

CITIZEN PETITION

The undersigned health care providers, specializing in the treatment of headache, submit this petition pursuant to the Food and Drug Administration's ("FDA's") regulations at 21 C.F.R. § 10.30 to request that the FDA require certain additional information to be included in the product labeling of drugs for the acute treatment of headache. We believe that this information will help to relieve the headache-related disability and economic burden associated with overuse of over-the-counter combination analgesic headache medications.

I. ACTION REQUESTED

This petition requests that manufacturers of pre-existing over-the-counter pain medications be required to include a specific line under "Warnings" informing patients about the potential for medication overuse headaches, in addition to the already present statement "Stop use and ask a doctor if your migraine is not relieved or worsens after first dose." We believe that this statement in its current form is insufficient to alert patients of the specific potential for medication overuse headache.

II. STATEMENT OF GROUNDS

A. BACKGROUND INFORMATION

Medication overuse headache is defined as headache occurring on 15 or more days per month developing as a consequence of regular overuse of acute or symptomatic headache medication for more than 3 months.¹ It is a significant source of disability for patients, as well as economic burden for both individual patients and the American healthcare system as a whole. The prevalence of this condition in the general population is 1 to 2 percent, but noted to be as high as 80% in specialty headache clinics. Overuse of acute migraine medications on 10 or more days per month is associated with an increased risk of the condition, which has been noted to be greatest for narcotic, butalbital-containing-products, and combination analgesics, like Excedrin Migraine.² The importance of this condition is highlighted by the marked improvements in headache noted in > 2/3 of patients following successful withdrawal of the overused analgesic.

B. RATIONALE AND SUPPORTING INFORMATION

We recommend that a specific warning about medication overuse headache should be included on over-the-counter combination analgesic headache medications based on the following rationale:

1. Medication overuse headache is responsible for individual disability resulting in lower productivity and quality of life.^{3,4,5}

Based on the recent Global Burden of Disease study, it is speculated that MOH is responsible for a significant number of years of life lost due to disability.^{3,4} A recent assessment of costs associated with headache disorders in Europe showed that individual costs of MOH were higher than those of migraine, and that total national costs for MOH were higher than those for migraine.⁵ We predict that the proposed warning label would significantly lower the incidence of MOH and therefore help to alleviate some of this societal burden.

2. *Patient education is an effective strategy to both prevent and treat medication overuse headache.*^{6,7,8,9,10}

Medication overuse headache is a preventable problem, but awareness of the seemingly counter-intuitive advice that a headache treatment could actually worsen headache is poor among both patients and pharmacy staff, alike.^{6,7} Primary prevention of MOH is a matter of patient education and would be greatly aided by implementation of the labeling suggestion presented in this petition. Further, simple advice has been advocated based on clinical studies as a first-line intervention for treatment of MOH.^{8,9} In fact, advice alone was just as effective as pharmacological treatment of MOH in a randomized, open-label study.¹⁰

3. *The FDA has already acknowledged that an MOH label warning should be included for new acute migraine drugs.*

In October 2014, the FDA released a guidance document acknowledging that MOH should be addressed in the warning section of new drugs for acute treatment of migraine, which would include the following information:

Medication Overuse Headache: Overuse of acute migraine drugs (e.g., ergotamine, triptans, opioids, or a 356 combination of drugs for 10 or more days per month) may lead to exacerbation of headache (i.e., medication overuse headache). Medication overuse headache may present as migraine-like daily headaches or as a marked increase in frequency of migraine attacks. Detoxification of patients including withdrawal of the overused drugs and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

We would suggest this same language to be applicable to currently available over-the-counter combination analgesics, including Excedrin Migraine.

C. SUMMARY

In addition to the positive development of inclusion of MOH warning in new acute migraine medications, we urge the FDA to require manufacturers of pre-existing over-the-counter combination analgesic headache medications to include a specific line under "Warnings" informing patients about the potential for medication overuse headache. Medication overuse headache is preventable and treatable by patient education interventions, and knowledge of this subject is poor among patients and pharmacists. Therefore, this intervention would be a cost-effective and important intervention to improve headache-related disability and burden in the United States. Thank you for your consideration.

III. ENVIRONMENTAL IMPACT

We claim a categorical exclusion from the requirement to submit an environmental assessment pursuant to 21 C.F.R. 25.30.

IV. CERTIFICATION

The undersigned certifies that, to the best of the knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and it includes representative data and information known to the petitioners, which are unfavorable to the petition.

Respectfully Submitted,

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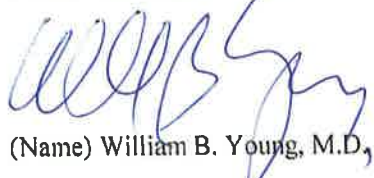
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¹ Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* 2013; 33:629.

² Garza, I, Schwedt, T. Medication overuse headache: Etiology, clinical features and diagnosis. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on November 25, 2014.)

³ Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2163–2196.

⁴ Steiner T. Can we know the prevalence of MOH? *Cephalalgia*. 2014;34(6):403–404.

⁵ Linde M, Gustavsson A, Stovner LJ, et al. The cost of headache disorders in Europe: the Eurolight project. *Eur J Neurol*. 2012;19(5):703–711.

⁶ *J Headache Pain*. 2014 Feb 13;15:10. doi: 10.1186/1129-2377-15-10. Should we educate about the risks of medication overuse headache? Lai JT, Dereix JD, Ganepola RP, Nightingale PG, Markey KA, Aveyard PN, Sinclair AJ¹.

⁷ *Headache*. 2014 Jun;54(6):1019-25. doi: 10.1111/head.12350. Epub 2014 Apr 25. Medication overuse headache: self-perceived and actual knowledge among pharmacy staff. Hedenrud T¹, Babic N, Jonsson P.

⁸ *Eur J Neurol*. 2011 Mar;18(3):396-401. doi: 10.1111/j.1468-1331.2010.03157.x. Short-term effectiveness of simple advice as a withdrawal strategy in simple and complicated medication overuse headache. Rossi P¹, Faroni JV, Nappi G.

⁹ *Eur J Neurol*. 2011 Jan;18(1):129-37. doi: 10.1111/j.1468-1331.2010.03094.x. Reduction in medication-overuse headache after short information. The Akershus study of chronic headache. Grande RB¹, Aaseth K, Benth JS, Lundqvist C, Russell MB.

¹⁰ *Cephalalgia*. 2006 Sep;26(9):1097-105. Advice alone vs. structured detoxification programmes for medication overuse headache: a prospective, randomized, open-label trial in transformed migraine patients with low medical needs. Rossi P¹, Di Lorenzo C, Faroni J, Cesarino F, Nappi G.