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A New Potential Medication for Effective Prevention of Morning Headaches

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Letter to editor

Dear Editor,

The introduction of the term Morning Headache (MH) is ascribed to Guilleminault et al. dating back to the late 1970's, when these authors first described that a significant proportion (36%) of patients with Sleep Apnea Syndrome (SAS) complained a diffuse headache upon waking, and named the condition as morning headache [1,2]. Subsequently, MH has been formally recognized by the International Classification of Headache Disorders (ICHD), starting from their first edition (1988), where the term morning headache was mentioned as a symptom, but not yet defined as a separate entity [3]. More recently, Kristiansen et al. (2012) [4] helped formalize the criteria and definitions of MH as a distinct entity, leading to its recognition in sleep medicine and headache classifications [5].

MH is characterized by the occurrence of the symptoms upon waking, with severity ranging from mild discomfort to severe pain with profound impact on an individual's quality of life [4]. This prevalent and often debilitating condition affects 5% to 8% of the general population, women being affected more frequently than men. The prevalence is also higher among individuals aged between 45 to 64 years [6,7].

A comprehensive review on MHs was published recently by Hong et al. (2025), with a thorough discussion on the symptoms, criteria, causes and treatment of MH [8]. These authors admit that the lack of universally accepted diagnostic criteria for MH hampers the understanding of the causes, predisposing factors and possible preventive treatments, all being essential for creating effective management strategies for these patients [3,5,8]. In principle, however, the causes of MHs can include both i) primary headache disorders such as migraines and Cluster Headaches (CH), as well as ii) secondary causes, like sleep disorders, hypertension, and brain parenchymal disease [8]. As originally proposed [1,2], it now seems that sleep-related factors, including Obstructive Sleep Apnea (OSA), circadian disruption, and poor sleep hygiene, are particularly significant, because of their direct influence on sleep quality and overall health [8]. In epidemiological studies, the most significant associated comorbidities were anxiety, depression, sleep disorders, circadian rhythm disorder, sleep related breathing disorder, hypertension, musculoskeletal diseases, use on

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anxiolytic medication as well as and heavy alcohol consumption [6]. Interestingly, however, 11,7% of the MH patients had none of previously listed comorbidities [6,7].

In the lack of detailed information about its pathophysiology, there is no single specific treatment for MHs but the therapeutic efforts are focused on identifying the risk factors and attempting to alleviate the associated symptoms [8]. Until now, there is only one randomized clinical trial with dietary intervention to treat MHs [9]. Increasing dietary ω-3 intake by modifying the ω-6/ω-3 ratio in a Mediterranean-style diet was shown to reduce the severity and impact of MHs, decrease dependence on pain medication, and improve inflammatory profiles in adults with MH [9]. However, considering the severity of headaches in the study subjects arouses a possibility that also migraine patients were included in this study cohort [9].

For some years by now, we have tested a novel means for prevention of migraine attacks by using a patented formulation of slow-release L-cysteine (Acetium® capsule, Biohit Oyj, Finland) [10,11]. The idea was prompted by increasing number of case testimonials from migraine patients, reporting that Acetium® capsule (containing 100mg L-cysteine) used in its original indication (inactivation of acetaldehyde in the stomach), proved to effectively inhibit their migraine attacks [10]. The rational is based on the principle that eliminating acetaldehyde (a potent histamine liberator in the mast cells) in the stomach by L-cysteine could block (or reduce below the critical threshold levels) histamine liberation from the tissue mast cells. That could arrest the multitude of histamine functions, including the formation of NO synthetase, a known trigger of migraine attacks [10].

The new hypothesis was tested in a Randomized Clinical Trial (RCT) with 218 migraine patients, where Acetium® capsules were compared with placebo in prevention of migraine attacks during a 3-month trial period [11]. The primary study endpoint was reduction in the Number of Migraine Days (NMD). Although Acetium® was not more effective than placebo in reducing the NMD in the global analysis, certain subgroups of migraine patients were identified who might benefit from Acetium® intervention considerably more than migraine patients collectively [10,11]. These subgroups of particular interest were subjects who reported a "histamine-related" cause (alcohol, cigarette smoke, dietary) as a trigger of their migraine attacks [10,11]. In fact, Acetium® was up to 50% more effective than placebo in NMD reduction by various cut-offs (≥20%, ≥25%, ≥50%), with the highest OR=1.569 (95%CI 0.743-3.312) achieved in NMD reduction (≥20% cut-off) among the subjects reporting dietary triggers of their migraine attacks [10].

Given that migraine is among the most common primary headache disorders associated with MH [6-8], it was feasible to test the efficacy of this novel medication in prevention of MHs as well. Accordingly, subjects complaining MH, often with previous migraine headache history and recent worsening of their migraine headaches, most often around 50 years of age, have been administered this experimental treatment in our clinic since the mid 2010's. In addition, subjects with no previous history of headaches with unexpected appearance of MH were tested for responsiveness to Acetium® capsules as well. All the other causes for MH were excluded before introducing L-cysteine. The subjects consumed 100 to 200 mg of L-cysteine at bedtime and were evaluated for efficacy at two weeks (or later) after initiation of L-cysteine treatment. During the past 10 years, more than 300 subjects with MH have been treated with L-cysteine. The efficacy in clinical practice seems to be very good; according to our best estimates (not based on exact data analysis yet), above 80% of these subjects report reduction in the frequency of their morning headaches. In addition, migraine headaches seemingly aggravated by MH also tend to decrease in frequency with introduction of L-cysteine, being consonant with the evidence provided by our previous migraine trial, where specified sub-groups of migraine patients responded favorably to L-cysteine prophylaxis [10].

In the next step, we are planning to conduct a register-linked study for a quantitative analysis of the treatment efficacy in these hundreds of MH patients treated in our clinic, to be reported as carefully analyzed case series. In addition, a substantial proportion of these subjects also have longitudinal (follow-up) data on medium- to long-term results, which enables a design of a retrospective cohort study. Once these steps are completed, a formal RCT will be designed using cross-over setting to compare the efficacy of Acetium® capsules with placebo in prevention of MH episodes [10].

Given that L-cysteine is a natural (semi-essential) amino acid, converted to inert substance (MTCA) in the alimentary tract, Acetium® capsule would comprise an ideal means to conduct MH prophylaxis for years, without concern about the side effects. If the efficacy will be formally proven in the planned studies (case-series, cohort study, RCT), the concept of using Acetium® capsules in prophylactic treatment of MH would represent a major step forward in a better clinical control of these frequently cumbersome syndromes.

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