do not note any serious adverse events or serious side effects from the use of oxygen among cluster headache patients. CMS has cited no evidence to support such a safety concern specifically among cluster headache patients, either in CAG-00296R or subsequently.

Current CMS Guidelines for Home Oxygen Therapy (ICN 908804; October 2016) provide for coverage of home use of oxygen for "morning headaches" that are "hypoxia-related". This clinical indication is directly comparable to cluster headache since cluster headache attacks often awaken patients from sleep (i.e. "morning headaches"), and are also strongly linked to hypoxic mechanisms, including sleep apnea. It is undetermined if CMS required a similar prospective efficacy and safety trial before coverage of home oxygen was granted to Medicare beneficiaries with "hypoxia-related" "morning headaches".

Feasibility of a prospective clinical trial under Coverage with Evidence Development (CED).

The clinical study mandated by CMS is unfeasible. A prospective study limited to patients 65 years or older with cluster headache would meet multiple, likely insurmountable, challenges to enroll and retain subjects for a duration sufficient for completion of the study.

Prevalence estimates indicate that fewer than 50,000 Americans with cluster headache are 65 years or older (i.e. Medicare eligible). Therefore, cluster headache in this population is effectively an "orphan disease".

The recruitment experience of the (Pearson et al. 2019) survey study is informative. This study took 26 months to recruit and enroll a total of 139 subjects that were 65 years of age or older from an on-line global catchment. 90 of these subjects had used oxygen previously to treat cluster attacks. To control for bias, enrolled subjects in any mandated prospective trial would need to be oxygen therapy – naïve. Extrapolating from (Pearson et al. 2019), perhaps 50 oxygen – naïve subjects 65 years or older might be enrollable over two years via global on-line recruiting, of which only ~30 subjects (60%) would be from the United States.

The recruitment experience of the (Rozen and Fishman 2011) study (reference #7 above) is comparable. Of 1,134 enrolled US cluster headache subjects recruited over 3 months, only 57 subjects (5%) were 61 years or older. Further, only 34% of the total enrolled subjects were oxygen therapy – naïve. Extrapolating, the (Rozen and Fishman 2011) study likely enrolled only ~19 US subjects who were both oxygen therapy – naïve and were 61 years or older.

Note that these enrollment estimates from (Pearson et al 2019) and (Rozen & Fishman 2011) are based upon single interaction, on-line survey studies, not prospective treatment intervention trials that require transportation of subjects from home to investigator clinics for multiple visits over an extended period of time – perhaps totaling years.

The study population for a prospective oxygen trial would also have to be free from cardiovascular disease. It would be unethical for a prospective clinical trial of an acute treatment for an excruciating pain condition, such as cluster headache, to include a placebo arm, or to not permit effective rescue therapy, if one was available. Sumatriptan and injectable dihydroergotamine (DHE) are the only acute therapies proven effective and FDA-approved for cluster headache treatment, and both are contraindicated in the presence of significant cardiovascular risk factors.

Therefore, all enrolled subjects would need to be free of significant cardiovascular risk factors, so that they could either be randomized to an active comparator arm (sumatriptan or DHE), or receive sumatriptan or DHE rescue therapy, should oxygen be ineffective for acute attacks.

This cardiovascular exclusion would likely significantly limit trial enrollment. Cluster headache patients have a significantly higher prevalence of smoking which magnifies cardiovascular risks. Furthermore, 19% of Medicare beneficiaries have diagnosed heart disease, 42% self-report at least one heart condition, and > 69% have some form of cardiovascular disease (CMS: https://www.cms.gov/Research-Statistics-Data-and-Systems/Research/MCBS/Downloads/HeartConditions_DataBrief_2017.pdf, CDC: https://www.cdc.gov/dhdsp/maps/quick-maps/costs-hd-prevalence.htm, AHA: https://www.heart.org/idc/groups/ahamah-public/@wcm/@sop/@smd/documents/downloadable/ucm_502138.pdf?utm_campaign=sciencenews17-18&utm_source=science-news&utm_medium=heart&utm_content=heart07-25-18).

CAG-00296R mandates that the prospective trial design pay particular attention to patient subgroups such as women and minorities. It is unclear from CAG-00296R how many total socio-demographic subgroups must be included in the trial analyses, such as sexual orientation, ethnic, and socio-economic demographics. For a prospective study in this orphan population to be powered to report meaningful efficacy and safety data in numerous such subgroups would be nearly impossible. For example, cluster headache is far less prevalent among women than men; in both the (Pearson et al. 2019) and the (Rozen and Fishman 2011) studies, only a third of enrolled subjects were women.

Study subjects in the prospective trial would need to be enrolled by investigators at study sites proximate to subjects' homes to permit adequate trial management and scheduled or emergent study follow-up visits. It is unclear how many enrollable subjects would live near enough to the few US cluster headache clinical trials investigators who might agree to participate in the study.

Further, cluster headache attacks occur sporadically in "cluster periods" and it is unclear how long individuals would need to be followed to ensure an adequate number of treated attacks could be studied, in order for the studies to be adequately powered both for efficacy and safety endpoints.

Finally, prospective longitudinal studies in the elderly are often challenging to complete due to higher drop-out rates secondary to significant mobility, morbidity, or mortality concerns. To generate valid safety data, a longitudinal study with a sufficient number of treatment exposures would be necessary. It is unclear how many treated attacks, how many treated subjects, and how many months/years of treatment, would be required for a trial to achieve sufficient power to draw valid safety conclusions.

Harms of pursuing a prospective clinical trial under Coverage with Evidence Development (CED).

Denial of CMS coverage of home oxygen for cluster headache attacks causes significant harm to Medicare beneficiaries, and delay in reconsideration and reversal of CAG-00296R in order to pursue a prospective trial prolongs those harm exposures.

Cluster headache attacks must be treated without delay. These attacks typically occur with sudden ferocity reaching excruciating levels of pain within seconds. Attacks may resolve spontaneously after approximately an hour, and then

recur up to 8 times per day, every day for several months during a "cluster period". In chronic forms of the disease, attacks may occur every day without relief.

In your letter to Representative Harris, you state: "*Patients seeking relief from cluster headaches may go to the emergency department or to their physician's office where high dose oxygen is administered in these controlled settings.*" This is a misrepresentation of the nature of this clinical problem as generally there is no time for a patient to travel to an emergency department or physician's office to receive oxygen to abort an attack effectively, and before that attack typically is resolving spontaneously. Even under ideal hypothetical circumstances where patients might receive oxygen at an emergency department or physician's office immediately at the onset of an attack, this could not be a clinically acceptable or cost effective treatment option for attacks up to 8 times daily for months.

The persistent lack of coverage of home oxygen also increases risks of other major harms. As noted in the (Pearson et al 2019) data above, opioids are typically ineffective for cluster headache treatment and associated with adverse outcomes. These harms may include opioid use disorders and overdose. In a reported cluster headache cohort, 41% of subjects were actively prescribed opioids and the cohort was associated with a 3-fold higher incidence of drug dependence (Choong et al. *Headache* 2017;57,S3:181). Patients with cluster headache seeking interim relief also may be treated with recurrent courses of corticosteroids, thus exposing them to risks of avascular osteonecrosis, diabetes, etc. Untreated cluster headache is also associated with a 20 fold increased risk of suicide.

CMS response to this "Formal Request for National Coverage Determination Reconsideration"

Since the issuance of CAG-00296R in (1/4/11), CMS has received repeated appeals to review and reconsider the denial of coverage of home oxygen coverage for cluster headache.

Leaders of the American Headache Society, the American Academy of Neurology, the Alliance for Headache Disorders Advocacy, and Clusterbusters, have appealed to CMS and met with CMS representatives on multiple occasions since 2010 to instate coverage of home oxygen for Medicare beneficiaries with cluster headache.

On (1/9/14), Dr. William Young of the Alliance for Headache Disorders Advocacy formally requested reconsideration of CAG-00296R (letter attached). Further, in May 2014, Members of the US Senate (Senators Coons, Johaans, Inhofe, Durbin, Fischer, Tester, Ayotte, Warren, Markey, Merkley, Manchin, Pryor, Casey, Carper, Shaheen) and US House of Representatives (Representative Eshoo) also wrote to then CMS Administrator Marilyn Tavenner to appeal CAG-00296R (letters attached). On (6/24/14), Administrator Tavenner denied reconsideration (letter attached).

In June 2017, Mr. Bryan Shuy, Deputy Chief of Staff for Representative Andy Harris, MD discussed this issue directly with Dr. James Rollins of CMS Coverage and Analysis Group, who reiterated the requirement for a prospective clinical trial. On (3/22/18), Representative Harris wrote to you, as noted above.

From CMS–3284–N, we understand that CMS has "*determined that 60 days is usually a reasonable time period for us to make a decision to accept or reject decline an external NCD reconsideration request*". CMS also "*strives to complete NCD-related activities in a timely and efficient manner, often before statutory deadlines*" and "*prioritizes requests based on the magnitude of the potential impact on the Medicare program and its beneficiaries*".

Providing relief to elderly Americans with the most excruciating pain that humans can experience, must meet CMS criteria as the highest "*magnitude of the potential impact on the Medicare program and its beneficiaries*".

For all the reasons cited above, we urge you to accelerate review of the current request for reconsideration of CAG-00296R, and overturn it as a highest priority.

Further, should you conclude that reversal of CAG-00296R is again to be denied, we hereby request, in advance, to meet with you personally to discuss this issue at your very earliest opportunity.

Thank you very much for your consideration.

Sincerely,

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Research Submissions

Effectiveness of Oxygen and Other Acute Treatments for Cluster Headache: Results From the Cluster Headache Questionnaire, an International Survey

Stuart M. Pearson, MA; Mark J. Burish, MD, PhD; Robert E. Shapiro, MD, PhD; Yuanqing Yan, PhD; Larry I. Schor, PhD

Objective.—To assess the effectiveness and adverse effects of acute cluster headache medications in a large international sample, including recommended treatments such as oxygen, commonly used medications such as opioids, and emerging medications such as intranasal ketamine. Particular focus is paid to a large subset of respondents 65 years of age or older.

Background.—Large international surveys of cluster headache are rare, as are examinations of treatments and side effects in older cluster headache patients. This article presents data from the Cluster Headache Questionnaire, with respondents from over 50 countries and with the vast majority from the United States, the United Kingdom, and Canada.

Methods.—This internet-based survey included questions on cluster headache diagnostic criteria, which were used as part of the inclusion/exclusion criteria for the study, as well as effectiveness of medications, physical and medical complications, psychological and emotional complications, mood scores, and difficulty obtaining medications. The diagnostic questions were also used to create a separate group of respondents with probable cluster headache. Limitations to the methods include the use of nonvalidated questions, the lack of a formal clinical diagnosis of cluster headache, and the grouping of some medications (eg, all triptans as opposed to sumatriptan subcutaneous alone).

Results.—A total of 3251 subjects participated in the questionnaire, and 2193 respondents met criteria for this study (1604 cluster headache and 589 probable cluster headache). Of the respondents with cluster headache, 68.8% (1104/1604) were male and 78.0% (1245/1596) had episodic cluster headache. Over half of respondents reported complete or very effective treatment for triptans (54%, 639/1139) and oxygen (54%, 582/1082). Between 14 and 25% of respondents reported complete or very effective treatment for ergot derivatives (dihydroergotamine 25%, 42/170; cafergot/ergotamine 17%, 50/303), caffeine and energy drinks (17%, 7/41), and intranasal ketamine (14%, 5/37). Less than 10% reported complete or very effective treatment for opioids (6%, 30/541), intranasal capsaicin (5%, 7/151), and intranasal lidocaine (2%, 5/241). Adverse events were especially low for oxygen (no or minimal physical and medical complications 99%, 1077/1093; no or minimal psychological and emotional complications 97%, 1065/1093), intranasal lidocaine (no or minimal physical and medical complications 97%, 248/257; no or minimal

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Conflict of Interest: The authors SM Pearson, MJ Burish, Y Yan, and LI Schor have no conflicts of interest. RE Shapiro has served as a paid consultant to Eli Lilly as a member of the Data Monitoring Committee for galcanezumab multi-center clinical trials for both cluster headache and migraine.
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Stuart M. Pearson and Mark J. Burish contributed equally to this work as first authors.

psychological and emotional complications 98%, 251/257), intranasal ketamine (no or minimal physical and medical complications 95%, 38/40; no or minimal psychological and emotional complications 98%, 39/40), intranasal capsaicin (no or minimal physical and medical complications 91%, 145/159; no or minimal psychological and emotional complications 94%, 150/159), and caffeine and energy drinks (no or minimal physical and medical complications 89%, 39/44; no or minimal psychological and emotional complications 91%, 40/44). This is in comparison to ergotamine/cafergot (no or minimal physical and medical complications 83%, 273/327; no or minimal psychological and emotional complications 89%, 290/327), dihydroergotamine (no or minimal physical and medical complications 81%, 143/176; no or minimal psychological and emotional complications 91%, 160/176), opioids (no or minimal physical and medical complications 76%, 416/549; no or minimal psychological and emotional complications 77%, 423/549), or triptans (no or minimal physical and medical complications 73%, 883/1218; no or minimal psychological and emotional complications 85%, 1032/1218). A total of 139 of 1604 cluster headache respondents (8.7%) were age 65 and older and reported similar effectiveness and adverse events to the general population. The 589 respondents with probable cluster headache reported similar medication effectiveness to respondents with a full diagnosis of cluster headache.

Conclusions.—Oxygen is reported by survey respondents to be a highly effective treatment with few complications in cluster headache in a large international sample, including those 65 years or over. Triptans are also very effective with some side effects, and newer medications deserve additional study. Patients with probable cluster headache may respond similarly to acute medications as patients with a full diagnosis of cluster headache.

Key words: cluster headache, trigeminal autonomic cephalalgia, probable cluster headache, oxygen, triptan, Medicare

Abbreviations: BDI Beck Depression Inventory, CHQ Cluster Headache Questionnaire, HDSQ Hopelessness Depression Symptom Questionnaire, ICHD International Classification of Headache Disorders

(*Headache* 2019;0:1-15)

INTRODUCTION

Cluster headache is a primary headache disorder characterized by severe unilateral pain lasting 15–180 minutes, occurring up to 8 times daily, that is associated with cranial autonomic features and/or restlessness.[1] In the acute treatment of cluster headache, options are limited and high-flow oxygen has received much attention for several reasons. First, oxygen is 1 of only 3 acute treatments with level A evidence from either American or European guidelines, along with sumatriptan (subcutaneous and nasal formulations) and zolmitriptan (nasal formulation).[2,3] Oxygen is also the preferred acute treatment in pregnancy and lactation.[4,5] Second, oxygen has minimal side effects, contraindications, and limitations whereas triptans such as sumatriptan and zolmitriptan have side effects, vascular contraindications, and limitations for the number of times they can be used daily.[6] Third, oxygen is not always reimbursed by insurance carriers for cluster headache. In the United States, oxygen for cluster headache was covered by at least 4 private commercial health insurance companies but not all,[7] and more insurance companies covered sumatriptan than oxygen.[8] In addition, oxygen was not covered by the US Centers for Medicare and Medicaid Services,[7] which includes coverage for many patients 65 years and older. In a survey of headache societies worldwide, which did not include the United States, oxygen was reimbursed for cluster headache in 50% of the 22 countries that responded, with only 3 countries having restrictions for patients 65 years and older.[9]

We aim to investigate how oxygen compares to other acute medications recommended by current guidelines, such as the triptans and intranasal lidocaine, as well as to other frequently used medications such as opioids, caffeine, and, more recently, intranasal ketamine. We also aim to investigate treatments and complications in the subgroup of respondents 65 years and older. This dataset has previously been presented as an abstract.[10]

METHODS

The Cluster Headache Questionnaire (CHQ) is a self-administered internet-based survey conceived and constructed by authors SMP and LIS, with authors MJB and RES asked to provide input as neurologists and assist in analysis and interpretation, and author YY asked to provide statistical analysis. The CHQ consists of 152 items organized into 8 separate sections: (1) Sign up and Verification; (2) Symptom Screening; (3) Demographics; (4) Experience; (5) Medications/Treatment; (6) Beck Depression Inventory; (7) Hopelessness Depression Symptom Questionnaire; and (8) End of Survey – Contact Options. Sections 1–5 were newly created by the authors and were tested on 10 cluster headache respondents and reviewed by 1 neurologist prior to

release of the final version; however, these questions were not otherwise validated. The scope of this manuscript focuses primarily on "Medications/Treatment" in Section 5. Several of the questions for Sections 2 and 5 are shown in Supplemental Figure 1. The study was performed in Qualtrics, which enabled the authors to construct, distribute, collect, and securely store responses. Qualtrics is an online survey company that provides web-based survey software, encrypted cloud-based data storage, and controlled user access. The University of West Georgia holds a Qualtrics software license and datacenter.

Informed Consent. Respondents were given a summary of the intent and purpose of the research as well as a brief summary of each section. In the frame following, respondents were required to verify their age (18 years or older) as well as agree to participate in the survey. Due to concerns about suicidality, international suicide prevention resources were embedded in the CHQ and respondents could skip some questions that were deemed to be potential triggers. At the end of the survey, respondents could elect to share their contact information for further follow-up, but this was not required.

Distribution and Data Collection. Recruitment, distribution, and data collection consisted of 3 concurrent efforts: direct email through the Clusterbusters member listserv, web-site hosting through Clusterbusters and the International Headache Society, and advertising on Google via Google AdWords as well as Reddit forum. Clusterbusters is a nonprofit organization with a mission statement that includes "research, education, support, and advocacy related to cluster headache"[11] and thus their website would be expected to select for respondents interested in more information on several aspects of cluster headache. The survey was open without a password. It was voluntary and accessible internationally by anyone with internet access; however, the survey utilized cookies and recorded IP addresses to identify unique survey respondents and prevent multiple submissions. The survey was presented in the same order to all respondents and displayed a progress bar; respondents could use a "back button" to review their responses before submission, and progress was saved (based on IP address) allowing respondents to close their browser or navigate away. No incentives were offered for taking the survey. IRB approval was obtained in January 2016 from the University of West Georgia, the survey was piloted in February 2016 with 10 cluster headache respondents and a neurologist, and the survey was open online from March 2016 to April 2018.

Participants. For inclusion, participants must have: (1) stated that they were at least 18 years of age; (2) stated that they had been diagnosed with cluster headache by a medical professional; (3) completed at least 90% of the survey including all inclusion/exclusion questions; and (4) filled out the English version (other versions were generated in Google translate but have not been fully verified by native speakers). For exclusion, participants answered several questions that addressed the full International Classification of Headache Disorders (ICHD) 3-beta criteria for cluster headache and probable cluster headache,[12] including all autonomic features except for rhinorrhea, and all other criteria except criterion E ("not better accounted for by another ICHD-3-beta diagnosis"). Because we asked respondents about their longest period of remission in the last year, the definitions of episodic and chronic cluster headache reflect the new ICHD-3 criteria that were released during this study (ie, 3 months of headache freedom for episodic cluster headache).[1] Chronic cluster headache was defined as a remission period lasting less than 3 months in the last year; episodic cluster headache was defined as all respondents who stated that they were episodic, as well as all respondents who stated they were chronic but the headache remission period was 3 months or longer. Authors MJB and RES reviewed these questions and excluded all respondents who did not meet the criteria for cluster headache or probable cluster headache. However, the authors did not corroborate a formal clinical diagnosis of cluster headache. The diagnoses of cluster headache and probable cluster headache were never combined in the analysis and were always examined independently.

Development. Qualtrics provides an adaptive/responsive display framework in conjunction with response validations, thus not all respondents received all 152 questions. Questions were grouped on each screen so that an individual screen could contain between 1 and 30 questions. At a minimum, the survey prompted and required all respondents to answer "yes," "no," or "decline to answer" for each treatment subcategory. Section 5 (Medications/Treatment) divided interventions into 4 subsections: preventive medications, abortive medications, unregulated treatments, and surgical/neuromodulation treatments. For the abortive medication section, the first question displayed a list of common abortive medications

in "Check Box" format: (1) Triptans; (2) 100% Oxygen; (3) Cafergot/Ergotamine; (4) Intranasal Ketamine; (5) Lidocaine Nasal Drops; (6) DHE–IV (Migranal); (7) Intranasal Capsaicin; and (8) Opiates, as well as 3 additional "other" boxes for respondent write-in (see Supplemental Fig. 1). Questions about triptans referred not to specific medications or specific routes of delivery but to the class of triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan). Questions about oxygen mentioned 100% oxygen but did not specify a flow rate, flow duration, or type of delivery mask or cannula used. For the purposes of the survey, oxygen was included as a "medication." Intranasal capsaicin was included as an abortive despite being recommended as a preventive medication that may take several days for effect[13] because some patients have found immediate relief and use it in an abortive fashion. Questions for each medication were asked as follows:

1. Effectiveness: This question carried forward and displayed only the previously checked medications. Respondents then evaluated the effectiveness of each medication as: (1) completely ineffective; (2) minimally effective; (3) somewhat effective; (4) very effective; and (5) completely effective. No further explanation or definitions of these choices were provided.
2. Access: This question asked respondents "how difficult it was to obtain" each medication as: (1) no difficulty; (2) slight difficulty; (3) some difficulty; (4) extreme difficulty; and (5) unable to get. No further explanation or definitions of these choices were provided.
3. Adverse events: Respondents were subsequently asked to evaluate the psychological or emotional complications as well as the physical or medical complications of each medication in 2 separate questions. For both questions, respondents chose from (1) none; (2) minimal complications; (3) some complications; or (4) severe complications. These questions also displayed text/write-in option allowing respondents to describe if they marked "severe" complications. No further explanation or definitions of these choices were provided.

One category of abortive medications – caffeine and energy drinks – was created after the survey was closed because a free text box was allowed and there were a high number of entries for caffeine, coffee, espresso, and energy drinks. We excluded combination medications such as caffeine plus aspirin or acetaminophen plus caffeine plus butalbital. While the study did ask about abortive neuromodulation devices such as sphenopalatine ganglion stimulation and vagus nerve stimulation as acute treatments, there were less than 25 responses for each and the type of device used could not be verified, thus they were not included in the analysis.

Statistical analysis: All statistical analyses were performed in R, version 3.4.2 (www.r-project.org). For categorical variables, a multinomial test was used to test the null hypothesis of equal value. To test the relationship between nominal and ordinal variables, we calculated Freeman's Theta and performed a Cochran–Armitage test for trend. A Bonferroni correction was used to adjust P values, and adjusted P values less than .05 were considered statistically significant. A separate Bonferroni correction was calculated for each analysis (ie, a specific Bonferroni correction was calculated for each figure). Two-tailed tests were used throughout the study.

To compare medications, we reduced the Likert scales from 5 categories to 2 categories to increase statistical strength, limited our analysis to the 3 most commonly used treatments in the survey (oxygen, triptans, and opioids), then performed a generalized linear mixed-effects model using these 3 medications as the predictors. The significance was then evaluated by likelihood ratio tests; post hoc pairwise comparisons of oxygen, triptans, and opioids were examined using Tukey's method through the "lsmeans" package in R version 3.4.2.[14] The categories were reduced from 5 to 2 before analyzing the data after discussion between authors. The reduced categories were as follows: (1) high effectiveness (completely effective and very effective) vs low effectiveness (somewhat effective, minimally effective, and completely ineffective); and (2) high complications (severe complications and some complications) vs low complications (minimal complications and no complications).

No statistical calculation of power was performed prior to the study. Sample size was based on a previous study.[15] Due to the rarity of the disorder, the study was open for 2 years to ensure sufficient time for the widest reach internationally. In this study, we analyzed 2 subsets of respondents: (1) probable cluster headache, decided after the survey started but before analysis began, and (2) respondents 65 years

and older, a subset decided before the survey began in part to investigate the difference in insurance coverage in this age group. All other analyses were planned either before the survey began (by authors SMP and LIS) or after the survey started but before analysis began (by authors MJB, RES, and YY).

Missing data are as follows. For cluster headache respondents, 8 respondents did not provide an answer for chronic vs episodic (n = 1596), 3 respondents did not answer duration of headache (n = 1601), and 1 respondent did not answer the Beck's Depression Inventory II (n = 1603). There were several respondents that answered questions on complications and access to medications that did not answer the question about effectiveness, suggesting missing data on effectiveness for 25 triptans, 11 oxygen, 6 dihydroergotamine, 24 cafergot/ergotamine, 3 ketamine, 8 opioid, 8 capsaicin, 3 caffeine and energy drinks, and 16 lidocaine. The full range of missing data for medications, however, is unknown: in our survey design, a blank response could mean the respondent did not try a medication, but could also mean that they forgot that they tried a medication. For probable cluster headache respondents, 1 respondent did not provide an answer for age of onset (n = 588), and 2 respondents did not provide an answer for chronic vs episodic (n = 587).

RESULTS

A total of 4876 IP addresses were recorded on the website representing 4876 potential subjects. A total of 3251 subjects agreed to participate in the questionnaire, and 2193 (1604 cluster headache and 589 probable cluster headache) met inclusion and exclusion criteria for the study (Fig. 1). Demographics and locations of included respondents with cluster headache are shown in Table 1. Compared to published reports,[15,16] the participants represent a typical sample of cluster headache patients in terms of sex, age of onset, duration of headaches, and proportion with restlessness; however, they reported a slightly lower proportion of episodic cluster headache and slightly higher average frequency of attacks per day. They include a wide range of ages, with 139 respondents age 65 and older. The participants reported from 6 continents and 56 countries/territories (Supplemental Table 1), with the majority (80.5%, 1292/1604) from 3 countries: the United States, the United Kingdom, and Canada. Compared to the cluster headache sample, respondents with probable cluster headache had a similar age of onset and a similar proportion of restlessness, with a higher proportion of women, a lower proportion of episodic cluster headache, a longer duration of headaches, and a higher frequency of attacks (Supplemental Table 2).

Figure 2 shows responses for the effectiveness of acute medications in all respondents (Fig. 2A) and in respondents 65 years and older (Fig. 2B) (data also reported in table format in Supplemental Table 3). In all respondents, triptans and oxygen were reported as completely effective or very effective in 54% each, dihydroergotamine in 25%, cafergot/ergotamine in 17%, caffeine and energy drinks in 17%, opioids in 6%, intranasal capsaicin in 5%, and intranasal lidocaine in 2%. Respondents 65 years and older reported similar effectiveness: triptans were reported as completely effective or very effective in 61%, and oxygen in 56%. There was a small sample size of respondents 65 and older taking other treatments, and findings were not significant.

We specifically compared the effectiveness of oxygen, triptans, and opioids and observed a statistical significance of the association ($P < .001$). We further tested which medication differed in effectiveness and found: (1) triptans and oxygen were not statistically different in effectiveness ($P = .99$); (2) triptans were more likely to be effective than opioids (odds ratio 19.77, 95% confidence interval [CI] 16.18-24.16, $P < .0001$); and (3) oxygen was more likely to be effective than opioids (odds ratio: 19.94 (95% CI 16.32-24.38), $P < .0001$). The subgroup of respondents age 65 and older had a smaller sample size and was not investigated in this comparative analysis.

Further analysis was performed on respondents with complete effectiveness to 1 or more medications to see if any categories might be predictive of an excellent response to cluster headache medications. Complete effectiveness did not vary significantly by sex, age, country, or cluster headache features; however, complete effectiveness of triptans interestingly did associate with the effectiveness of calcium channel blockers and corticosteroids, while no other acute medication had any significant associations (Supplemental Table 4).

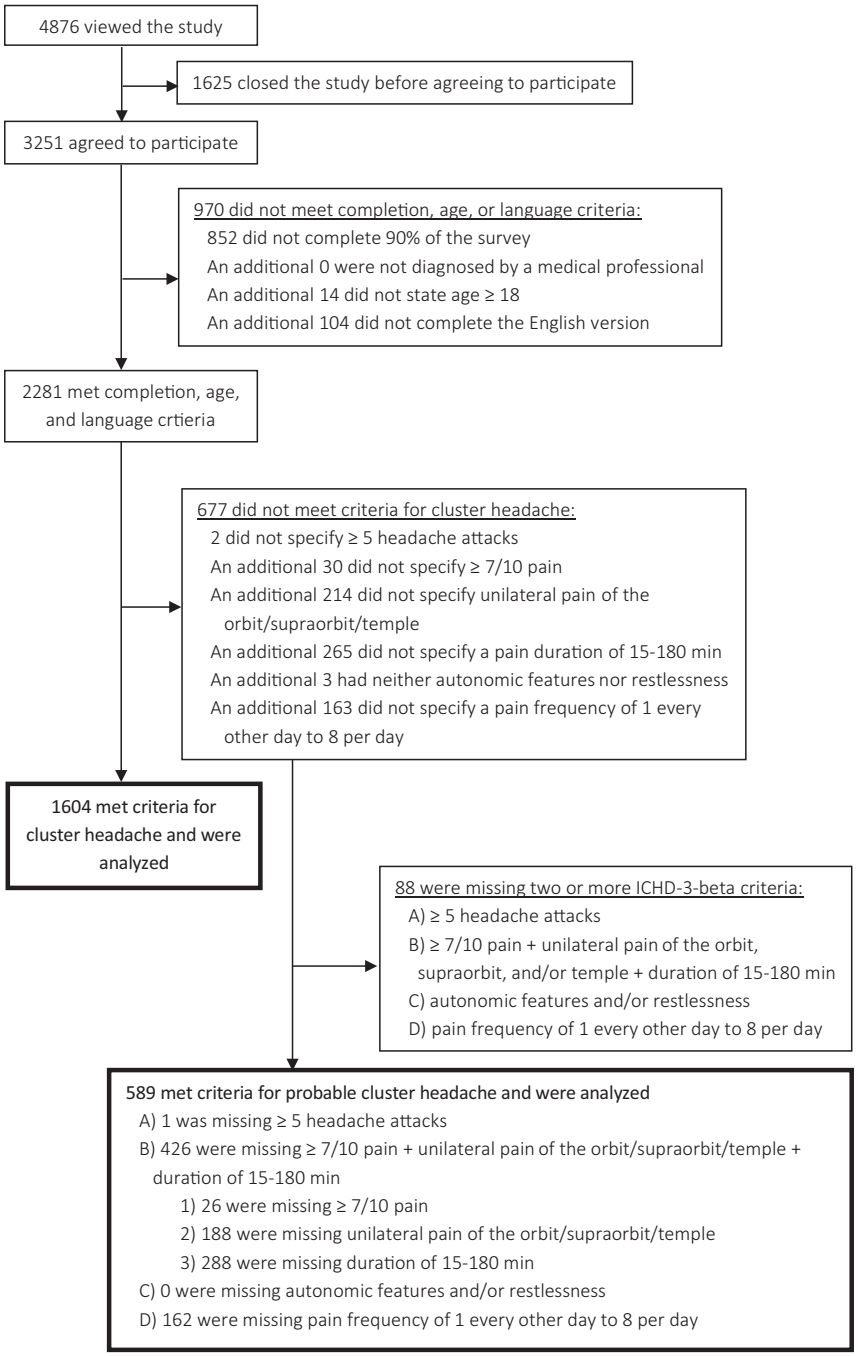

Fig. 1.—Flow diagram of inclusion and exclusion. Respondents who opened the study were identified by IP addresses; for all other portions of the flow chart, respondents were identified based on answers to screening questions. Probable cluster headache was defined as respondents with all but one of the ICHD-3-beta criteria for cluster headache; of note the study did not ask about rhinorrhea or about criterion E, "not better accounted for by another ICHD-3-beta diagnosis."

Further analysis was also performed after dividing respondents into episodic and chronic cluster headache. Oxygen gas was more effective in episodic cluster headache than in chronic cluster headache (adjusted $P = .0007$, see Supplemental Fig. 2). No significantly different responses between episodic and chronic cluster headache were seen for triptans, dihydroergotamine, cafergot/ergotamines, intranasal ketamine, opioids, intranasal capsaicin, caffeine and energy drinks, or intranasal lidocaine (data not shown).

Respondents were also asked about any side effects of acute medications. Figure 3 shows

Table 1.—Demographics of Survey Respondents With Cluster Headache

	Cluster headache (total n = 1604)
Basic demographics	
Age in years	46 (13)
Age 65 and older in years	139 (8.7%)
Sex	1104 male (68.8%), 497 female (31%), 3 other (0.2%)
Headache characteristics	
Episodic vs chronic diagnosis	1245 episodic (78.0%), 351 chronic (22.0%)
Age of onset of cluster headache in years	27 (13)
Duration of headache in hours	1.4 (0.7)
Frequency of headache in attacks/day	3.9 (2.1)
Respondents with restlessness	1550 (96.6%)
Continent of residence	
North America: 7 countries/ territories responding	1074 (67%)
Europe: 30 countries responding	382 (23.8%)
Australia/Pacific Islands: 2 countries responding	77 (4.8%)
Africa: 4 countries responding	33 (2.1%)
Asia: 9 countries responding	31 (1.9%)
South America: 4 countries responding	7 (0.4%)

Data reported as either "average (standard deviation)" or as "total number (% of total)." For frequency of headache, episodic cluster headache respondents were asked about the frequency during the peak of their headache cycle. Respondents with probable cluster headache are not included in this Table (see Supplemental Table 2) nor is a full list of countries (see Supplemental Table 1). Chronic cluster headache was defined as a remission period lasting less than 3 months in the last year; all other patients were considered episodic, including those with chronic cluster headaches in previous years.

physical and medical complications. In all respondents (Fig. 3A), there were no or minimal physical and medical complications for oxygen at 99%, intranasal lidocaine at 97%, ketamine at 95%, and intranasal capsaicin at 92%. There were also no or minimal physical and medical complications for caffeine and energy drinks at 89%, cafergot/ergotamine at 83%, dihydroergotamine at 81%, opioids at 76%, and triptans at 73%. Complications did not vary significantly by sex or age, though triptan complications did vary by country (Supplemental Table 5). Physical and medical complications generally associated with psychological and emotional complications for the same medication. Complications did not vary with depression or hopelessness inventories for any medication. In respondents 65 years and older (Fig. 3B), no or minimal physical and medical complications were seen for oxygen at 97%, intranasal lidocaine at 96%, triptans at 79%, cafergot/ergotamine at 69%, and opioids at 68%.

Figure 4 shows psychological and emotional complications, which show similar findings to physical and medical complications. In all respondents (Fig. 4A), there were no or minimal psychological and emotional complications for intranasal lidocaine at 98%, ketamine at 98%, oxygen at 97%, intranasal capsaicin at 94%, dihydroergotamine at 91%, and caffeine and energy drinks at 91%. There were also no or minimal psychological and emotional complications for cafergot/ergotamine at 89%, triptans at 85%, and opioids at 77%. In respondents 65 years and older (Fig. 4B), no or minimal psychological and emotional complications were seen for oxygen at 100%, triptans at 89%, cafergot/ergotamine at 86%, and opioids at 82%. Respondents 65 years and older reported very few complications from oxygen overall, with 91% (82/90) showing no, 6% (5/90) showing minimal, and 3% (3/90) showing some physical and medical complications, and 97% (87/90) showing no and 3% (3/90) showing minimal psychological and emotional complications.

We also tested the association of oxygen, triptans, and opioids with physical and medical complications and observed a statistical significant association ($P < .001$). The post hoc testing to evaluate which medication differed in complications revealed: (1) oxygen was less likely to have physical or medical complications than triptans (odds ratio 464.43, 95% CI 300.94-716.73, $P < .0001$); (2) oxygen was less likely to have physical or medical complications than opioids (odds ratio 1628.18, 95% CI: 981.78-2700.15, $P < .0001$); and (3) triptans were less likely to have physical or medical complications than opioids (odds ratio 3.51, 95% CI 2.68-4.59, $P < .0001$). In this study, the extremely high odds ratios were due to missing medication information: only 27.7% of respondents trialed all of oxygen, triptans, and opioids; furthermore, there were very few respondents with complications from oxygen (28 respondents). We then analyzed the data of the 27.7% of respondents who had trialed all 3 of oxygen, triptans, and opioids (394 respondents) and again found similar patterns: oxygen had less complications than triptans or opioids, and triptans

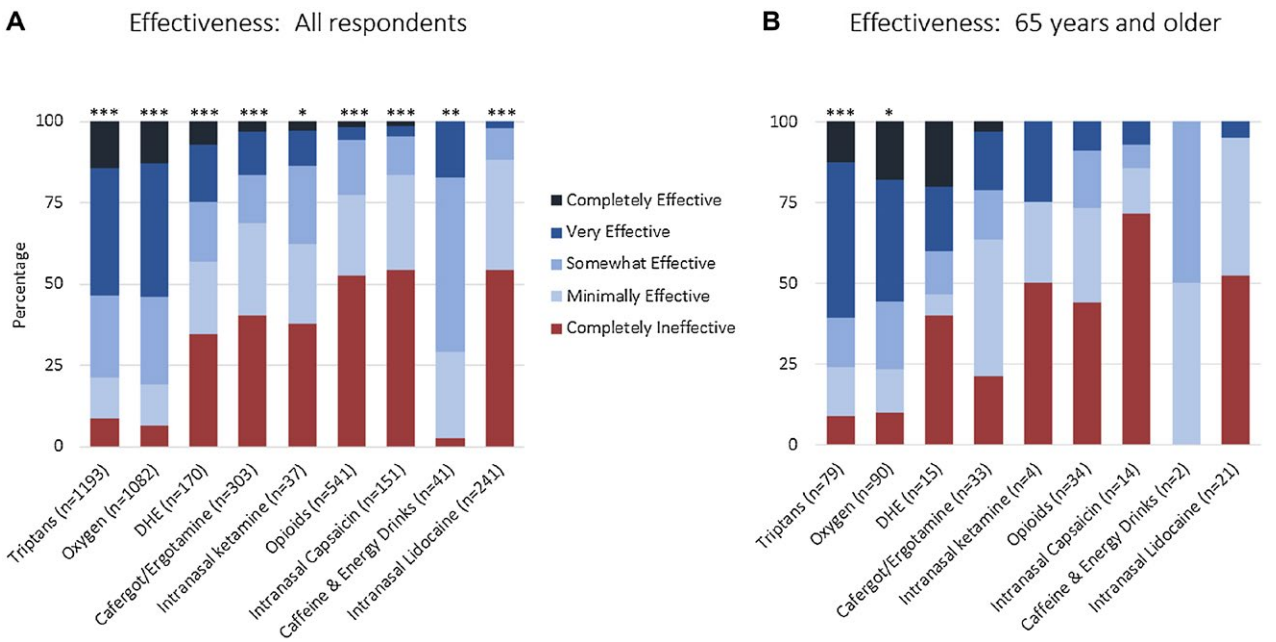

Fig. 2.—Effectiveness of acute medications in cluster headache based on an international survey. Figure shows all respondents (A) and respondents age 65 and older (B). Not all respondents trialed every medication, thus the number of responses for each medication is shown. Adjusted *P* values compare completely effective, very effective, somewhat effective, minimally effective, and completely ineffective for individual medications; asterisks denote adjusted *P* value <.05 (*), <.001 (**), and <.0001 (***). Values for this figure are listed in Supplemental Table 3.

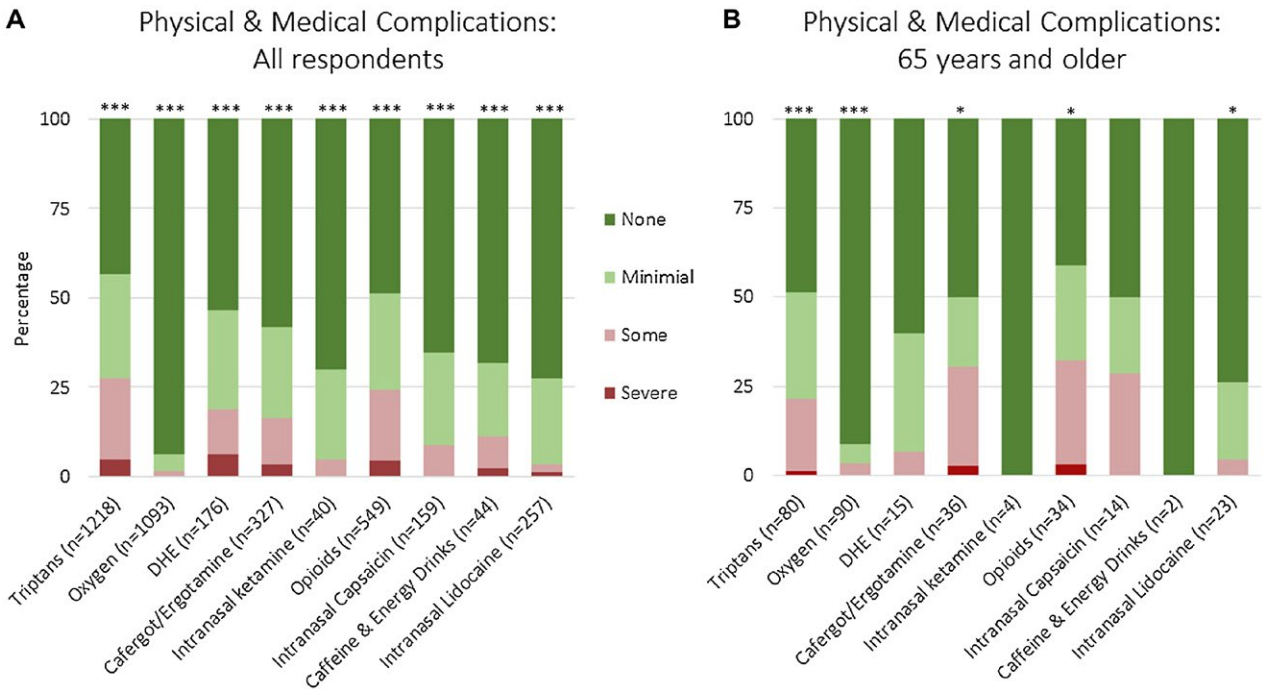

Fig. 3.—Physical and medical adverse effects of acute medications in cluster headache based on an international survey. Figure shows all respondents (A) and respondents age 65 and older (B). Not all respondents trialed every medication, thus the number of responses for each medication is shown. Adjusted *P* values compare no, mild, some, and severe adverse effects for individual medications; asterisks denote adjusted *P* value <.05 (*), <.001 (**), and <.0001 (***). Values for this figure are listed in Supplemental Table 3.

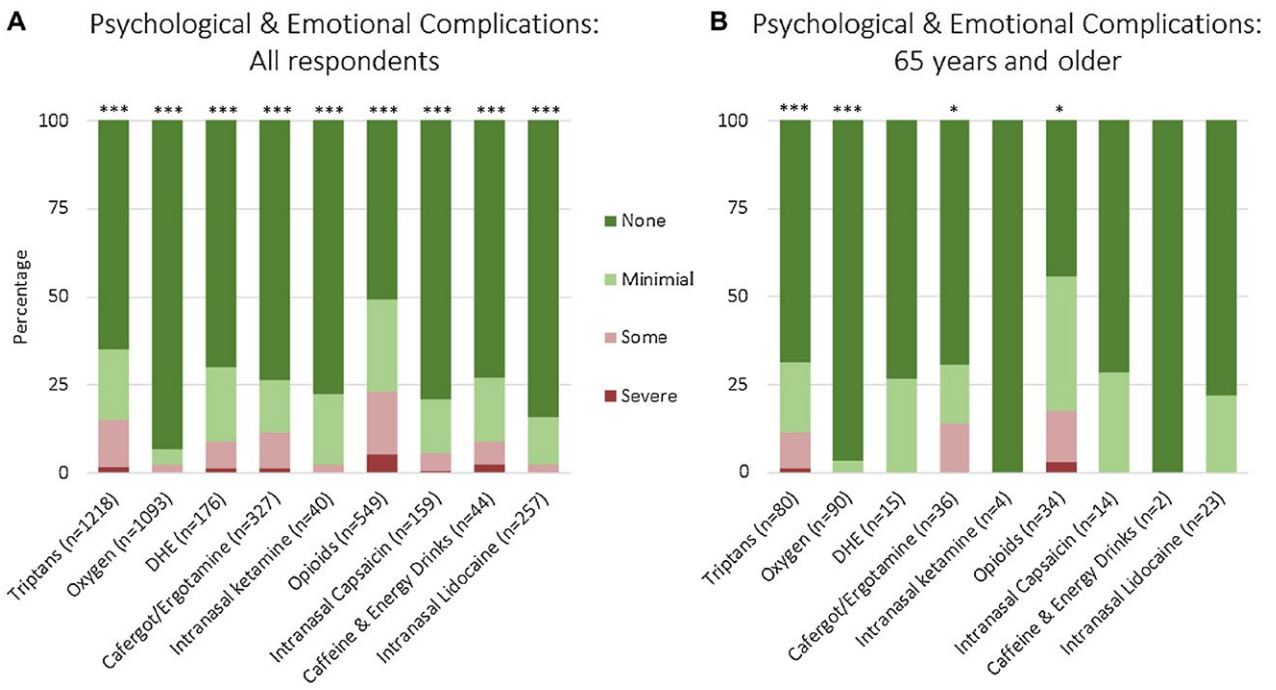

Fig. 4.—Psychological and emotional adverse effects of acute medications in cluster headache based on an international survey. Figure shows all respondents (A) and respondents age 65 and older (B). Not all respondents trialed every medication, thus the number of responses for each medication is shown. Adjusted *P* values compare no, mild, some, and severe adverse effects for individual medications; asterisks denote adjusted *P* value <.05 (*), <.001 (**), and <.0001 (***). Values for this figure are listed in Supplemental Table 3.

had less complications than opioids. Specifically, there was a significant association between physical or medical complications and medications ($P < .0001$) with odds ratios as follows: triptans vs opiates (odds ratio 2.31, 95% CI 1.85-2.90, $P < .0001$); oxygen vs opiates (odds ratio 15.54, 95% CI 10.70-22.57, $P < .0001$); oxygen vs triptans (odds ratio 6.71, 95% CI 4.67-9.65, $P < .0001$). The findings were identical for psychological or emotional complications: oxygen was less likely to have psychological or emotional complications than either triptans (odds ratio 464.43, 95% CI 300.94-716.73, $P < .0001$) or opioids (odds ratio 1628.18, 95% CI 981.78-2700.15, $P < .0001$), and triptans were also less likely to have psychological or emotional complications than opioids (odds ratio 3.51, 95% CI 2.68-4.59, $P < .0001$). The subgroup of respondents age 65 and older had a smaller sample size and was not investigated in this comparative analysis.

The questionnaire explored access to acute treatments for cluster headache. Figure 5 shows the ability to obtain medications in all respondents and in those 65 years and older. For all respondents, no difficulty or slight difficulty was seen for caffeine and energy drinks at 100%, intranasal capsaicin at 91%, intranasal lidocaine at 81%, cafergot/ergotamine at 77%, intranasal ketamine at 73%, dihydroergotamine at 64%, opioids and triptans at 60% each, and oxygen at 49%. For oxygen, an additional question was added for time to prescription (Supplemental Fig. 3A) and data were available for 566 respondents: 36% of respondents were able to obtain oxygen within 1 month of their diagnosis of cluster headache, 25% within 1-6 months, 11% within 6-12 months, 15% within 1-2 years, and 13% within 2-5 years. For respondents over age 65, data on 46 respondents were available: 37% were able to obtain oxygen within 1 month of their diagnosis of cluster headache, 24% within 1-6 months, 9% within 6-12 months, 15% within 1-2 years, and 15% within 2-5 years. For respondents with difficulty obtaining oxygen, reasons included that physicians did not believe it would be effective or covered by insurance, insurance would not cover it, there were problems obtaining the medication, the respondent was a smoker, and practicality (Supplemental Fig. 3B). However, access was ultimately available for all medications: very few respondents were unable to get any of the treatments.

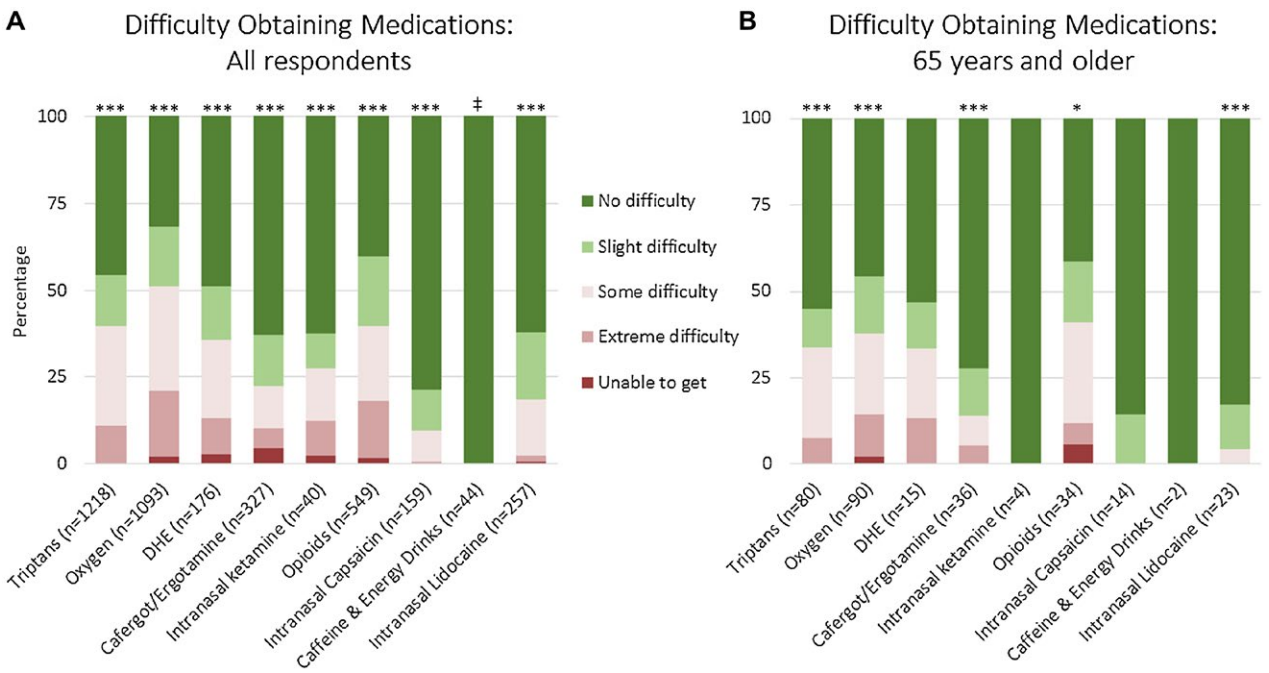

Fig. 5.—Difficulty in obtaining acute medications in cluster headache based on an international survey. Figure shows all respondents (A) and respondents age 65 and older (B). Not all respondents trialed every medication, thus the number of responses for each medication is shown. Adjusted *P* values compare no, mild, some, and severe adverse effects for individual medications; asterisks denote adjusted *P* value <.05 (*), <.001 (**), and <.0001 (***). ‡For "Caffeine & Energy Drinks" in all respondents, no respondent reported a side effect and therefore no statistical comparisons were necessary. Values for this figure are listed in Supplemental Table 3.

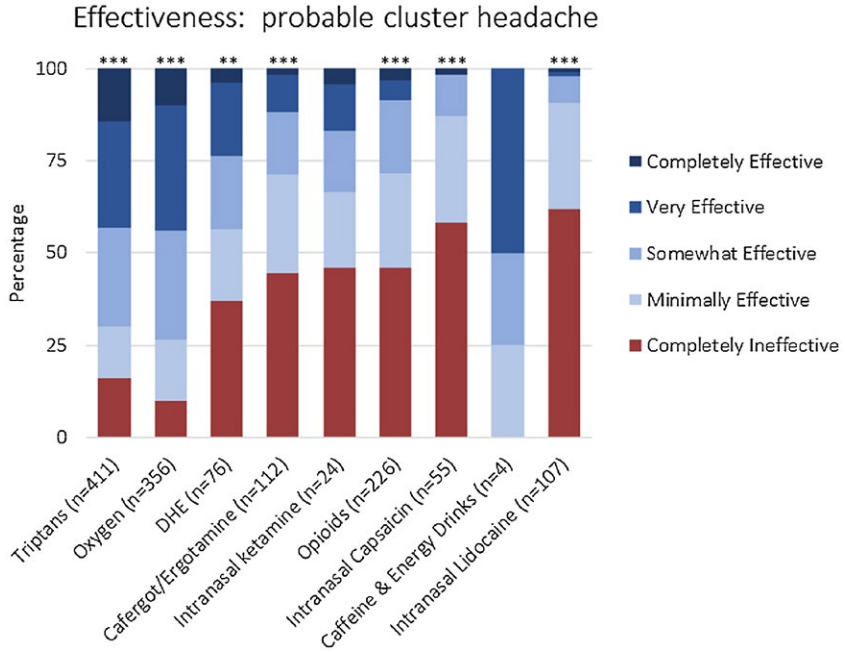

Fig. 6.—Effectiveness of acute medications in probable cluster headache based on an international survey. Not all respondents trialed every medication, thus the number of responses for each medication is shown. Adjusted *P* values compare completely effective, very effective, somewhat effective, minimally effective, and completely ineffective for individual medications; asterisks denote adjusted *P* value <.05 (*), <.001 (**), and <.0001 (***). Values for this figure are listed in Supplemental Table 3.

Finally, the questionnaire examined respondents with probable cluster headache (Supplemental Table 2). Respondents must have fulfilled criteria for 3 of Criteria A-D[1]: only 1/589 missed Criterion A ("at least 5 attacks"), 72% or 426/589 missed Criterion B ("severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes"), none missed Criterion C (cranial autonomic features and/or restlessness or agitation), and 28% or 162/589 missed Criterion D ("occurring with a frequency between one every other day and 8 per day"). For respondents with a duration outside of 15-180 minutes, the majority (89% or 256/288) reported headaches greater than 3 hours and the longest headache duration was 5 hours. For respondents with a frequency outside of 1 every other day and 8 per day, the majority (94.4% or 153/162) reported more than 8 headaches per day with the most attacks per day at 12. The effectiveness of acute medications in respondents with probable cluster headache (Fig. 6) were generally similar to respondents with a full diagnosis of cluster headache. Oxygen was reported as completely effective or very effective in 44% (178/411), triptans in 43% (178/411), dihydroergotamine in 24% (18/76), cafergot/ergotamine in 12% (13/112), opioids in 8% (19/226), intranasal capsaicin in 2% (1/55), and intranasal lidocaine in 2% (2/107). Intranasal ketamine and caffeine and energy drinks did not meet significance and had small sample sizes.

DISCUSSION

This is the largest cluster headache survey performed to date with respect to number of respondents to investigate the effect of acute medications in cluster headache. Oxygen in particular had a high rate of complete effectiveness, a low rate of ineffectiveness, and a low rate of physical, medical, emotional, and psychological side effects. However, respondents reported that it was difficult to obtain. Triptans also had a high rate of effectiveness but also had high rates of complications. Dihydroergotamine and cafergot/ergotamine had intermediate effectiveness and intermediate side effects, while intranasal capsaicin and intranasal lidocaine were easy to access with limited complications, but also limited effectiveness. This study is the first to investigate the effects of intranasal ketamine, opioids, and caffeine in a large sample. Intranasal ketamine has an intermediate rate of effectiveness and few side effects. It has primarily been used by our American respondents (31 of 40 from the United States, 7 of 40 from Canada, and 1 each from the United Kingdom and Spain). Opioids, in contrast, are completely ineffective in more than half of respondents, with only 1% finding them completely effective and 4% finding them very effective, and with physical, medical, psychological, and emotional complications reported in some respondents. This study does not differentiate between types of opioids, and it is not clear if 1 type may be more effective than another. Interestingly, caffeine and energy drinks did have some degree of effectiveness in the majority of respondents with low levels of complications. A recent study in Denmark showed that cluster headache subjects were more likely to drink energy drinks but not coffee compared to controls,[17] and energy drinks often have higher doses of caffeine. The effects of caffeine in our study were not collected systematically as they were obtained after the study from free text entries, but are interesting and require further examination.

When comparing the most commonly used medications, oxygen was more likely to be effective than opioids but not triptans. Oxygen was less likely to have complications than either opioids or triptans.

This study is also the first to investigate the effectiveness of acute medications in probable cluster headache in a large sample. Probable cluster headache may respond similarly to cluster headache, with triptans and oxygen having high levels of effectiveness. It should be noted, however, that the ICHD-3-beta Criterion E ("not better accounted for by another ICHD-3 diagnosis") was not included in this study, thus the definition of probable cluster headache requires meeting all but one of criteria A-D.

The effectiveness of oxygen for cluster headache attacks ranges between 56% and 82% across multiple controlled and open-label trials, as well as clinic and non-clinic based questionnaires.[8,18-27] This study is a non-clinic based questionnaire showing oxygen as completely effective in 13%, very effective in 41%, somewhat effective in 27%, minimally effective in 12%, and completely ineffective in 7%. This study adds to the current literature in several ways. First, this is a large international survey, and again

confirms that oxygen is reported by respondents to be highly effective for cluster headache. Second, given the size of the study we are able to comment on a large subgroup of older respondents. Respondents 65 years and older, like other respondents, find oxygen to be highly effective with minimal complications. The older respondents generally replicated the responses of all respondents: oxygen and triptans were effective but difficult to obtain, with triptans having some complications and oxygen having few complications. Opioids had intermediate levels of effectiveness and high levels of complications.

As the study did not specify the oxygen flow rate or mask type, the results in this study may in fact underestimate the effectiveness of the guideline recommendations for oxygen 6-7 L/min or higher.[2,3] While oxygen is highly effective, it may not be the most effective treatment because all triptans were grouped together. Subcutaneous sumatriptan may be more effective than oxygen based on some previous questionnaires,[21,28] though a questionnaire that specifically compared oxygen >10 L/min to injectable sumatriptan found no difference in effectiveness.[27] Thus higher doses of oxygen at 10-15 L/min or more, which are used in clinical practice,[29] may be the most effective doses of oxygen. Similarly, cafergots and ergotamine were grouped together, as were all routes of administration for dihydroergotamine.

Previous studies have looked at factors associated with oxygen in an attempt to predict who might respond. Oxygen responsiveness has been positively associated with shorter attacks and a lack of interictal pain,[23] and negatively associated with photophobia or phonophobia during an attack,[30] nausea and vomiting during an attack,[26] or restlessness.[26] Previous studies have found conflicting results for associations with age,[18,23,26,27] sex,[18,23,31] and history of smoking.[23,26,27,30,32] Our findings show no association of responses to any acute therapies with any cranial autonomic features examined (rhinorrhea was not examined) and no association with restlessness, photophobia/phonophobia, nausea/vomiting, age (current age or age of onset of cluster headaches), sex, or any other feature examined. However, this study does find that respondents who respond to triptans are also more likely to respond to calcium channel blockers and steroids. While a subgroup of treatment-responsive patients may exist, another explanation is that these treatments all have the highest level recommendation in European guidelines[2] and thus it may not be surprising that patients respond to all of these medications. The current literature does not suggest a genetic subgroup of patients that respond to triptans, calcium channel blockers, and steroids: a report has linked the rs5443 polymorphism of the GNB3 gene to a positive triptan response in cluster headache, but this polymorphism was not related to verapamil or steroid response.[33] Our study had very few respondents that were completely refractory to all medications and our study did not collect information on cluster-like headaches as a result of intracranial lesions, carotid endarterectomies, or other disorders; therefore, we cannot comment on these aspects of cluster headache.

Recent studies have suggested that some treatments are more efficacious in episodic cluster headache than in chronic cluster headache, including 1 acute treatment (noninvasive vagal nerve stimulation[34,35]) and, in preliminary news releases, 2 preventive treatments (galcanezumab, fremanezumab[36,37]). Our study found that oxygen is significantly more effective in episodic cluster headache than chronic cluster headache, but there were no differences for other acute medications. The differential responses of vagal nerve simulation, galcanezumab, fremanezumab, and oxygen between episodic and chronic cluster headache require further investigation, as it is not clear what these 4 treatments share that is not shared by triptans, ergotamines, ketamine, capsaicin, caffeine and energy drinks, or lidocaine.

Most respondents were able to obtain all treatments in the study, but a higher percentage had difficulty obtaining oxygen. There is a variety of possible reasons. First, there are insurance barriers to obtaining oxygen. However, among US respondents 65 years or older, few were completely unable to get the medication; this could be because some respondents pay out of pocket for oxygen or have other types of insurance than Medicare. Further, respondents were not asked at what age they sought therapies, and some respondents may have obtained oxygen or other treatments prior to age 65 years. Physician barriers to access might also exist. In one previous study, 12% of providers refused to prescribe oxygen, and the respondents stated that the providers' reasoning was that either they did not think it would work (44%), they did not know about oxygen for cluster headache (32%), or they were not convinced by the medical literature on

oxygen effectiveness (16%).[8] Another proposed medical concern of oxygen includes mucosal damage and thinning of the temporal retinal nerve fiber layer;[38] furthermore there is a proposed safety concern with a flammable gas in a disease with a high rate of smokers.[39] There are also logistical barriers, as one study found that less than half of prescriptions specified a flow rate or mask type, and half of patients never received proper training.[8] Finally, there may be patient preferences, as patients may simply not prefer oxygen because it is expensive or inconvenient.[24] Oxygen may take longer for full effect than other treatments[8] or the headaches may return when the oxygen is stopped.[18,22,40] This study does not investigate these concerns specifically. However, the study does suggest that oxygen has a lower rate of complications than other acute medications used for cluster headache.

There are several limitations to this study. First, this is a self-administered questionnaire with an inherent recall bias. Furthermore, questions about physical, medical, psychological, and emotional complications may be interpreted differently by different respondents. Second, the study did not confirm a diagnosis of cluster headache. Several questions related to the ICHD-3-beta criteria were asked in an attempt to increase accuracy; however, all ICHD-3-beta criteria were not included. There is significant symptomatic overlap between cluster headache and other headache disorders, in particular paroxysmal hemicrania and hemicrania continua. Both of these headache disorders are completely responsive to indomethacin, and this study did not inquire about indomethacin effectiveness. However, the population prevalence of these disorders is substantially less than cluster headache. Third, as the oxygen flow rate was not specified and all triptans were grouped together, the study may have misestimated the side effects and access to these medications. However, in clinical trials there were no serious adverse effects of oxygen at 12 L/min,[20] and in a study of different oxygen masks for cluster headache with oxygen at 15 L/min, all adverse events were determined to be unrelated to the study.[39] Also, oxygen may be easier to obtain at lower flow rates, and certain triptans may be easier to obtain than others. Fourth, this study did not include all recommended acute treatments for cluster headache, notably it did not ask about octreotide and did not have sufficient numbers of responses for sphenopalatine ganglion stimulation or vagus nerve stimulation. And finally, the study did not specify when respondents had tried various treatments: for some, treatment response may have changed over time; in the subgroup of patients over 65, some of the treatments likely had been tried before the age of 65 for some respondents.

In conclusion, oxygen is reported by survey respondents to be a highly effective treatment with few complications in cluster headache in a large international sample. When choosing among acute treatments, this study suggests that oxygen be considered first-line therapy for cluster headache patients regardless of age, as supported by recent clinical trials[20] and current guidelines.[2,3]

STATEMENT OF AUTHORSHIP

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(b) Acquisition of Data

Stuart M. Pearson, Larry I. Schor

(c) Analysis and Interpretation of Data

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Category 2

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Category 3

(a) Final Approval of the Completed Manuscript

Stuart M. Pearson, Mark J. Burish, Robert E. Shapiro, Yuanqing Yan, Larry I. Schor

Acknowledgments: We thank Robert Wold and Stewart Tepper for insights into study design. We thank Clusterbusters and the International Headache Society for promoting the questionnaire. This study received funding support from Autonomic Technologies, Inc. and Clusterbusters. Clusterbusters did not have a direct role in analysis or interpretation but the following should be noted: (1) Robert Wold is a founding member of Clusterbusters; (2) two of the authors (RES and LIS) have served in advisory roles for Clusterbusters; (3) preliminary data from this study were presented at a Clusterbusters annual conference.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web site.

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March 22, 2018

The Honorable Seema Verma
Administrator
Centers for Medicare & Medicaid Services
US Department of Health and Human Services
200 Independence Avenue SW
Washington, DC 20201

Dear Administrator Verma,

I write to request your urgent reconsideration of the Centers for Medicare & Medicaid Services (CMS) non-coverage determination (NCD) of home use of oxygen therapy for acute treatment of cluster headache (CAG-00296R).

Cluster headache is widely recognized as one of the most severely painful disorders known. Approximately 500,000 people in the US may experience cluster headache, where pain occurs in abrupt and agonizing attacks, in cyclical patterns that can last for weeks to months. Fifteen percent of people with cluster headache experience attacks of excruciating pain every day.

High flow rate 100% oxygen therapy provides critical relief from the acute pain of cluster headache so that patients can regain quality of life. Oxygen therapy for the treatment of cluster headache is effective within minutes. This is a crucial therapeutic benefit for a condition where recurrent individual attacks often reach extreme pain levels within seconds. It is the only reliable, safe, and effective acute therapy available for individuals living with cluster headache.

I have both personal and professional familiarity with this specific medical issue. I have experienced the excruciating pain of cluster headache attacks and I can attest to the extraordinary effectiveness, rapidity, and reliability of oxygen therapy for their relief. Moreover, as a practicing anesthesiologist, and past Chief of Obstetric Anesthesiology at the Johns Hopkins Hospital, I am highly familiar with the detailed benefits and risks of medical gas therapies, including those for oxygen. I am confident that high flow 100% oxygen therapy is safe for use at home by Medicare beneficiaries for the acute treatment of cluster headache attacks.

Oxygen therapy has been an undisputed first line agent for acute treatment for cluster headache attacks, since it was first reported in 1952. This medical consensus is supported by broad clinical experience and by controlled clinical trial research data that support its efficacy and safety, including enrolled subjects up to 70 years of age (Cohen et al. *JAMA*. 2009;302:2451-2457.). There are no published clinical trial reports or case reports, whatsoever, of any serious adverse events or serious side effects of use oxygen therapy for cluster headache in patients of any age group. As a consequence, oxygen therapy is cited as the standard of care in the practice guidelines and texts for cluster headache therapy of the National Institutes of Health, Agency for Healthcare Research Quality, American Headache Society, American Academy of Neurology, Health Resources & Services Administration, European Federation of Neurological Societies, National Headache Foundation, and the Institute for Clinical Systems Improvement. The Veterans Administration covers home oxygen therapy for its beneficiaries with cluster headache.

As a result of the NCD, Medicare and Medicaid covered cluster headache patients often receive unnecessary, costly, and typically ineffective, emergency department services and hospital admissions. The duration of cluster headache attacks (mean approximately one hour, maximum three hours) makes this treatment impractical in emergency departments; attacks often end before patients can reach hospital-based treatment. Furthermore, the common nocturnal timing of attacks, and their frequency (i.e. often multiple times per day, every day, for weeks) makes emergency department treatment infeasible.

There is no safe and effective alternative to oxygen therapy for many Medicare eligible cluster headache patients. Available alternative acute therapies carry clear and serious risks. While 6mg subcutaneous sumatriptan is an FDA-approved treatment for this cluster headache indication, it is not proven safe for use more than twice per day, or daily for weeks on end. Cluster headache attacks may occur up to eight times per day. CMS also limits availability of sumatriptan, often to no more than 10 treatments per month. Sumatriptan is contraindicated in the setting of cardiovascular ischemic risks or stroke which are prevalent among Medicare eligible patients.

Lack of availability of home oxygen therapy has led to prescription of opioids for cluster headache patients resulting in adverse outcomes. Opioid medications are typically ineffective for this disorder, but carry established risks of dependency, abuse, and addiction. The lack of availability of home oxygen for relief from excruciating cluster headache attacks may also lead to patient self-harm; cluster headache is associated with a 20-fold increased risk of suicide. Finally, further financial hardship may fall to low-income Medicare or Medicaid beneficiaries if they have been prescribed home oxygen for cluster headache, but must pay for this out of pocket due to the NCD.

The NCD cites potential safety risks for home use of oxygen for cluster headache that are not necessarily relevant in this setting. For example, the NCD cites a "risk of suppression of the hypoxic drive to breathe" in unsupervised COPD patients receiving oxygen therapy. However, such hypothetical effects are usually associated with prolonged oxygen exposures not seen with cluster headache treatment. And, of course, oxygen is only available by prescription and the prescriber would take co-existing diseases into account. Oxygen therapy when delivered, as indicated, for cluster headache attacks is only deployed for a maximum of 20 minutes at a time, as needed, typically once or twice daily, and up to a maximum of 8 times per day.

The NCD also cites oxygen therapy as leading to risks of significant tissue damage, such as "blindness and pulmonary fibrosis". Yet the NCD again cites publications stating that "the first signs of toxicity appear after 10 hours of oxygen at 1 ATA [atmosphere]" (Tinits, P, *Ann Emerg Med*. 1983;12:321) and that "100% oxygen can be tolerated at sea level for about 24-48 hours without any serious tissue damage" (Patel et al, *Journal Indian Academy of Clinical Medicine*, 2003; 4:234). This latter publication further mentions toxicity risks from prolonged oxygen that are certainly irrelevant to Medicare beneficiaries, such as blindness from retrolental fibroplasia (almost exclusively reported in premature infants) or deafness from dysbaric osteonecrosis (almost exclusively reported in astronauts in space). These remote potential risks of oxygen therapy cited in the NCD should certainly not weigh against the manifest relief from recurrent excruciating pain.

Current CMS Guidelines for Home Oxygen Therapy (ICN 908804; October 2016) do, in fact, appear to already cover home use of oxygen for cluster headache, though this is not recognized by CMS. That is, CMS covers home use of oxygen in the setting of "morning headaches", if these symptoms are deemed to be "hypoxia-related". This clinical indication is directly comparable to cluster headache. That is, cluster headache attacks often occur with nocturnal timing, awakening patients from sleep (i.e. "morning headaches"). Cluster headache is also strongly linked to hypoxic mechanisms. Apart from cluster headache attacks being relieved by high-flow 100% oxygen, sleep apnea is associated with hypoxia and has a greater than 8-fold higher prevalence among cluster headache patients.

Prior to granting CMS coverage of home oxygen for cluster headache, the NCD mandated that an approved prospective clinical study be performed to prove the safety of this therapy in a cohort of Medicare eligible patients (Coverage with Study Participation (CSP) form of Coverage with Evidence Development (CED)). This demand presents multiple, likely insurmountable, challenges. Prevalence estimates indicate that fewer than 50,000 Americans with cluster headache are 65 years or older (i.e. Medicare eligible). The NCD also mandates that adequate safety assessments be performed in particular patient subgroups of that elderly population. Specifically these subgroups include racial, sex, sexual orientation, ethnic, and socio-economic

demographics. Further, for validity, study subjects would likely be excluded from the trial if they had previously received oxygen therapy for cluster headache. A valid trial would also exclude subjects that had significant cardiovascular risks (common among Medicare eligible patients) since this would contra-indicate the use of subcutaneous sumatriptan, either as rescue therapy or as a positive treatment control arm. It would be unethical to include a placebo arm in the proposed trial given the availability of a therapy with proven efficacy (i.e. sumatriptan) for these severely painful attacks. Moreover, subjects in this study would need to live sufficiently close to investigator study sites for appropriate study follow-up visits, either scheduled or possibly emergent. This proposed large, diverse, elderly study cohort would then need to be followed longitudinally for possibly ten years of participation to generate meaningful long-term safety results. In other words, it would be essentially impossible to identify and recruit study subjects in sufficient quantity and for sufficient duration for the required study to be successfully executed. Finally, such a safety trial would also likely be exorbitantly expensive to undertake, with no obvious funding mechanism in sight. Did CMS require a similar prospective safety trial before coverage of home oxygen was granted to Medicare beneficiaries with "hypoxia-related" "morning headaches"?

Since 2010, leaders of the American Headache Society, the American Academy of Neurology, the Alliance for Headache Disorders Advocacy, and Clusterbusters (the national cluster headache patient advocacy organization) have appealed to CMS on multiple occasions to instate coverage of home oxygen use for cluster headache. These appeals were uniformly denied.

In May 2014, a number of my US congressional colleagues (Senators Coons, Johaans, Inhofe, Durbin, Fischer, Tester, Ayotte, Warren, Markey, Merkley, Manchin, Pryor, Casey, Carper, Shaheen, and Representative Eshoo) also wrote to then-CMS Administrator Marilyn Tavenner to appeal the NCD. Her formal response to them from (6/24/14) was to continue the non-coverage policy, with her explanation limited to stating that "no clinical trials involving the home use of oxygen to treat CH have been approved by the Centers for Medicare & Medicaid Services".

On June 1st of last year, my Deputy Chief of Staff, Mr. Bryan Shuy, spoke directly with Dr. James Rollins (Director, Division of Items and Devices, Coverage and Analysis Group, CMS) about reversing the NCD. At that time, Dr. Rollins re-iterated the CMS requirement for new trial safety data. Subsequent to Mr Shuy's conversation with Dr. Rollins, new clinical data have, in fact, emerged that further strongly support reversal of the NCD.

Investigators at the University of West Georgia recently shared with me not-yet published retrospective survey data of patients diagnosed by physicians with cluster headache. Among 61 cluster headache patients aged 65 or older (mean age 70 years old, oldest 98 years old) who

had used oxygen therapy for cluster headache attacks (mean 2503 oxygen treatments per respondent lifetime), none had ever experienced any severe psychological, emotional, physical, or medical complications of oxygen therapy. Moreover, sixty four percent of these respondents reported oxygen to be either very or completely effective for acute treatment of cluster headache attacks.

In summary, it is the uniform consensus medical opinion that home use of oxygen for cluster headache is very safe and highly effective. This is beyond dispute. The value of this therapy is not in clinical equipoise. It is therefore unethical for CMS to continue to withhold coverage of this treatment from Medicare and Medicaid patients.

I respectfully request your urgent review and reversal of the anomalous and wholly unsupported NCD that denies coverage of home use of oxygen to treat cluster headache attacks among Medicare and Medicaid beneficiaries.

I would greatly appreciate your careful and timely attention to this request and response. I would welcome the opportunity to discuss this with you further.

Sincerely,

Andy Harris, M.D.

Member of Congress

DEPARTMENT OF HEALTH & HUMAN SERVICES

Centers for Medicare & Medicaid Services

Administrator
Washington, DC 20201

AUG 23 2018

The Honorable Andy Harris
U.S. House of Representatives
Washington, DC 20515

Dear Representative Harris:

Thank you for your letter regarding Medicare coverage of home use of oxygen to treat cluster headaches (CH). I appreciate hearing from you on this issue.

The national coverage determination (NCD) referenced in your letter is specific to the home use of oxygen to treat CH, and the NCD finalized coverage for this treatment under the coverage with evidence development paradigm for beneficiaries enrolled in an approved clinical study. Please note, the NCD does not prevent patients with CH from seeking treatment using oxygen in hospitals and other healthcare settings.

As you are aware, there are currently no clinical trials involving the home use of oxygen to treat CH that have been approved by the Centers for Medicare & Medicaid Services (CMS). We acknowledge that there are numerous anecdotal studies in the medical literature that demonstrate that high dose oxygen in a controlled setting is effective in the treatment of cluster headaches.

Patients seeking relief from cluster headaches may go to the emergency department or to their physician's office where high dose oxygen is administered in these controlled settings. We appreciate you bringing the issues you raised in your letter regarding the current NCD to our attention. In order to move forward on this topic, published studies demonstrating that the use of high dose oxygen for CH in the home setting leads to improved health outcomes needs to be provided to CMS.

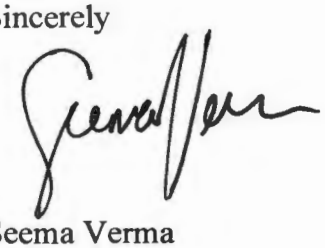
In our previous conversations with relevant stakeholders, we've encouraged them to submit any new evidence specific on the home use of oxygen prescribed under the durable medical equipment benefit for the treatment of CH. Your letter mentions not-yet published retrospective survey data. We would gladly review this information either in advance of publication or following publication, as well as any other newly published data available in the public domain.

A NCD reconsideration may be possible if the newly available evidence meets the criteria governing NCD reconsiderations as noted in our 2013 Federal Register Notice, which can be found here: https://www.federalregister.gov/articles/2013/08/07/2013-19060/medicare-program-revised-process-for-making-national-coverage-determinations. We look forward to engaging with

you and other stakeholders as additional evidence is generated and published to support an NCD reconsideration.

Thank you again for taking the time to write and we appreciate your interest in this important topic. CMS looks forward to continuing to work with you to provide high-quality care to all Medicare beneficiaries. If you or your staff have further questions please feel free to call the CMS Office of Legislation at 202-690-8220.

Sincerely



Seema Verma

January 9, 2014

Louis Jacques, MD
Director, Coverage and Analysis Group
Center for Clinical Standards and Quality
Centers for Medicare & Medicaid Services
7500 Security Boulevard
S3-02-01
Baltimore, MD 21244
Submitted via email: Louis.jacques@cms.hhs.gov

RE: Decision Memo for Home Use of Oxygen to Treat Cluster Headache (CAG-00296R)

Dear Dr. Jacques:

The Alliance for Headache Disorders Advocacy (AHDA) is an association that advocates for policy changes to improve the medical care and lives of persons with headache disorders such as migraine, cluster headache, and post-concussive headache. Our stakeholders include twelve professional and patient organizations whose mission relates to headache. We are the voice to policy makers for the more than 36 million persons in the US who have headache disorders, many of whom are suffering, disabled, and stigmatized.

We understand that the Centers for Medicare & Medicaid Services (CMS) have limited coverage for the use of oxygen to treat cluster headache (CH) through the Coverage with Study Participation (CSP) form of Coverage with Evidence Development (CED). We are writing to request CMS reconsider their decision and would like to further discuss this important issue with staff in the Coverage and Analysis Group (CAG). The CMS determination stated 100% oxygen acute therapy (O2) was a "promising" treatment and encouraged further study in a Medicare eligible population. We believe that this determination is unreasonable and infeasible.

O2 is established as a safe and effective acute therapy for CH.

O2 has been used in the treatment of CH since 1952, and has been studied and found to be effective in one well-designed placebo-controlled trial (see discussion below), two inadequately-designed controlled studies, and many case series. It is currently a standard-of-care acute therapeutic option cited in essentially every textbook that addresses the treatment of CH. Nowhere is there a published expression of concern by any clinical expert that this therapy is *not* safe and effective for this indication. Several US federal agencies list O2 as appropriate first-line acute therapy in their guidelines for CH management, including AHRQ (http://www.guideline.gov/content.aspx?id=34898) and NINDS (http://www.ninds.nih.gov/disorders/headache/detail_headache.htm). The Veterans Administration provides coverage of O2 for CH.

Apart from O2, for many patients no safe and effective therapy is currently available for the acute treatment of CH attacks, particularly those who are Medicare-eligible by age and some of those who are Medicaid-eligible.

Alliance for Headache Disorders Advocacy

Alliance for Patient Access
American Academy of Neurology
American Headache Society
Clusterbusters
Headache Cooperative of New England
Headache Cooperative of the Pacific
Migraine Research Foundation
Miles for Migraine Races
National Headache Foundation
National Migraine Association
Ohio Headache Association
PFO Research Foundation

For more information: http://www.allianceforheadacheadvocacy.org/
Contact: William B. Young, MD (william.b.young@jefferson.edu)

The only FDA-approved acute therapy for CH attacks is subcutaneous sumatriptan. However, this therapy is not proven safe either for use on an ongoing daily basis or for use more than twice in a day, which is often the frequency of excruciating CH attacks. Without the availability of O2 therapy, many CH patients are forced to endure disabling pain. Furthermore, sumatriptan is contraindicated in individuals with cardiovascular disease or stroke, as may be particularly true for patients who are Medicare-eligible. Sumatriptan injections are also potentially far more difficult to deliver safely under the stress of extreme CH pain (e.g. expose skin, swab with alcohol, etc.) and are noted for frequent disagreeable side effects. Sumatriptan is contraindicated in pregnancy, which might affect Medicaid-eligible CH patients. CMS also expressed a concern that some "*...portable oxygen systems are cumbersome...",* though we fail to see how the presumed inconvenience of this therapy would bear at all on a determination of its safety and efficacy. Finally, treatment with subcutaneous sumatriptan is far more expensive than O2 therapy, though we appreciate that CMS is mandated to not consider relative costs of therapies in determining their safety and efficacy.

The CMS Decision Memo requires a new placebo controlled trial of O2 for CH in Medicare- eligible patients (hereafter referred to as the "Medicare trial") and positive outcomes from this trial before further consideration of coverage. We believe that such a study would be infeasible, unnecessary, and unethical.

Conduct of a Medicare trial would be unethical. Since O2 is accepted as a standard of care, safe, and effective therapy for CH with no dissent among expert treating providers and included in AHRQ and NINDS treatment guidelines, this issue in not considered to be in clinical "equipoise." That is, it would be unethical to expose subjects to placebo acute treatments for CH in a clinical trial compared to O2, particularly given the extreme severity of pain and the resulting disability caused by CH attacks. Furthermore, it is unethical to withhold O2 coverage for *Medicaid*-eligible CH patients unless and until data supporting *Medicare*-eligible CH patients are generated.

Conduct of a Medicare trial would be infeasible. Recruitment for such a trial would be extremely difficult, with enrollment likely extending over many years. First, active CH is uncommon in individuals over 65 years, likely affecting fewer than 25,000 Americans total. Secondly, patients with CH who are over 65 years are more likely to have co-morbid cardiovascular and stroke-risk factors that would contraindicate the use of sumatriptan as a rescue treatment, and these individuals would, therefore, also be excluded from the study. Thirdly, patients with CH who are over 65 years are highly likely to have had CH for many years and, therefore, to have previously used O2 for CH attacks and thus would be ineligible for inclusion in a well-designed clinical trial. Fourthly, CH studies are notoriously difficult to enroll, given the tendency for affected individuals to go "out of cycle" during the period of study. Finally, in the Decision Memo, the CMS cites the desirability of including study subgroups of CH patients (e.g., "racial, ethnic, socioeconomic, sexual orientation", etc.) that would likely require very large and unachievable enrollments in order to show statistically meaningful effects.

Conduct of a Medicare trial is unnecessary. The Decision Memo stated that "CMS has determined that the evidence does not demonstrate that the home use of oxygen to treat cluster headache improves health outcomes in Medicare beneficiaries with cluster headache (CH)." The CMS determination found several presumed faults with the pivotal and most relevant study to the CMS determination, the 2009 Cohen JAMA study. We will respond to the CMS concerns directly.

"... Cohen et al., reported in 2009 [that of] 109 subjects considered eligible and randomized (out of 334), 33 did not receive treatment for one reason or another, leaving 76 participants, who ranged in age from 18-70 years. The mean age was reported as 39 years, significantly younger than the general Medicare beneficiary population."

There is no clinical evidence to suggest a different response to O2 treatment in older versus younger CH populations, and, in fact, age was not a factor in determining response in the Cohen study. If a study is enriched for older individuals, sumatriptan is lost as a rescue treatment since it is generally contraindicated in the Medicare population.

The CMS Decision Memo emphasized potential safety risks of oxygen therapy in older CH patients who are more likely to have COPD, while not acknowledging that these risks are from chronic, continuous O2 exposure, not short-term, 15-minute exposures, and also without considering the essential role and responsibility of prescribing providers to not prescribe treatment for patients who might be at such potentially increased risk. CMS also cited the risk of 100% O2 therapy leading to *"blindness and pulmonary fibrosis"*, which are essentially only seen in premature infants rather than Medicare-eligible individuals.

CMS also mentioned a risk of fire when O2 is used by individuals who smoke, without acknowledging the warnings written on O2 tanks cautioning unsafe use, or similar warnings on cans of hairspray, which do not prohibit their use by smokers. CMS also failed to consider the counterbalancing risks in older individuals of increased use of opioids and triptans, which are potential vasoconstrictors, for treatment of disabling pain as severe as CH. As individuals age, the safety of O2 increases relative to the alternative treatments that individuals actually use for CH. As CH is one of the most painful conditions known to man, and notoriously may drive individuals to self-medicate in unsafe ways, it is inappropriate to use a safety argument that might be applicable to a limited subset of the CH patient population to deny coverage of O2 for the treatment of CH for all Medicare and Medicaid recipients. Finally, while it is true that 33 potentially eligible and randomized subjects did not receive treatment in the Cohen study, 17 of these subjects came "out of cycle" and thus had no headaches to treat, and one died before receiving treatment. Only 15 subjects were lost to follow up or withdrew from the study.

"The gender was reported in the study but males and females were not analyzed separately, therefore we could not determine the treatment effects between males and females... [Subjects with episodic or chronic cluster headache] were not analyzed separately though there may be a difference in the responsiveness between these two groups".

This is incorrect. The study allowed for a dichotomous outcome and used a generalized linear model and logistic regression approach to determine the effect of active treatment and treatment order, gender, and cluster headache type (episodic or chronic cluster headache). In this logistic model, the terms for gender, cluster headache type, and attack order were not significant.

"[Subjects] were not included in an intention to-treat (ITT) analysis."
A priori, an ITT population can be defined as those randomized with at least baseline data and then treated; not including subjects who do not treat a CH attack is statistically valid, provided there is no basis to think such subjects would have a systematic lack of response. This is the standard for ITT analysis according to the International Classification of Headache Disorders Guidelines (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Statistical Principles for Clinical Trials. In: European Medicines Agency, editor. Geneva: International Conference on Harmonization; 1998.)

"(S)election of cases bias exists, as only a minority of the potentially eligible subjects were randomized."
The excluded cases included the following: 1) Individuals who had oxygen already (it would have been inappropriate to include those who had tried oxygen as only responders would have entered—this is a conservative exclusion; 2) Subjects who were out of cycle (how can one include individuals not having cluster attacks?); 3) Subjects who did not have cluster headache; 4) 11% who declined and 5% to 7% who were on a

preventive medication. "(S)election bias occurred because patients were taken on a convenience basis from a number of CH focus groups across the country."

Given the rarity of CH, subjects cannot be recruited from public health or population-based efforts; they can only be recruited from either support groups or multiple specialist clinics in a single country or internationally. This type of recruitment favors more refractory cases that are less likely to respond to treatment.

Conclusions

In summary, a single Class I study and several lower quality studies, along with 60 years of clinical experience, have led to the acceptance of O2 treatment as safe and effective by all expert clinical providers, every relevant textbook, every evidence-based guideline cited by CMS, several federal agencies, as well as by professional societies that have addressed the issue. CMS should reverse their determination and cover home O2 for CH because of the medical evidence and the overwhelming consensus of the medical community supporting its use.

Thank you for the opportunity to provide our comments on CAG 00296R. Should you have questions please contact me at 215-858-3500 (cell number) or email at william.b.young@jefferson.edu.

Sincerely,

William B. Young, MD, FAAN, FAHS, FANA, FCPP
President, Alliance for Headache Disorders Advocacy

United States Senate
WASHINGTON, DC 20510

May 23, 2014

The Honorable Marilyn Tavenner
Administrator
Centers for Medicare & Medicaid Services
U.S. Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

Dear Administrator Tavenner:

We are writing in response to the Centers for Medicare & Medicaid Services (CMS) determination of non-coverage of oxygen for cluster headache (CAG-00296R). Our constituents recently shared with us their heartbreaking experiences with cluster headache (CH), which is often identified as one of the most painful conditions known to medical science. Given the excruciating pain associated with CH and the proven effectiveness of oxygen in treating this disorder, we urge you to promptly review your decision.

Approximately 500,000 Americans suffer from CH. Many of the constituents we have heard from experienced debilitating pain for hours at a time over the course of months until they were properly diagnosed and began receiving oxygen treatment. This therapy enables them to live fuller, more productive lives with the assurance that a treatment is available to end CH pain when it strikes. We find the need for accessible CH treatment compelling, especially considering the suicide rate for CH patients has been estimated to be up to 20 times the national average.

Not only do our constituents attest to the effectiveness of this treatment, but medical experts indicate that the majority of published guidelines on the treatment of CH identify oxygen as a well proven and established treatment. According to their research, it is cited as a safe treatment in essentially every textbook that addresses CH management, and there is no published expression that oxygen therapy is an unsafe treatment. In fact, oxygen has been accepted as the standard of care for the treatment of CH since 1952.

Several federal entities, including the National Institutes of Health (NIH) and the Agency for Healthcare Research and Quality (AHRQ), list oxygen as an appropriate acute therapy for CH. We find this notable, in particular, because the mission of the National Quality Measures Clearinghouse within AHRQ is to provide evidence-based health care quality measures and information for health care providers, health plans, and delivery systems. Furthermore, the Veterans Administration provides coverage of oxygen for CH. We find it contradictory that a number of federal entities specify that oxygen is an evidenced-based treatment option and even disseminate this information in medical guidelines across the country, yet CMS has determined that this effective and low-cost therapy option should not be covered under Medicare. We ask that you work to rectify these inconsistencies and engage in a dialogue with the appropriate medical experts at these federal agencies as you review your decision.

We also urge you to consider that aside from oxygen therapy, no safe or effective therapy is available for many individuals with CH, particularly those who are Medicare-eligible. For example, sumatriptan is an FDA-approved treatment to terminate cluster headaches. However, this therapy is not proven to be safe for use more than twice a day, and cluster headaches, by definition, are a grouping or "cluster" of reoccurring headache attacks that may last up to three hours and occur up to eight times a day. Furthermore, medical guidelines indicate sumatriptan, and other CH therapies, are not advised for individuals at risk for cardiovascular disease or stroke, which could preclude much of the Medicare-eligible population from using these therapies.

Alternatively, without oxygen treatment or other therapies, a CH sufferer could be rushed to the emergency room by ambulance only to have the condition treated by oxygen at the hospital. Therefore, denying CH sufferers coverage for home oxygen could unnecessarily drive up health care costs at a time Congress and the Administration should be finding new ways to contain them. We are deeply concerned that because Medicare does not cover oxygen therapy, CH patients are pursuing potentially harmful therapies, seeking costly and unnecessary care in the emergency room, or enduring this disabling pain.

While we appreciate that CMS did not completely dismiss future coverage of oxygen therapy and acknowledged that it is a "promising" treatment option, we are also concerned about CMS's proposal to further study the therapy in a controlled trial. Several obstacles will make it difficult logistically and ethically for CMS to study oxygen treatment in elderly CH patients. The sporadic onset and end of CH cycles could make it difficult to study an appropriate number of Medicare-eligible patients. Additionally, most of these patients would not be eligible for a clinical trial because they have already tried oxygen to treat CH. Treatment with a placebo may also be difficult to justify because the efficacy of oxygen is considered a settled issue by the expert community and because CH is extremely painful. Therefore, we question whether further study of oxygen therapy is feasible.

In our opinion, the proven effectiveness of oxygen treatment of CH, shortcomings of other treatment options, and incredible pain associated with CH warrant further review of your coverage determination. We appreciate your careful consideration of this request and look forward to your response. Thank you for your attention to our concerns.

Sincerely,

Mike Johanns
United States Senator

Christopher A. Coons
United States Senator

James M. Inhofe
United States Senator

Richard J. Durbin
United States Senator

Deb Fischer
United States Senator

Jon Tester
United States Senator

Kelly Ayotte
United States Senator

Elizabeth Warren
United States Senator

Edward J. Markey
United States Senator

Jeff Merkley
United States Senator

Joe Manchin III
United States Senator

Mark L. Pryor
United States Senator

Robert P. Casey Jr.
United States Senator

Thomas R. Carper
United States Senator

Jeanne Shaheen
United States Senator

Congress of the United States
House of Representatives
Washington, D.C. 20515

Anna G. Eshoo
Eighteenth District
California

May 20, 2014

Ms. Marilyn Tavenner, Administrator
Centers for Medicare and Medicaid Services
7500 Security Boulevard
Windsor Mill, Maryland 21244-1849

Dear Administrator Tavenner,

I write to you about the very serious medical condition of cluster headaches and the lack of adequate, reimbursable therapies to treat them.

This issue was brought to my attention by my constituent, Dr. Robert Cowan, Professor of Neurology and Director of the Headache Program at Stanford University. As you know, in 2010, CMS made a non-coverage decision on oxygen therapy use for cluster headache (CAG-00296R). Given the excruciating pain associated with cluster headaches, and the lack of adequate therapies for some patients, I urge you to conduct a careful review of this decision.

Cluster headaches are excruciating attacks of pain in one side of the head, often felt behind the eye. Sufferers often call them "suicidal headaches" because they are so severe. Even the NIH and AHRQ recommend oxygen therapy to alleviate the pain that cluster headaches cause. Additionally, there are no published studies to indicate that oxygen therapy is an unsafe treatment.

I understand that CMS did not completely dismiss future coverage of oxygen therapy and acknowledged that it is a "promising" treatment option. What I am concerned about is CMS's proposal to further study the therapy in a controlled trial. Studying the use of oxygen therapy in the Medicare population may be difficult: most of the patients would not likely be eligible for a clinical trial because they have already tried oxygen to treat cluster headaches. Treatment with a placebo may also be difficult to justify because the efficacy of oxygen is considered a settled issue by the expert community and because cluster headaches are extremely painful.

I urge you to fully review your decision not to cover oxygen therapy for cluster headaches. I appreciate your consideration and I look forward to your timely response to our concerns.

Most gratefully,

Anna G. Eshoo
Member of Congress

DEPARTMENT OF HEALTH & HUMAN SERVICES

Centers for Medicare & Medicaid Services

Administrator
Washington, DC 20201

JUN 24 2014

The Honorable Christopher A. Coons
United States Senate
Washington, DC 20510

Dear Senator Coons:

Thank you for your letter regarding Medicare coverage of oxygen to treat cluster headaches (CH).

Our national coverage determination (NCD) does not prevent patients with CH from seeking treatment using oxygen in hospitals and other health care settings. In such circumstances, Medicare contractors are able to determine whether the treatment is reasonable and necessary after considering the patient's particular medical circumstances.

The NCD referenced in your letter is specific to the home use of oxygen to treat CH, and covers this treatment under coverage with evidence development. Again, this NCD only applies to home use of oxygen to treat CH.

Currently, no clinical trials involving the home use of oxygen to treat CH have been approved by the Centers for Medicare & Medicaid Services. However, you may be interested to know that we are communicating with several organizations, including two academic medical centers, interested in conducting a clinical trial that meets the requirements of the NCD. In addition, we encourage all stakeholders to submit any new evidence specific to home use of oxygen prescribed under the durable medical equipment benefit for the treatment of CH.

We appreciate your interest in this important topic. Please do not hesitate to contact me with any further thoughts or concerns. I am also sending this response to the co-signers of your letter.

Sincerely,

Marilyn Tavenner

Marilyn Tavenner