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Review Article

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Comorbidities in Medication Overuse Headache

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Comorbidities

Comorbidity means that two medical diseases develop in the same patients at higher rates than if these diseases were to occur by chance. In medication ovretiuse headsache (MOH) patients with a secondary head ache, it seems difficult to clarify the boundary between co morbidity and the risk factors. It is not surprising that most research has reported psychiatric disorders as comorbidities of MOH. In a study from six EU countries and based on results using the HADS, MOH was found to be associated with depression and anxiety. Anxiety was found to have a 10.4-fold increase in males and 7.1-fold in women compared with the no headache control patients [1]. In the COMOESTAS project, 40% of MOH patients had depression and 57.7% anxiety [2,3]. A similar result was also reported in the Brief Intervention for MOH (BIMOH) study, showing that MOH patients had a significantly higher anxiety scale based on the HADS [4]. In the SAMOHA study, the Beck Depression Inventory, Beck Anxiety Inventory and a direct psychiatrist interview by Modified Mini International Neuropsychiatric Interview (M-MINI) were used for psychopathological assessment; the authors compared the psychiatric disturbances between MOH, episodic migraine and heathy control groups. The frequency of moderate to severe anxiety was significantly higher in MOH patients than in episodic migraine patients, as well as in heathy controls. However, the frequency of depression in MOH was higher than that in healthy control patients but not in episodic migraine patients [5]. In the same study, the Leeds Dependence Questionnaire (LDQ) score and Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score were administered.

Clinically relevant obsessive-compulsive disturbances for drug abuse assessed by the Y-BOCS appeared to have a higher representation in the MOH group, while the prevalence of this trait in the EM group was comparable to that of healthy controls [6,7]. Similar results were also reported in one Italian clinic-based study [8]. However, it is still controversial whether obesity is associated with MOH. One Danish cross-sectional population-based survey showed obesity was significantly associated with MOH [29], but this was not the case in the Nord-Trøndelag health studies [7,8]. Physical inactivity was also controversial regarding its association with MOH; it was reported to be related to MOH in one study but not another one [9,10]. Of note, daily smoking and stress were also reported as being comorbid with MOH [11].

Comorbidity refers to the occurrence of two medical conditions in the same patients at rates that are higher than what would be expected by chance. In patients with Medication Overuse Headache (MOH) who also experience secondary headaches, distinguishing between comorbidity and risk factors can be challenging. It is not unexpected that numerous studies have identified psychiatric disorders as comorbidities associated with MOH. A study conducted across six EU countries, utilizing the Hospital Anxiety and Depression Scale (HADS), revealed a correlation between MOH and both depression and anxiety. Specifically, anxiety was observed to increase 10.4 times in males and 7.1 times in females when compared to patients without headaches [12,13]. Within the COMOESTAS project, it was found that 40% of MOH patients experienced depression, while 57.7% reported anxiety [4,5]. A comparable finding was noted in the Brief Intervention for Medication Overuse Headache (BIMOH) study, which indicated that MOH patients exhibited significantly elevated anxiety levels as measured by the HADS [4]. In the SAMOHA study, various assessment tools including the Beck Depression Inventory, Beck Anxiety Inventory, and a direct psychiatric interview using the Modified Mini International Neuropsychiatric Interview (M-MINI) were employed to evaluate psychopathological conditions; the researchers compared psychiatric disturbances among MOH, episodic migraine, and healthy control groups. The incidence of moderate to severe anxiety was significantly greater in MOH patients than in those with episodic migraine and healthy controls. Conversely, while the prevalence of depression was higher in MOH patients compared to healthy controls, it was not significantly different from that observed in episodic migraine patients [14]. Additionally, in the same study, the

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Leeds Dependence Questionnaire (LDQ) and the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) were utilized. Clinically significant obsessive-compulsive disturbances related to drug abuse, as assessed by the Y-BOCS, were found to be more prevalent in the MOH group, whereas the occurrence of this trait in the episodic migraine group was similar to that of healthy controls [14-16]. Similar findings were also documented in an Italian clinic-based study [17]. Nevertheless, the controversy surrounding this topic remains.

Burden The quality of life for patients suffering from Medication Overuse Headache (MOH) is significantly poorer compared to those experiencing episodic headaches [18-22]. Due to productivity loss, absenteeism, and direct medical expenses, MOH can incur substantial costs. According to the Eurolight study, the annual expense for MOH is €3561 per patient, which is nearly three times greater than that of episodic migraine and ten times that of tension-type headache [23]. In this research, indirect costs represent approximately 90% of the total expenses [23]. In fact, the overall financial burden amounts to €5–10 billion across Italy, Spain, and France. A recent study conducted in Italy revealed that the comprehensive cost for MOH patients lacking adequate treatment was €2835 over a three-month period, with males incurring higher costs than females (€3885 compared to €2631); in this case, indirect costs constituted about 80% of the total expenditure. This finding, however, is considerably higher than the costs reported in the Eurolight study. The authors hypothesized that the differences stemmed from the methodology used in calculating costs, as the variables related to medication prices, including NSAIDs, triptans, and opioids, as well as productivity loss, were meticulously assessed in this Italian study. They propose that the costs reported in earlier studies were likely underestimated, as the average medication prices were only roughly approximated and only losses of work exceeding half a day were factored in [23,24]. The current findings corroborate the elevated prevalence of anxiety and depressive disorders among MOH patients as indicated by previous research [25]. The confidence intervals observed are broad for individual disorders due to the limited patient sample; however, aggregating by broader disorder categories facilitated more accurate odds ratio estimates. In a study with a comparable design, an increased likelihood of experiencing major depressive disorder, panic disorder, and social phobia was also noted [26]. Nevertheless, the conflicting results regarding generalized anxiety disorder may be attributed to the application of DSM-IIIR criteria in the earlier study, while DSM-IV was utilized in the current investigation.

The findings also reveal a significant comorbidity with substance use disorders. Regarding the mechanisms of association that underlie the various forms of comorbidity, the observation that all psychiatric conditions were more likely to precede rather than follow MOH supports their classification as risk factors. Nevertheless, the lack of a definitive time sequence between the onset of daily headaches and the initiation of medication overuse prevents us from concluding whether psychiatric comorbidity should be viewed primarily as a risk factor for the exacerbation of headache frequency (which is then followed by medication overuse) or as a risk factor for medication overuse (which is then followed by an increase in headache frequency). Nonetheless, the results highlight the idea that certain migraine patients may be predisposed to developing MOH due to either a personal history of substance use disorders or other indicators of addiction vulnerability. Analyses of family history data suggest that substance use disorders are more prevalent among the families of MOH patients, regardless of whether the patient has a personal history of substance abuse (excluding analgesic medication). Conversely, it is also plausible that MOH occurs more frequently in the families of individuals suffering from substance-related disorders, irrespective of whether the patient has a personal history of MOH. These findings imply a cotransmission of these two conditions, stemming from a shared underlying vulnerability. Consequently, MOH may partially arise from a broad family-based susceptibility to addiction, which heightens the risk of both acute migraine medication and analgesic misuse, as well as substance use disorders in general. Addiction is a broad term that encompasses all behaviors characterized by a lack of control and their continuation despite the individual's awareness of the negative consequences. This term does not suggest any antisocial behavior, which is often seen in certain types of drug addiction. In fact, such behavior is rarely observed in patients with headaches. The average percentage of MOH patients displaying an addiction-related behavior is… The burden Patients with MOH have a significantly lower quality of life than those with episodic headaches [5,18,21,22].

The current results support previous studies' findings that MOH patients have significant rates of anxiety and depression disorders [25-27]. Due to the small number of patients, the observed CIs for individual diseases are wide; nevertheless, more accurate OR estimations were obtained by aggregating by broad disorder categories. An elevated incidence of major depressive disorder, panic disorder, and social anxiety was also noted in research with a similar methodology [6]. However, the use of DSM-IV criteria in the current study and DSM-IIIR criteria in the previous one may have contributed to the disparate findings regarding generalized anxiety disorder.

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The small number of patients and the use of indirect, but well validated, markers of family psychopathology (mood disorders, anxiety disorders, alcohol and illicit drug-related disorders) limit the investigation's preliminary results. Furthermore, there was no prior validation for the evaluation of MIG and MOH family histories. The sample's recruitment from a university specialty clinic, for example, may limit its generalization to other migraine groups. Regarding other methodological concerns, the study sample's recruitment from a headache clinic may be responsible for the high prevalence of mental comorbidity in both the MOH and MIG groups.

In summary, it has been observed that over 60% of patients suffering from MMOH exhibited at least one comorbidity, with one-third of these individuals classified as true cases of multimorbidity. These patients tended to be older, had lower levels of education, were more frequently unemployed, experienced a higher frequency of headaches, exhibited greater disability, and reported lower quality of life (QoL) levels. Additionally, they were more likely to misuse opioids or barbiturates, attend emergency rooms, relapse into chronic migraine (CM), and require further withdrawal treatment within 12 months following a structured withdrawal program. Patients with medication overuse headache (MOH) and multimorbidity constitute a particularly vulnerable population. Consequently, it is essential to exercise caution when managing these patients due to the risks associated with polypharmacy, potential drug interactions, and cross-contraindications among medications prescribed for their various coexisting conditions. There is a pressing need for further research that systematically addresses multimorbidity in CM-MOH. Increased awareness and enhanced understanding of this issue could significantly inform research initiatives, clinical practices, and ultimately public health policies aimed at alleviating the personal and societal impacts of CM-MOH.

The findings of our research indicated that, within a cohort of patients suffering from CM-MOH who participated in a structured withdrawal program, one-third exhibited multimorbidity. Those with multimorbidity tended to be older, had lower educational attainment, were more frequently unemployed, reported a higher frequency of headaches, experienced greater disability, and had diminished quality of life (QoL) levels. Additionally, they were more likely to be overusers of opioids or barbiturates, and somewhat less frequently overusers of triptans. After 12 months post-discharge, these patients were more prone to visit the emergency room, relapse into chronic migraine (CM), and necessitate another withdrawal treatment. The most prevalent comorbidities identified included Persistent mood disorders (19.6% of patients), Essential hypertension (17%), Allergies of any type (15.5%), anxiety disorders (14.9%), and Obesity (7.7%). Our findings align closely with existing literature that highlights elevated comorbidity rates between CM and conditions such as depression, hypertension, and obesity. Furthermore, we discovered associations with other less commonly reported conditions, including allergies (16%), digestive disorders (6%), and musculoskeletal diseases (5%). Our patient population reported a notably lower prevalence of depressive and anxiety disorders than anticipated, with diagnoses occurring in 20% and 15% of patients, respectively. In contrast, a recent literature review indicated prevalence rates ranging from 30% to 47% for depressive disorders and from 19% to 47% for anxiety disorders. It is plausible to suggest that the state of multimorbidity and CM-MOH are interrelated. Existing literature suggests that excessive medication use is linked to the chronicification of migraines, and that two factors—specifically, a predisposition to migraines and the overuse of symptomatic medications—must coexist. Moreover, the presence of comorbidities is recognized as a risk factor for both the onset and persistence of CM. Certain conditions, and in alignment with earlier studies assessing multimorbidity within general populations, our patients exhibiting multimorbidity were older and experienced a poorer socio-economic status (characterized by lower education levels and a higher unemployment rate) in comparison to those without multimorbidity, with no observed gender disparities. Furthermore, they reported an average of approximately three additional headaches per month, increased disability, and diminished quality of life (QoL), while no significant differences were noted between the groups concerning BDI-II scores and the commonly accepted cutoff of 14 points. According to this threshold, 40% of our patients displayed moderate-to-severe depressive symptoms, a statistic that appears to align with existing literature. Notably, although clinician-diagnosed depression was more prevalent among patients with multimorbidity, no differences were identified when evaluating BDI-II scores. We posit that this discrepancy arises because the BDI-II serves as a questionnaire designed to assess the severity of depressive symptoms rather than functioning as a diagnostic instrument. A recent review examining the accuracy of various tools and severity measures for major depression in adult clinical populations indicated that, using the standard cutoff score of 14, the BDI-II demonstrated an average sensitivity of 92% and a specificity of 72%, although these figures varied between 50% and 84%. Our findings corroborate these results: CM-MOH patients with multimorbidity were more frequently diagnosed with depression than their counterparts without multimorbidity, and the presence of depressive symptoms is a common characteristic among CM-MOH patients. The low prevalence rate.

Burden

The quality of life of patients with MOH is much worse than that of patients with episodic headaches [29].

Because of the loss of productivity, absenteeism and direct medical costs, MOH can be very costly. In the Eurolight study, the annual cost of MOH is €3561 per patient, almost three times higher than that of episodic migraine and 10 times that of tension-type headache [23]. In this study, the indirect cost accounts for about 90% of the total costs [23]. Indeed, the overall cost is €5–10 billion in Italy, Spain and France. In a recent Italian study, the detailed total cost of MOH patients without adequate treatment was €2835 on a 3-month basis, which was higher in males than females (€3885 vs. €2631); here, the indirect cost accounted for about 80% of the total cost. This result, though, is much higher than the costs found by the Eurolight study. The authors suspected the discrepancies resulted from the methodology of cost calculation because the variables of medication price, such as NSAIDs, triptans and opioids, and loss of productivity were both calculated in detail in this Italian study. They suggest that the cost addressed in previous studies was likely underestimated because the average medication price was only roughly calculated and only a loss of work of more than half a day was included [23-25].

The present findings confirm the high rates of anxiety and depressive disorders in MOH patients reported by past investigations [23–26]. The observed CIs are large for individual disorders due to the small number of patients, but aggregating by broad disorder categories allowed for more precise OR estimates. In a study with a similar design [6], an increased risk of suffering from major depressive disorder, panic disorder and social phobia was also observed. However, the discrepant results concerning generalized anxiety disorder may be related to the

use of DSM-IIIR criteria in the former study, and DSM-IV in the present one.

The results also demonstrate a strong comorbidity with substance use disorders. Concerning the mechanisms of association underlying the different forms of comorbidity, the fact that all psychiatric conditions were more likely to precede than to follow MOH lends support to their conceptualization as risk factors. However, the absence of a clear time sequence between onset of daily headaches and onset of medication overuse does not allow us to determine if psychiatric comorbidity is best seen as a risk factor for the worsening of headache frequency (followed by medication overuse) or rather as a risk factor for medication overuse (followed by worsening of headache frequency). The findings nonetheless underscore the notion that some migraine patients may be vulnerable to developing MOH due either to a personal history of substance use disorders, or to other markers of addiction vulnerability. Analyses of family history data indicate that substance use disorders are more frequent in the families of MOH patients, whether or not the patient has a personal history of substance abuse (other than analgesic medication). The opposite relationship could also be tenable: MOH may be more frequent in the families of patients suffering from substance related disorders, whether or not the patient has a personal history of MOH. These results suggest a cotransmission of these two conditions, due to a common underlying vulnerability. For this reason, MOH may result in part from broad family-based vulnerability to addiction that increases the risk of acute migraine drugs and analgesic abuse, as well as of substance use disorders in general. Addiction is a general term which concerns all behaviour characterized by a lack of control and by its expression despite the patient's awareness of its negative consequences. This term does not imply any antisocial behaviour, as often observed in certain forms of drug addiction. Indeed, such behaviour is seldom present in headache patients. The average percentage of MOH patients exhibiting an addictive behaviour, rather than misuse or overuse behaviour secondary to a worsening of their headache, remains unknown. While it has been suggested that such patients are not a majority (16), clarification of this issue should be a priority for future investigations.

The conclusions of this investigation are preliminary and are limited by the small number of patients as well as by the use of indirect, albeit well-validated, measures of family psychopathology (mood disorders, anxiety disorders, alcohol and illicit drugs-related disorders). Moreover, the assessment of family history specifically of MIG and MOH was not previously validated. Certain characteristics of the sample, such as its recruitment from a university specialty clinic, may also limit generalization to other migraine populations. Concerning other methodological issues, the high psychiatric comorbidity rates in both the MOH group and the MIG group may be attributable to the fact that the study sample was recruited from a headache clinic. The retrospective assessment of the age of onset of disorders can also be considered as a limitation, although the focus on substance use disorder comorbidity is in itself novel. The inclusion of migraine without MOH as a comparison disorder and family history assessments underscore the salient individual and family risk factors for MOH patients. Additional research is needed to further understand psychiatric comorbidity in MOH, but the development of close consultation between neurologists and psychiatrists already appears to be clearly warranted in the treatment of this disorder. It is of considerable importance that signs of addiction as well as anxiety and depressive symptomatically be monitored in MOH patients when medication withdrawal is proposed.

In conclusion, it has been found that more than 60% of patients with MMOH showed at least one comorbidity, and that one-third of them were true multi-morbidity cases. These patients were older, less educated, more frequently unemployed, had higher headaches frequency, higher disability and lower QoL levels, were more often overuses of opioids or barbiturates, and were more likely to attend ER, to relapse into CM, and to require a further withdrawal treatment by 12 months from a structured withdrawal treatment. Patients with MOH and multi-morbidity represent a particularly frail group: Attention should therefore be paid when dealing with these patients, in reason of the risks deriving from poly pharmacy, possible interactions and cross-contraindications among drugs prescribed to treat the different coexisting conditions. Further studies addressing multi-morbidity in CM-MOH in a standardized way are needed. Awareness and a better knowledge on this topic may inform research, clinical practice, and eventually public health policies to reduce the personal and societal burden of CM-MOH.

The results of our study showed that, among a sample of patients with CM-MOH attending a structured withdrawal treatment, one third had multi-morbidity. Patients with multimorbidity were older, less educated, more frequently unemployed, reported higher headache frequency, higher disability and lower QoL levels, were more often overuses of opioids or barbiturates, and slightly less often triptan over users. By 12 months from discharge, they were more likely to attend ER, relapse into CM and require another withdrawal treatment. The most common comorbidities were Persistent mood disorders (19.6% of patients), Essential hypertension (17%), Allergies of any kind (15.5%), anxiety disorders (14.9%), and Obesity (7.7%). Our results are basically in line with previous literature showing high comorbidity rates between CM and depression, hypertension and obesity. In addition, we found comorbidities with other less frequently reported conditions, including allergies (16%), digestive (6%), and musculoskeletal diseases (5%). Our patients reported quite a low prevalence of depressive and anxiety disorders than expected, diagnosed in 20% and 15% of patients, respectively: a recent literature review, on the contrary, reported rates between 30% and 47% for depressive disorders, and between 19% and 47% for anxiety disorders.12 It is reasonable to suppose that multi-morbidity state and CM-MOH are interconnected. Literature shows that excessive consumption of medication is connected to migraine chronification and that two factors—namely predisposition to migraine and overuse of symptomatic compounds—have to be present 27 and, moreover, the presence of comorbidities is a risk factor for the onset and maintenance of CM.12 Some conditions, and in particular obesity and depression, may share common pathophysiological mechanisms. With regard to obesity, it can be considered as a pro-inflammatory condition: in fact, interleukin and calcitonin gene-related peptide are among the inflammatory mediators that are increased in obese individuals and are of importance in migraine pathophysiology too.28 With regard to depression,

shared environmental or genetic risk factors, and common pathophysiological mechanisms have been postulated12: in particular serotonergic and dopaminergic dysfunctions are common to both depression and migraine, and because altered serotonin levels have been observed during migraine attacks, triptans, which are selective serotonin agonist, are used to treat migraine headaches.29,30 The most interesting result of our study is connected to the association between multimorbidity and some clinical and psychosocial aspects. Consistently with previous reports evaluating multimorbidity in general populations,1-4 our patients with multimorbidity were older and had a worse socio-economic status (less educated and with higher unemployment rate) when compared to those without multimorbidity, while no gender differences were found. In addition, they reported approximately three more headaches per month, higher disability, and lower QoL, while no differences were found between groups with regard to BDI-II scores and it is commonly used cutoff of 14 points. Based on this cutoff, 40% of our patients had moderate-to-severe depressive symptoms, a figure which seems to be more consistent with previous literature data. It is of interest to see that, while clinician-diagnosed depression was more common among patients with multimorbidity, no differences were found when BDI-II score was addressed. We believe that the reason for this is that the BDI-II is a questionnaire for the evaluation of the severity of symptoms of depression, and not a diagnostic tool. A recent review addressing the accuracy of different instruments and severity measures for major depression in clinical adult populations showed that, with the standard cutoff score of 14, the BDI-II had an average sensitivity of 92% and a specificity of 72%, which, however, varied between 50% and 84%.31 Our results are consistent with these findings: CM-MOH patients with multimorbidity were more frequently diagnosed with depression compared to those without multimorbidity, and the presence of depressive symptoms is a general trait of CM-MOH patientsThe low prevalence rate of musculoskeletal disorders (5%) shown in our results contrasts with data reported by Buse and colleagues, who found that arthritis had 34% prevalence among CM participants to AMPP study.14 Two are the reason that we believe explain these differences. First, the AMPP study derived this information on self-reports of a previous physician diagnosis (SRPD), that is, patients were asked whether they have ever been told by a doctor that they have a given diagnosis. SRPD is a viable approach for population studies, but accuracy levels are not always adequate,32,33 as it does not allow to distinguish between past and present diagnoses, thus leading to an overestimation on the present state. Second, our sample had a dramatic lower incidence of obesity compared to that found by Buse and colleagues (8% vs 25.5%), and obesity is deemed to be implicated in arthritis development.34 The AMPP also produced estimates for allergies and respiratory conditions, showing a prevalence of 59.5% in CM patients, while among our patients, the corresponding rate was 17%: The reasons might again be the use of SRPD in AMPP together with a nondisclosure of non-neurological conditions by our patients, in particular if not associated to specific therapies or not requiring specific dietary approaches. The only previous literature reference directly addressing multimorbidity and headache disorders was the primary care Dutch population study of persons aged >55 by Sinnige and colleagues, in which 70% of migraine cases had multimorbidity, with an average of 2.62 conditions per subject (95% CI 1.96-3.28).6 There are, however, difference between ours and Sinninge's study which can explain these lower figures: in particular, the younger age of our patients and the different definitions of multimorbidity (two or more in or more in Sinnige's study, three conditions or more, ie. CM and other two, in our study). Previous research specifically addressing comorbidities ofCM did not directly address multimorbidity. However, two available studies on chronic and episodic migraine sufferers from the general population in the United States and on CM patients in Taiwan13,14 show that chronic migraineurs report significantly more comorbidities compared to the episodic counterparts, including some of the major drivers of multimorbidity identified in our study, that is, hypertension, depression, allergies, and obesity. Therefore, it is reasonable to suppose that multimorbidity was present in part of the studied samples taken from the Taiwanese National Health Insurance Research Database13 and from the AMPP study.14 Another indirect information on multimorbidity of migraine was available from a study addressing comorbidity patterns of depression, in which a multimorbidity pattern with migraine was also included as follows35: Results showed that the comorbidity pattern of migraine included other headaches, high cholesterol, diabetes, depression, postnatal depression, anxiety, and vertigo. In another study, the authors evidenced that migraine was, as expectable, twice more prevalent among women in the multimorbidity pattern provided by a population health survey in Catalonia.36 Our results also pointed out that patients with multimorbidity often overused opioids or barbiturates, while it was less frequently triptans overusers. These findings add further evidence to the efficacy and safety profile of triptans contrasted to opioids, and reinforces the opportunity to avoid them in the management of migraine, because chronic opioid therapy in migraineurs is associated to worse disability and QoL and to psychiatric comorbidity.37,38 To address whether the rate of comorbidities and multimorbidity different from the general population of Italian adults, we compared the results from our sample to that of three different population studies. The first study described the association between overweight, obesity, and the presence of selected comorbidities 39; the second was on the premature onset of age-related comorbidities among HIV-infected and noninfected general population40; the third was on the burden of multimorbidity in relation to age, gender, and immigrant status.41 Results show that in our sample, diabetes was quite low in prevalence (1%) compared to the population results, which showed prevalence rates between 3.9% and 6.6%. Hypertension had similar prevalence between our data (19.6%) and the population study (18%-27.8%). Obesity seemed to have a slightly lower prevalence in our data (7.7%) compared to the population study (10.1%). Depressive disorders (defined as the sum of F32-Depressive episode, F33-Recurrent depressive disorder, F34-Persistent mood disorders) were more prevalent in our sample (21.1%) than in population studies (3.1%-7.1%). The same is valid for anxiety disorders that in our sample were significantly more prevalent (14.9%) than in the population studies (0.8%-1.5%). Results from the multimorbidity population study showed that the average number of comorbidities was between 1.73 and 1.82 (females and males, respectively), while in our patients—that were on average 20 years younger—the average number of chronic condition was 2.2 (when CM with

MOH was included in the count).41 In this study, 15.3% of cases were multimorbidity cases, compared to 32% of our sample: It has, however, to be considered that we employed a more strict approach to the definition of multimorbidity (ie, three or more conditions, if CM with MOH is included in the count) compared to the Italian multimorbidity study (ie, two or more conditions). Therefore, the impact of CM with MOH seems to be relevant in terms of predisposition to multimorbidity. Some limitations need to be acknowledged. First, sample representativeness. The study was conducted in a single specialty center, and all patients had MOH: Therefore, our results are representative only of the most severe spectrum of CM. Moreover, the sample was relatively small and we did not have any control group, for example, composed of patients with EM or with CM without MOH, for a baseline comparison. Second, no multimorbidity cases were lost to follow-up and we do not know whether lost patients were "successful cases" or whether they simply decided to move to another institution. The implication of this is that the rates of the outcomes evaluated at the follow-up were underestimated. Third, comorbidities were defined on the basis of clinical examination carried out in a neurological institution, and by a group of clinicians with high specialty in headache disorders. Although patients were requested to provide information on their clinical history, we cannot exclude that some information was not disclosed by patients, for example, minor allergies to food or cases of mild rhinitis not requiring medical treatment and common conditions of nonsevere degree, such as "trivial" visual disturbances. In addition to this, the reliance on ICD-10 codes did not enable us to account for the severity of each condition. The absence of a structured comorbidity questionnaire likely limited the inclusion of conditions that, if systematically addressed, might have emerged. Conversely, this is also a strength, as we were not limited to a predetermined list of conditions. Fourth, in our longitudinal analysis, we did not account for the presence of inadequate lifestyle behaviors, such as poor sleep, inadequate physical activity, eating or hydration, which might have an impact on relapse rates.42

Identification of comorbidities in medication overuse headache (MOH) is important for examining their connection, causality, common etiology, pathogenesis, etc. Psychiatric comorbidities are common, especially anxiety and depression (167, 168, 181). In the COMOESTAS study, 40% of patients with MOH met the criteria for depression, 27.7% met the criteria for anxiety (182). In EUROLIGHT, a cross-sectional study conducted in 10 European Union countries, the findings were similar, with a greater difference in the frequency of these comorbidities compared with a group that had migraine without excessive use of analgesic therapy (183). In the SAMOHA study, the frequency of psychopathological comorbidities was investigated in patients with MOH compared with patients with episodic migraine and healthy subjects (170). The frequency of moderate to severe anxiety was higher in both headache groups, while the frequency of addiction was significantly higher in patients with MOH. Patients with MOH had more frequent and more psychiatric comorbidities. An association between obsessive-compulsive disorder and MOH has been shown (170). A third of patients with MOH may have a subclinical form of obsessive-compulsive disorder, which is a recognized risk factor for headache chronicity (184, 185). MOH may be associated with behavioral disorders related to addiction to various substances. Although similar neurobiological mechanisms have been hypothesized for these two entities, it has been shown that personality traits are different in patients with MOH and those with addiction syndromes [26, 27]. Obesity is a risk factor for chronic headache, although some studies dispute this association [28, 29]. An association has been shown for obesity, physical inactivity, smoking, and the occurrence of MOH [29]. The association between obesity and MOH has been observed in children [21,30]. Patients with MOH have more frequent sleep disorders [12]. The diagnosis of MOH (medication-induced headache) occurs 15 or more days per month and develops as a result of regular excessive use of acute symptomatic headache therapy (10 or more, or 15 or more days per month, depending on the type of medication), for a period of at least 3 months. The exact number of days after which the use of a particular medication is considered overuse is based on expert recommendations [4]. In a patient with pre-existing primary headache who, in a temporal relationship with medication overuse,If a new headache type or a significant worsening of a pre-existing headache occurs and both meet the criteria for MOH, both MOH and pre-existing headache should be diagnosed [4]. A patient may have more than one subtype of MOH. For example, a patient who meets the criteria for triptan overuse headache and one of the subtypes of common analgesic overuse headache should be diagnosed with both of these diagnoses. In the case of overuse of combination analgesics, a diagnosis of combined analgesic overuse headache is made; overuse of each of the individual components of the combination analgesic is not made. There is a possibility of frequent use of different types of medications for acute/symptomatic headache that meet the criteria for overmedication based on the total number of days used, even though no single drug or group of drugs is overused. In these patients, a diagnosis of MOH attributable to multiple drug classes is made. In patients who overuse multiple medications for acute/symptomatic headache but do not provide accurate information about these medications individually, the diagnosis of MOH is made, which is attributed to unverified overuse of different classes of medications. On average, half of patients who have headache 15 or more days per month for a period longer than 3 months also have MOH [4,19].

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