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Original

Medication overuse headache: a pragmatic 5-year, real-world study

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Background
Medication overuse headache (MOH) impacts 1-7% worldwide. Effective treatment involves the abrupt discontinuation of the overused medication, the implementation of transition therapy during the initial period, and the simultaneous commencement of preventive treatment.

Objective
To describe a 5-year follow-up of patients with chronic migraine and MOH, focusing on the effectiveness of withdrawal treatment, use of traditional preventive medication, and requirement of anti-CGRP monoclonal antibodies.

Method
A single-center, prospective, and descriptive study was conducted. Convenience sampling of consecutive patients diagnosed with chronic migraine and MOH was the inclusion criterion. Demographics and clinical data at baseline, at 12 months, and during a follow-up period of 5 years, were collected in clinical records. The statistical analyses were performed with the Statistical Package for Social Sciences (SPSS®) version 18.2.2.

Results
We were able to follow one hundred and forty-two patients (116 W, 26 M), ages 18-78 years (mean 42.1±14.3) for 5 years. The diagnosis was carried out 24.9±14.7 years after the onset of the headache, and 6.3±7.6 years, was the time with headache ≥15 days per month. On baseline, the average number of headache days per month (HDM) was 25.2±5.9. There was a meaningful reduction in HDM. At 1 year and 5 years, a ≥ 75% reduction in HDM was observed, respectively, in 51.4% and 70.4% of the sample.

Conclusions
After five years, patients with chronic migraine and MOH who withdrew from excessive medication, used preventive pharmacological agents, and optionally added anti-CGRP monoclonal antibody showed a significant decrease in HDM frequency.

Keywords:
Chronic migraine
Medication-overuse headache
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Introduction

Medication-overuse headache (MOH) is a prevalent, debilitating condition in neurological practice. It affects 1% to 7% of the global population and impacts over 60 million individuals (1–4). The burden of MOH is significant, impairing quality of life and work productivity. Frequently, there are comorbid sleep and psychiatric disturbances, further exacerbating the suffering and the healthcare costs (1,2,5).

MOH arises from excessive medications used for the acute treatment, often seen in patients with preexisting migraine or tension-type headache (4,6). Different overuse patterns and pathophysiological mechanisms underlying MOH initiation and progression remain uncertain (7–11). Despite these uncertainties, it is widely recognized that MOH primarily affects individuals with primary headache disorders (12–17).

It is a clinical challenge to treat patients with MOH. There is no consensus on the best approach, particularly across different geographic realities (18–26).

Effective treatment strategies are limited by patients' adherence issues and varying responses, reinforcing the need for a comprehensive and individualized approach (4,5,19). Currently, the complete and sudden withdrawal of overused medications is considered a crucial measure for the management of MOH, despite recent challenges (23,24). In addition, the close follow-up with multidisciplinary support may reduce headache frequency without necessarily starting preventive medications. However, bridge therapies may be needed in a subset of patients with specific patterns of drug overuse (4,9,25,27,28).

The initiation of preventive pharmacological agents or biological therapies following the withdrawal process remains controversial. Some evidence supports their use to improve outcomes, including anti-CGRP monoclonal antibodies (22,27–29). However, long-term headache frequency reduction and the risk of relapse into medication overuse are not well understood. Combining medication withdrawal with preventive treatment appears to be the most effective strategy (4,9,25,26,30,31).

This study aimed to discuss these knowledge gaps by following consecutive patients with chronic migraine and MOH over five years. We observed the effectiveness of a comprehensive treatment approach involving medication withdrawal, traditional preventive agents, and the addition of anti-CGRP monoclonal antibodies. This long-term study at a Brazilian tertiary headache center offers essential insights into effective MOH management strategies.

Patients and methods

Study Design and Patients.

It was an observational, prospective, uncontrolled, and descriptive study that involved a non-random sampling of consecutive patients diagnosed with chronic migraine and medication overuse headaches, treated at a single tertiary clinic over five years. Data collection for this study spanned from August 2018 to July 2019.

Inclusion and Exclusion Criteria.

Patients aged 18+ with chronic migraine (15 headache days/month, ≥8 with typical migraine features) and medication overuse headaches (15 headache days/month, 10-15 days of medication use for ≥3 months), as per ICHD-3 criteria (6), seen consecutively during the period comprising July 2018 to July 2019 were included. The trial excluded patients who used botulinum toxin within the previous six months, had used traditional pharmacological agents for the prevention of migraine within the previous three months, or had detectable psychiatric comorbidities other than anxiety or not medicated depression during the initial consultation. Additionally, pregnant women or those not using effective contraceptive methods, as well as those planning to start a pregnancy within the next 12 months, were also excluded.

Data collection.

All included patients were invited to participate in the study by signing the informed consent. They were diagnosed with chronic migraine and medication overuse headaches based on the frequency of headache attacks over the past three months.

During initial long-lasting consultations, the patients were clearly and emphatically oriented, either with verbal and written instructions, to withdraw the excessive use of medications for headache attacks. However, they received the prescription of either rizatriptan or zolmitriptan, associated with a non-steroidal anti-inflammatory agent, to be used as needed up to two days a week. They were also prescribed a migraine prophylactic drug, either in monotherapy or in combination with other pharmacological agents. The entire patient population received a headache diary to be filled and presented in the follow-up visits, which had its intervals programmed, explained, and enforced. The choice of preventive medication was based on the history of previous use and failure of various medications, the possible existence of comorbidities, and the clinical experience of the attending physician.

Those patients who overused simple analgesics or analgesics combined with caffeine, ergots, or even both, had to withdraw, received the prescription of indomethacin for the initial 5 days (50 mg twice a day), and, from the 6th day onwards, were started on preventive treatment. They were allowed to take either rizatriptan or zolmitriptan plus a nonsteroidal anti-inflammatory drug (NSAID) on a maximum frequency of two days per week, clearly informed.

Those patients overusing triptans also had to withdraw, received the prescription of prednisone during the initial 6 days (60 mg/day for 2 days, 40 mg/day for 2 days, and 20 mg/day for 2 more days), and, from the 7th day onwards, started preventive treatment. These patients were also prescribed a triptan (rizatriptan or zolmitriptan) plus NSAID on a maximum frequency of twice a week, regardless of the previous overuse of a triptan. Collectively, studied patients withdrew; either received bridge therapy of indomethacin for 5 days or prednisone for 6 days, depending on the previously used symptomatic medications, and started preventive treatments from the 6th or the 7th day onwards. During follow-up, from the 12th to the 24th month, those patients who did not experience a ≥ 75% reduction in headache frequency, had the additional prescription of a monoclonal antibody (mAb) to the oral treatment.

Follow-up visits were performed by the same attending physician every two months during the first four months; every 4 months during the following 12 months, and every six months during the following 44 months or 3.6 years. The follow-up visits were emphatically requested and reminded to every patient to maintain adherence. The results were evaluated using headache diaries and patient information.

Statistical analysis.

All collected data were organized in a database. The Statistical Package for Social Sciences (SPSS®) version 18.2.2 for statistical analysis was used. The quantitative variables were expressed as mean, standard deviation, and minimum and maximum values, while qualitative variables were expressed as absolute and relative frequencies.

Results

Two hundred and forty-three consecutive chronic migraine and MOH patients were evaluated and diagnosed for the first time during the studied period. Among them, 200 patients (161 women and 39 men) met the inclusion criteria and were included in the study. From the first follow-up visit two months onwards, 29% (58/200) of patients did not return for subsequent consultations and were lost to follow-up. They were excluded from the trial. Therefore, the study sample consisted of 142 patients, with 81.7% (116/142) women and 18.3% (26/142) men. The average age at the time of inclusion was 42.1±14.3 years (18-84 years). The time with headache on 15 or more days per month was 6.3±7.6 years (1-40 years), and the diagnosis of chronic migraine and MOH was performed 24.9±14.7 years (mean 2-61 years) after the onset of the headache (Table 1).

Table 1. Clinical and epidemiological characteristics of 142 patients with chronic migraine and medication overuse headache

Variables	Frequency
Sex	
Female (n; %)	116 (81.7)
Male (n; %)	26 (18.3)
Age at diagnosis (years)	
Average (SD)	42.1±14.3
Variation	18-84
Time with headache (years)	
Average (SD)	24.9±14.7
Variation	2-61
Time with headache >15 days/months (years)	
Average (SD)	6.3±7.6
Variation	1-40

For the entire study sample, the average number of headache days per month at the time of inclusion was 25.2±5.9 (16-30 days). The patients were followed for 60 months. There was a reduction in the number of headache days per month, especially during the first year. At 12 months, the average headache frequency decreased to 7.6±6.1 days per month, representing a ≥75% reduction, which was observed in 51.4% (73/142) of the patients. At 60 months, the end of follow-up, the headache frequency was 5.7±4.1 days per month, meaning a reduction of ≥75% in 70.4% of the subjects (100/142). The average number of headache days during the entire follow-up period, by percentage, is shown in Tables 2, 3, and 4.

Table 2. Number of headache attacks per month during follow-up of 142 patients with chronic migraine and medication overuse headache

Assessment periods (months)	Frequency (average; SD; variation)
Baseline	25.2±5.9 (16-30)
at 2	12.0±7.9 (1-30)
at 4	8.2±6.1 (1-30)
at 8	7.1±5.1 (1-29)
at 12	7.6±6.1 (0-30)
at 18	6.7±4.8 (1-30)
at 24	6.7±4.9 (1-30)
at 30	6.3±4.4 (1-29)
at 36	6.4±4.3 (1-30)
at 42	6.4±4.5 (1-30)
at 48	6.4±5.0 (0-30)
at 54	6.4±3.9 (2-30)
at 60	5.7±4.1 (1-30)

Note: SD - standard deviation

Table 3. Reduction in the average monthly headache days in the 12th and 60th months of treatment in 142 patients with chronic migraine and medication

Improvement	At 12 months		At 60 months	
%	n	%	n	%
<50%	18	12.7	6	4.2
50% to 74%	51	35.9	36	25.3
≥75%	73	51.4	100	70.4

Table 4. Preventive treatment used in 142 patients with chronic migraine and medication overuse headache

Drugs	Frequency (n; %)
Oral medications (n=142) Amitriptyline and atenolol	4 (2.8)
Divalproex sodium	5 (3.5)
Divalproex sodium and tizanidine	8 (5.6)
Topiramate and nortriptyline	21 (14.8)
Nortriptyline and flunarizine	38 (26.8)
Nortriptyline, flunarizine and tizanidine	66 (46.5)
Monoclonal antibodies (n=57/142; 40.1%)	
Erenumab (Pasurta®)	8 (14.0)
Galcanezumab (Emgality®)	31 (54.4)
Fremanezumab (Ajovy®)	18 (31.6)

All patients were initially treated with oral preventive agents, generally as a combination of one or two drugs. The drugs used, in order of frequency, were amitriptyline and atenolol (2.8%), divalproex sodium (3.5%), divalproex sodium and tizanidine (5.6%), topiramate and nortriptyline (14.8%), nortriptyline and flunarizine (26.8%), and nortriptyline, flunarizine and tizanidine (46.5%). Of the 142 patients treated with oral medications, 57 (40.1%) have added an anti-CGRP monoclonal antibody, which was started at some time during their treatment, no less than two years after the initial treatment phase, as shown in Table 3. The specific combinations of nortriptyline and flunarizine, or nortriptyline, flunarizine, and tizanidine, were compounded in a single capsule to be taken daily, during dinner time, which reduces the cost of the medication in addition to individualizing the treatment. To prevent tolerability issues and maintain adherence, the maximum daily dose of flunarizine was 2 mg/day, amitriptyline and nortriptyline were 25 mg/day, tizanidine was 5 mg/day, sodium divalproate was 500 mg/day, and topiramate was 100 mg/day. It was based on the treating physician's clinical experience acquired with the use of these substances across decades. Adding an anti-CGRP monoclonal antibody was decided for those patients who didn't achieve a desired headache frequency reduction, or who requested the emerging therapy.

Discussion

The treatment approaches of MOH vary widely, influenced by different geographic realities and health care structures (19,22,30). This study followed chronic migraine and MOH patients over the long term at a specialized center in Brazil. While baseline headache frequency and symptomatic medication use were self-reported, which may introduce some bias, the results provide valuable insights into the management of MOH in this setting.

The significant reduction in headache frequency over five years is a positive finding, likely reflecting a comprehensive treatment approach that included long-lasting initial consultations, emphasis on stopping overused medications, and adherence to treatment strategies. Our study was comparable to the other two studies with similar outpatient approaches, including a detoxification program, which resulted in a two-thirds reduction in medication overuse within six months or a 50% reduction in headache frequency in nearly half the patients after 12 months (26,31,32). Additionally, we observed a similar reduction at two months, but a greater decrease in headache frequency at 12 months and beyond, with a >75% reduction in nearly 52% of patients at 12 months and even higher at 60 months.

Despite the withdrawal of overused medication being the primary treatment for MOH, the best strategies also include patient education, starting preventive treatments for the underlying primary headaches, and psychological support. An initial bridge therapy may help reduce headache escalation and adherence issues with the sudden interruption of symptomatic medications

in outpatient settings, along with immediate preventive treatment, which demonstrates superiority (9,22,25–27,31,33,33–35). However, inpatient strategies may be necessary for overuse involving certain drugs like opioids, barbiturates, or benzodiazepines, which was not the case in our series (9).

An obstacle to adherence is the relapse post-withdrawal (8,18,22,29,32). Although it may occur frequently, few studies evaluate long-term outcomes and real-world relapse rates, highlighting the usefulness of this trial despite striking differences in healthcare settings (22,27,36,37). While public health services in Brazil rarely have the infrastructure for long-term patient follow-up, the few high-standard private centers offer updated treatments, but may face adherence issues due to cost limitations. This study's strength lies in its complete data over time, showing that withdrawal, support, and effective prevention significantly reduce headache frequency, especially in the first four and twelve months (22,38,39).

However, the limitations of the study are acknowledged. There is a potential bias with the studied population, which included mostly highly motivated subjects treated at a specialized center. Moreover, we did not determine specific headache characteristics such as severity scores, pain intensity, and rates of cutaneous allodynia. Psychiatric comorbidities and substance use disorders were not scrutinized as well, which might have affected treatment responses and treatment adherence over time. In addition, comparing outcomes between patients overusing different pharmacological classes should have been interesting, but it was not performed, although benzodiazepine use was low, and none used opioids or barbiturates.

Regarding anti-CGRP monoclonal antibodies (mAbs), 40% of the studied patients added mAbs to their regimen after a few years of stable treatment. This study did not evaluate the performance of the monoclonal antibodies compared to the traditional agents. However, initiating prevention with both traditional agents and mAbs led to a higher decrease in headache frequency, regardless of the mAb used.

In conclusion, while evidence on the best MOH treatment strategy is limited, the discontinuation of overused symptomatic treatment alongside the early starting of prevention yields more favorable outcomes than withdrawal alone. Although combining medications with mAbs may be superior to monotherapy, more randomized controlled trials are needed to evaluate the safety and efficacy of various preventive regimens.

This prospective study of MOH patients at a Brazilian tertiary headache center enrolled 200 patients in a comprehensive treatment program. The program included the education of the subjects with clear orientation, the sudden overused medication interruption, the use of bridge medications for withdrawal, and the starting of the preventive treatments, with the addition of anti-CGRP monoclonal antibodies after two years to improve adherence. The study demonstrated positive outcomes regarding patient adherence and headache reduction, underscoring the effectiveness of a structured and supportive treatment approach. However, the specific impact of adding mAbs remains inconclusive and warrants further investigation.

Ethics statement

This study was approved by the Ethics in Research Involving Human Subjects Committee at the Federal University of Piauí, protocol number 3,305,167 and the National Ethics in Research System, registry number 08850918.0.0000.5214, on May 6, 2019.

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