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ORIGINAL ARTICLE

Withdrawal failure in patients with chronic migraine and medication overuse headache

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Abstract

Objectives: The management of chronic migraine (CM) with Medication Overuse Headache (MOH) consists of withdrawal therapy, education on medications' use and prescription of prophylaxis. Little attention has been given to patients who fail in achieving a successful short-term outcome after withdrawal: we aim to describe predictors of failure.

Methods: Patients with CM and MOH were enrolled at the Neurological Institute C. Besta of Milano, and included if they completed the three months follow-up. Withdrawal failure was defined as the situation in which patients either did not revert from chronic to episodic migraine (EM), were still overusing acute medications, or both did not revert to EM and kept overusing acute medications. Predictors of failure were addressed with a logistic regression, and for all variables, the longitudinal course in the two groups was described.

Results: In 39, out of 137 patients, withdrawal was unsuccessful: the predictors included day-hospital-based withdrawal (OR: 2.37; 95% CI: 1.06–5.29), emergency room (ER) access before withdrawal (OR: 2.81; 95% CI: 1.13–6.94) and baseline headache frequency >69 days/three months (OR: 2.97; 95% CI: 1.32–6.65). Patients who failed withdrawal did not improve on medications intake, use of prophylactic and non-pharmacological treatments, symptoms of anxiety and depression.

Conclusions: Patients who were treated in day-hospital, those who recently attended ER for headache, and those with more than 69 headache/3 months, as well as to those with relevant symptoms of anxiety and depression who did not improve should be closely monitored to reduce likelihood of non-improvement after structured withdrawal.

KEYWORDS
Anxiety, Chronic Migraine, Depression, Disability, Headache Frequency, Medication Overuse Headache, Quality of Life, Withdrawal Treatment

1 | INTRODUCTION

Chronic migraine (CM) represents a negative evolution of episodic migraine (EM). It is characterized by 15 or more headache days per month for more than 3 months and is frequently associated with the overuse of medication for acute treatment, a condition defined as medication overuse headache (MOH).[1,2] MOH is characterized by headaches occurring on 15 or more days/month for more than three months in patients with pre-existing primary headaches, it develops as a consequence of regular overuse of medications, and it usually resolves after the overuse is stopped. MOH prevalence range is 1–2% in the general population,[3,4] and it determines significant disability for patients and societal burden and cost[5-7]: its appropriate management is therefore a relevant clinical and social issue.

Approaches for treatment of MOH from CM include the cessation of overused symptomatic medications and prescription of prophylaxis. No consensus exists about the superiority of withdrawal alone vs. withdrawal associated with prophylaxis, about the approach to discontinuation of overused medications (eg abrupt or gradual), or about the superiority of hospital-based vs. 'at home' discontinuation.[4,8-11] Studies on patients followed in tertiary care centres indicate that withdrawal from overused symptomatic medications followed medical prophylaxis seems the most effective approach to reduce headache, interrupt MOH, and revert CM to EM.[11-15] The interruption of medication overuse and the reduction in headache frequency are the two main outcomes of treatment of MOH from CM.[8,10,16] The overuse of symptomatic medications is in fact one of the most relevant risk factor for chronification and, vice versa, high headache frequency is a driver for increased consumption of symptomatic drugs[17,18]: therefore, both medication intake and headache frequency reduction deserve to be addressed as treatment end points.

Reduction in headache frequency and medication intake are often accompanied by improvement in headache-related impact on ability to function, quality of life and economic burden.[7,13,19,20] However, not all patients improve: relapse rates have been observed in up to around 40% of patients at 12 months and up to around 45% of patients at three years.[12,21-23] The predictors of relapse into CM, with or without associated MOH, include the type of underlying primary headache, its frequency and the type of overused medication.[10,11] However, relapse may occur after a short period of time from withdrawal.[12,24] In such cases, rather than 'relapse into CM or into MOH' it would be more appropriate to refer to failure in reverting from CM to EM and interrupting MOH. The factors associated with such a failure have not systematically been investigated.

In this paper, we described the 3-month course of clinical and patient-reported outcome measures (PROMs) in a group of patients with MOH from CM that underwent structured hospital-based withdrawal treatment. The primary aim was to evaluate the predictors of short-term failure. Prior to this, we described the course of clinical variables and PROMs in patients who were successfully treated and among those who experienced withdrawal failure. Our main hypothesis is that patients who experience failure will also experience a worse outcome in terms of disability, quality of life (QoL), symptoms of anxiety and depression or other variables of interest.

2 | METHODS

2.1 | Participants and setting

This longitudinal observational study is based on secondary analyses of the MOH-Cost project, which was aimed to address the cost of MOH in Italy.[7,25] A group of consecutive patients with diagnosis of MOH based on the criteria of the beta-version of the International Classification of Headache Disorders, 3rd edition (ICHD-3-beta),[1] were enrolled between September 2015 and December 2017 on occasion of structured withdrawal treatment in our headache centre, either in day-hospital or in ward setting. Follow-up was concluded between December 2015 and March 2018 and was based on out-patient visit. Included patients matched the ICHD-3-beta criteria for both CM and MOH, were not submitted to a similar treatment in the previous three months and had to be available to provide information on their salary (which served for the main purpose of the MOH-Cost project). The present study is based on the subset of patients who completed the three months follow-up evaluation and had CM as primary headache. They were all volunteers and signed an informed consent form prior to inclusion in the study, which was approved by the Institute's ethical committee (protocol no. 379/2015).

The structured withdrawal programme lasted 5–7 days and included patients' education on medication management; abrupt interruption of overused drugs; intravenous hydration and corticosteroids as a 'bridge therapy' to avoid rebound headaches and withdrawal symptoms; intravenous paracetamol or indomethacin as rescue treatment for very severe headaches. Antiemetics were not regularly prescribed to all patients as per the structured withdrawal programme, but could be prescribed if needed on a tailored basis. Patients were prescribed a tailored prophylaxis and were recommended to consume three regular meals per day, to practice a moderate-level physical activity and to maintain a regular sleep-wake pattern. With regard to the use of acute treatments, patients are instructed to take Eletriptan (40 mg) and/or Almotriptan (12.5 mg) as first-line treatment, and indomethacin (50 mg) as second line; with regard to other NSAIDs, they were recommended to take those medications that had already proved to be effective and to avoid opioids. The use of acute medication should be restricted to headaches judged to be very disabling, that is rated as 8 or greater on a 0–10 scale.

We defined withdrawal failure as the situation in which patients either: a) did not revert from CM to EM, b) were still overusing acute medications, or c) did not revert to EM and kept overusing acute medications.

2.2 | The research protocol

Patients provided information on demographic data, disease duration, medication intake, filled in questionnaires on disability, QoL, anxiety and depressive symptoms. Disease duration was defined as duration of CM associated with MOH. Patients were asked to refer whether they attended emergency room (ER) in the three months before withdrawal, and whether they were submitted to a structured in-hospital withdrawal protocol in the three years before enrolment: those that were submitted to two or more structured withdrawals over three years were defined as 'frequent relapsers'.[26]

Disability was measured with the Migraine Disability Assessment (MIDAS)[27] and the World Health Organization 12-items Disability Assessment Schedule (WHODAS-12).[28] The MIDAS is composed of five items, the first two addressing the number of days with missed and impaired work-related activities, the third and the fourth addressing the number of days with missed and impaired homework activities, and the fifth addressing the number of days with missed leisure time activities. In addition to this, two items are included that address the number of days with headache and the average pain intensity. For all items, the timeframe is the previous three months. The WHODAS-12 is composed of 12 questions addressing daily activities which refer to domains such as understanding and communicating, getting around, self-care, getting along with people, life activities and participation in society. WHODAS-12 score range is 0–100, with higher scores reflecting greater disability.

QoL was measured with the Migraine-Specific Quality of Life Questionnaire Version 2.1 (MSQ). It is composed of 14 items grouped into three scales: Role Restriction (RR), Role Prevention (RP) and Emotional Function (EF). Each scale has a 0–100 score: low scores indicate poor QoL, and it has been validated also in patients with CM and MOH.[29,30]

Depressive symptoms were evaluated with the Beck Depression Inventory-second version (BDI-II), a 21-items questionnaire that addresses cognitive and somatic-affective components of depression. Each item is rated on a 0–3 scale and total score range is 0–63, with higher scores reflecting higher depressive symptoms.[31] BDI-II total score in the range 14–19 is indicative of mild depressive symptoms, in the range 20–28 of moderate depressive symptoms, and score ≥29 of severe depressive symptoms.[32] Symptoms of anxiety were assessed using the State-Trait Anxiety Inventory (STAI),[33] specifically only the 20 items referred to the trait subscale, which addresses how the respondent feels in general. Raw scores were converted into T-scores (mean 50, SD 10) on the basis of age and gender-based normative Italian scores[34]: clinically relevant anxiety was defined as a T-score ≥61.

2.3 | Data analysis

Descriptive statistics were used to present data: continuous variables were reported using means and 95% confidence intervals (95% CI), categorical variables with frequencies and percentages.

MOH was classified based on the type of overused compounds as per ICHD-3-beta criteria: overuse of simple analgesics (including non-steroidal anti-inflammatory drugs – NSAIDs) for 15 or more days/month, overuse of triptans for 10 or more days/months, overuse of opioids for 10 or more days/months. If more drug categories were overused together, patients were classified as poly-overusers.

We tested all variables for normality of distribution using Shapiro-Wilk test, and almost all of them (with the exclusion of age, STAI-Trait at baseline and MSQ-RR at follow-up) were non-normally distributed. Therefore, we preferred to rely on non-parametric analyses.

Short-term variation at the whole group level was tested using Wilcoxon test for continuous variables and McNemar test for categorical ones: the latter included being analgesics/NSAIDs, triptan and opioid overuser or being a poly-overuser (ie being an overuser of more than one compound category), and having relevant anxiety and relevant depression, defined as STAI-Trait score ≥61 and BDI-II score ≥14. We also computed the mean variation between baseline and follow-up, together with its 95% CI for continuous variables, and mean percentage variation for categorical ones. As this analysis was basically intended as a descriptive one, we did not employ any correction to statistical significance.

Short-term change was then tested separately for those patients whose withdrawal outcome was failure and for those whose outcome was successful. Wilcoxon and McNemar test were again employed, respectively, for continuous and categorical variables: for this analyses, we employed Bonferroni correction to statistical significance and, as 21 multiple comparisons were made for each group, significance was set a $p<.0024$ and two-tailed testing. The two groups were tested separately, thus obtaining only a time effect. To address the magnitude of change in each group, for continuous variables we user r as a measure of effect size (ES), where $r=Z/\sqrt{N}$ and r values around 0.1, 0.3 and 0.5 indicate small, medium and large ES, respectively; for categorical variables, we used phi, where values around 0.1, 0.3 and 0.5 indicate small, medium and large ES, respectively.[35]

To address whether baseline acute drug consumption might be somehow associated with withdrawal outcome, we tested the difference between patients with different outcome for total intakes (expressed as number of intakes/3 months) and total amount (as total mg/3 months) for each single compound among NSAIDs, triptans and opioids. Mann-Whitney test was used for this analysis: it was intended as a descriptive one, and therefore, we did not employ any correction to statistical significance.

We used logistic regression to predict short-term withdrawal failure. Given the descriptive purpose of this part of analysis, we relied on a wide amount of candidate predictors referred to baseline and to the variation between baseline and follow-up. Due to the lack of literature information on the predictors of withdrawal failure, we took into account the widest possible set of information that was available in our data set. With regard to the prophylactic treatment, we took into account those that were prescribed by the neurologists of our headache centre to address whether any specific association

could be found: due to the large amount of possible compounds and administration modalities, we based this analysis on the five main categories (ie antidepressants, anxiolytics, anti-hypertensives, anti-epileptics and the other drugs, which include levosulpiride, pizotifen and onabotulinumtoxin-A). Before running regression, we selected potential candidates by testing their association with the outcome withdrawal failure: we used chi-squared and retained those variables with a significance at two-tailed $p<.10$. Selected variables were entered together, and a backward approach was used to retain variables independently associated with the outcome withdrawal failure. The −2 log-likelihood difference with chi-squared was used to test the difference between the full model and the model based on the intercept only. The c-statistics, that is the area under the receiver operating curve (AUROC) for the predicted versus the actual data, was used to assess the whole explanatory power of the model.

Baseline categorical variables were as follows: gender; setting of withdrawal treatment (day-hospital vs. ward); education level (low vs high); marital status (married/cohabitating vs. not married/cohabitating); employment status (employed vs. not employed); overuse of medications defined as overuse of analgesics/NSAIDs, overuse of triptans, overuse of opioids, poly-overuse[1]; previous prescription of any pharmacological prophylaxis (vs. no previous prescription); being on any non-pharmacological treatment (vs. not being on non-pharmacological treatment); access to emergency room for headache in the previous three months. For continuous variables, dummy variables were created. For BDI-II and STAI, we relied on normative scores, that is BDI-II ≥14 and STAI-Trait ≥61. With regard to age, baseline headache frequency and baseline overall medication intake, we relied on their distribution in our sample and identified the worse group as that having a score higher than the upper bound of the 95% CI for age and CM duration (>50 and >16 years), three-month headaches' frequency (>69 days), three months and average medications intake per day (>164 intakes and >2.4 intakes/day). The same approach was employed to variation in STAI-Trait and BDI-II score, but in this case, we selected as the worse group that showing a lower variation in STAI-Trait (<4) and BDI-II (<3) scores.

Data were analysed with IBM SPSS statistics 26.0.

3 | RESULTS

A total of 176 patients were enrolled at baseline: of them, 137 patients had CM as primary headache and completed the 3 months follow-up (see Figure 1). Table 1 shows the main features of included patients: most of them were female and employed, the mean age was 48.2, and mean CM duration was 14.3 years. One-third of the patients reported at least one withdrawal treatment in the three years prior to enrolment, and 27 (19.7%) were frequent relapsers. At the whole group level, almost all clinical variables and PROMs showed a general improvement: the only one that remained stable was the use of any non-pharmacological treatment (see Table S1 in supplementary information file). No difference was observed between patients with successful and non-successful withdrawal with

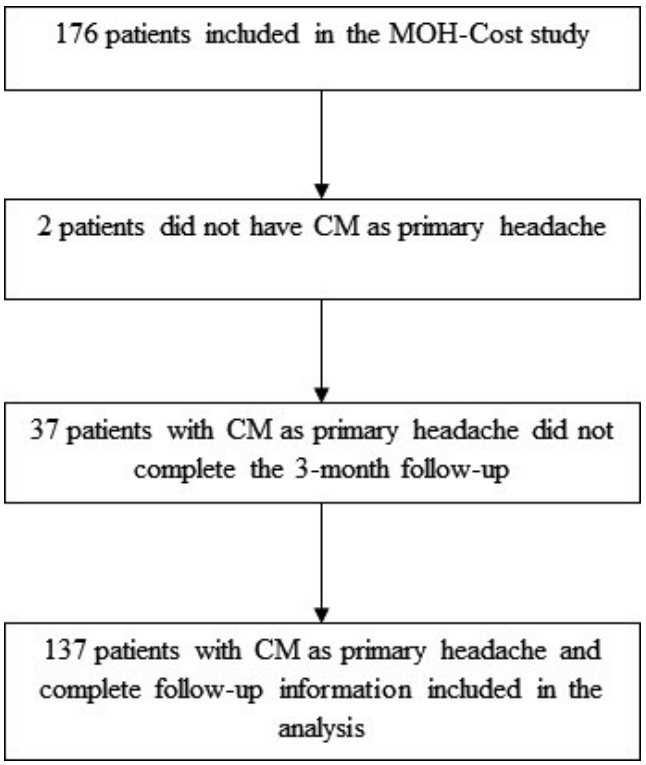

FIGURE 1 Patients' flowchart

regard to baseline total intakes and total amount of consumed drug in any drug for acute treatment (see Table S2 in supplementary information file).

Out of 137 patients, 39 matched our definition of withdrawal failure: four because did not revert to EM, 24 because were still medication overusers and 11 because of both. As shown in Table 2, most of the variables improved significantly in both groups, with an ES that for most cases was large for continuous variables and small to moderate for categorical ones. Exception to this included: amount of acute medications per migraine day, analgesics/NSAIDs overusers category, opioids intake and opioids overusers category, being under any medical prophylaxis, anxiety test score, having relevant anxiety and having relevant depression, which did not decrease significantly among patients with withdrawal failure; being under any non-pharmacological treatment, which did not change in any of the two groups; it has then to be noted that all patients with withdrawal success interrupted analgesics/NSAIDs and opioids overuse (which did not enabled to calculate McNemar test and phi). Taken as a whole, these results show a better outcome among patients with successful withdrawal. Patients who failed withdrawal reported a worse baseline profile with regard to PROMs, that is lower QoL and higher disability.

Most candidate variables for the regression model were not associated with withdrawal failure. Significant associations were found for treatment setting, with stronger associations observed for patients treated in day-hospital setting (Chi-Squared=4.11; $p=.043$), younger age (Chi-Squared=2.76; $p=.096$), female gender (Chi-Squared=3.06; $p=.097$ with Fisher correction), ER attendance

TABLE 1 Socio-demographic variables at baseline

Female Gender, N (%)	119 (86.9%)
Age, Mean (95% CI)	48.2 (46.3–50.2)
Educational level, N (%)	
Primary/secondary	42 (30.7%)
High/academic	95 (69.3%)
Employment status, N (%)	
Employed	97 (70.8%)
Unemployed	40 (29.2%)
Living situation, N (%)	
Married/cohabitating	102 (74.5%)
Not married/cohabitating	35 (25.5%)
Duration CM, Mean (95% CI)	14.3 (12.4–16.2)
Treatment setting, N (%)	
Inpatient	85 (62.0%)
Day-Hospital	52 (38.0%)
Previous withdrawal, N (%)	48 (35.0%)
Frequent relapsers, N (%)	27 (19.7%)
ER access before withdrawal, N (%)	29 (21.2%)

Notes: CM, Chronic Migraine; 95% CI, 95% CI, 95% Confidence Interval.

(Chi-Squared=4.83; p=.028) and higher headaches frequency (Chi-Squared=7.47; p=.006).

These five variables were entered in the logistic regression model predicting withdrawal failure, reported in Table 3. The model was solid as shown by −2 log-likelihood analysis and c-statistic. Patients who attended withdrawal in day-hospital, those that referred ER access before withdrawal and those with baseline headache frequency higher than 69 days in the three months before withdrawal (ie 23 days on a monthly basis) had two to three higher risk of experiencing withdrawal failure by 3 months.

4 | DISCUSSION

Our study shows that 28.5% of patients with MOH for CM submitted to withdrawal (39 out of 137) underwent withdrawal failure. Such a failure was predicted by higher baseline headache frequency (>69 days over three months), access to ER before withdrawal and being treated in day-hospital and not in ward. Patients for whom withdrawal was successful improved in almost all variables, as expectable. On the contrary, patients who underwent withdrawal failure did not improve on medications intake (intakes per day, overall opioids intake, and on the percentage of analgesics/NSAIDs, triptans and opioids overusers), they did not follow indications for medical prophylaxis and non-pharmacological treatments, they did not show a decrease in anxiety test score, and maintained, at BDI-II and STAI, score suggestive of relevant symptoms of anxiety and of depression. No differences were observed between the two groups of patients with regard to the baseline number of intakes and total amount of consumed compounds in mg/3 months. Taken as a whole, these results show a worse course in several outcome measures among patients with withdrawal failure. Finally, these patients showed higher disability and lower QoL at baseline.

Available literature indicates that a wide range of factors may contribute to treatment outcomes in patients with MOH, as reported by recent reviews.[10,11] However, the results of these studies should be interpreted with caution, in reason of differences in populations (ie MOH associated with CM or to another headache disorder), duration of follow-up and type of treatment offered to patients, namely presence or absence of structured withdrawal associated or not with prophylaxis. In addition to this, studies generally address predictors of positive outcome, and not of short-term failure. Follow-up periods range between 2 and 3 months up to five years and, as shown in the review by Chiang and colleagues,[10] a gradient in negative outcome associated with follow-up duration exists (20.6% for studies with follow-up up to six months and 30.7% for those with follow-up comprised between one and five years). More specifically, relapse rates may be relatively high already by 6 months after discontinuation, with up to 34% showing a relapse,[10] and the first year after discontinuation is the most critical period. In fact, more than 90% of relapsers usually experience relapse by the first year,[12] and short-term (two months) negative outcome at 2 months is likely associated with long-term failure, as shown by Ghiotto and colleagues.[36] These pieces of literature support the hypothesis that patients may progress again into CM and eventually MOH on a reasonable amount of time, such as 12 months, after they had achieved a positive outcome: this identifies the case in which patients relapse into CM and/or into MOH. However, some patients might not achieve any positive outcome, even in a shorter period: this corresponds to what we described here, that is failure of the withdrawal procedure. As short-term negative outcome is associated with long-term one, an early identification of such cases is of importance to early treat these patients, by adjusting medical prophylaxis or suggesting non-pharmacological treatments. This has, however, to be considered as a partial conclusion, since our analysis did not yield any association between the main categories of prescribed prophylaxis and the short-term outcome.

Previous literature on factors associated with negative outcome, with variable length of follow-up, found the following: younger age,[37,38] female gender,[37] high headache frequency,[39] high disability,[15,37,40] high baseline medication intake,[40,41] history of recent in-hospital withdrawals,[39] smoking, alcohol consumption and dependence problems[42,43] and concomitant anxiety and depression,[39,44,45] traumatic childhood experiences and recent stressful events.[45] Some of these factors were retrieve in our study too: younger age and female gender were associated with withdrawal failure, whereas high baseline headache frequency was also found as a predictor of failure in the logistic regression model. Furthermore, other two factors, that is ER accesses before withdrawal and being treated in a day-hospital setting and not in ward, were significant predictors of withdrawal failure.

The influence of treatment setting was not considered among the possible predictors in most published studies. A superiority of an

TABLE 2 Clinical variables at baseline and follow-up by group

Variable	Withdrawal Outcome	Baseline	Follow-up	P-value	Effect Size
Headache Frequency, Mean (95% CI)	Success	63.7 (60.4–67.0)	19.5 (17.3–21.6)	<.001	0.87
	Failure	73.7 (68.3–79.0)	45.5 (38.1–52.8)	<.001	0.80
All Acute Medications intake, Mean (95% CI)	Success	139.4 (117.6–161.1)	21.5 (18.4–24.6)	<.001	0.87
	Failure	154.9 (110.1–199.8)	77.9 (62.7–93.1)	<.001	0.67
Acute medications per headache day, Mean (95% CI)	Success	2.2 (1.9–2.5)	1.5 (1.1–1.9)	<.001	0.53
	Failure	2.2 (1.5–2.8)	2.3 (1.7–2.9)	.845	–
Analgesics/NSAIDs intake, Mean (95% CI)	Success (N=83)	102.2 (78.6–125.7)	12.7 (10.3–15.2)	<.001	0.84
	Failure (N=37)	113.0 (68.6–157.4)	59.6 (41.5–77.6)	<.001	0.59
Analgesics/NSAIDs overusers, N (%)	Success	57 (58.2%)	0 (0%)	Nc	–
	Failure	23 (59%)	23 (59%)	1.00	–
Triptans intake, Mean (95% CI)	Success (N=66)	62.6 (53.6–71.5)	13.0 (10.7–15.3)	<.001	0.87
	Failure (N=22)	65.0 (45.8–84.2)	28.0 (20.9–35.1)	<.001	0.72
Triptans overusers, N (%)	Success	54 (55.1%)	8 (8.2%)	<.001	0.27
	Failure	19 (48.7%)	13 (33.3%)	.109	–
Opioids intake, Mean (95% CI)	Success (N=23)	36.3 (10.4–62.2)	1.4 (−0.6–3.5)	<.001	0.85
	Failure (N=13)	25.1 (1.9–48.4)	3.9 (−4.6–12.5)	.009	–
Opioids overusers, N (%)	Success	7 (7.1%)	0 (0%)	Nc	–
	Failure	4 (10.2%)	1 (2.6%)	.250	–
Poly-overusers, N (%)	Success	29 (29.6%)	3 (3.1%)	<.001	0.02
	Failure	14 (35.9%)	2 (5.1%)	.002	0.07
Any medical prophylaxis, N (%)	Success	56 (57.1%)	86 (87.8%)	<.001	0.24
	Failure	28 (71.8%)	32 (82.1%)	.424	–
Any non-pharmacological treatment, N (%)	Success	45 (45.9%)	48 (49%)	.711	–
	Failure	20 (51.3%)	20 (51.3%)	1.00	–
MIDAS, Mean (95%CI)	Success	69.9 (60.7–79.1)	23.3 (19.2–27.4)	<.001	0.81
	Failure	108.4 (85.7–131.1)	56.1 (41.9–70.4)	<.001	0.69
WHODAS–12, Mean (95%CI)	Success	25.3 (22.5–28.1)	17.0 (14.7–19.4)	<.001	0.55
	Failure	30.6 (25.2–36.1)	23.0 (18.5–27.5)	<.001	0.53
MSQ-RR, Mean (95%CI)	Success	33.3 (29.8–36.7)	59.2 (55.7–62.6)	<.001	0.84
	Failure	27.1 (21.0–33.2)	45.9 (39.7–52.0)	<.001	0.72

(Continues)

TABLE 2 (Continued)

Variable	Withdrawal Outcome	Baseline	Follow-up	P-value	Effect Size
MSQ-RP, Mean (95%CI)	Success	51.6 (47.4–55.9)	71.8 (68.3–75.3)	<.001	0.72
	Failure	39.7 (31.9–47.5)	56.7 (50.1–63.3)	<.001	0.64
MSQ-EF, Mean (95%CI)	Success	42.9 (37.4–48.3)	72.4 (68.1–76.7)	<.001	0.78
	Failure	33.0 (24.0–41.9)	53.2 (43.9–62.4)	<.001	0.66
STAI-Trait, Mean (95%CI)	Success	57.0 (55.2–58.8)	50.4 (48.5–52.2)	<.001	0.70
	Failure	56.5 (53.3–59.7)	52.3 (49.2–55.3)	.003	–
Relevant anxiety, N (%)	Success	39 (39.8%)	16 (16.3%)	<.001	0.49
	Failure	14 (35.9%)	9 (23.1%)	.180	–
BDI-II, Mean (95%CI)	Success	14.4 (12.6–16.2)	9.6 (7.9–11.2)	<.001	0.62
	Failure	16.4 (13.0–19.8)	12.5 (9.3–15.6)	<.001	0.58
Relevant depression, N (%)	Success	49 (50%)	23 (23.5%)	<.001	0.41
	Failure	19 (48.7%)	13 (33.3%)	.109	–

Notes: N=98 and 39, respectively, for patients experiencing withdrawal success and failure unless differently indicated. Significance set at α=.0025 after Bonferroni correction.

Abbreviation: NSAIDs, non-steroidal anti-inflammatory drugs; MIDAS, Migraine Disability Assessment; WHODAS-12, 12-items World Health Organization Disability Assessment Schedule; MSQ, Migraine-Specific Quality of Life; MSQ-RR, MSQ-Role Restriction; MSQ-RP, MSQ-Role Prevention; MSQ-EF, MSQ-Emotional Function; STAI, State-Trait Anxiety Inventory: BDI-II, Beck Depression Inventory-second version; 95%CI, 95% Confidence Interval; Nc, not computed.

TABLE 3 Logistic regression predicting three-month withdrawal failure

	N. (%) among whole sample	N. (%) among withdrawal failures	B (SE)	OR (95% CI)	*P*-value
Withdrawal in day-hospital	52 (40%)	20 (51.3%)	0.86 (0.41)	2.37 (1.06–5.29)	.035
ER access before withdrawal	29 (21.2%)	13 (33.3%)	1.03 (0.46)	2.81 (1.13–6.94)	.026
Higher-Frequency headache (>69/90 days)	66 (48.2%)	26 (66.7%)	1.09 (0.41)	2.97 (1.32–6.65)	.008

Notes: Model based on intercept only −2 log likelihood =163.7; final model −2 log likelihood =147.2; chi-squared =16.5, df =3, p =.001. Intercept: B −2.12, SE 0.41. AUROC=.716 (95% CI.626 -.805; p<.001)

Abbreviation: OR =odds ratio; 95% CI =95% Confidence Interval.

in-patient regimen was reported only in the short-follow-up (2 months after withdrawal) study published by Rossi and colleagues,[46] in which a higher rate of interruption of MO was evident in patients treated by an in-patient withdrawal programme associated with prophylaxis, than in those who had received only advice or an out-patient withdrawal. On the other hand, those studies aimed to directly assess the possible predicting role of being treated in an out-patient or in-patient withdrawal programme associated with prophylaxis after a long follow-up, found no significant difference in outcomes between these two treatment settings.[14,40,41]

The issue of ER attendance, in the present study, was referred to pre-withdrawal and not to the period between withdrawal and follow-up: it has, however, to be noted that, in the period immediately after withdrawal, patients usually experience a considerable clinical improvement which limits the likelihood to attend ER. In previous studies, ER attendance was associated with presence of multiple comorbidities[47] and is a driver of increased healthcare service utilization and cost.[48] The results of the present study are consistent with previous findings and suggest that attention should be given to those patients who attended ER before withdrawal: more than half of them,

in our series, underwent withdrawal failure and, compared to patients who did not attended ER before admission, showed higher rates of severe depression (39% vs 9%) and severe anxiety (51% vs 35%).

Overall, the results of this study support the idea that some patients are more prone than others not only to relapse into CM, as previously concluded,[26,39,49] but also to undergo short-term failure, and should therefore be monitored in a close period of time in order to make adjustments to therapy, to provide lifestyle indications, or to suggest specific treatment for comorbidities. Although anxiety and depression levels were not found as significant predictors, those patients who underwent withdrawal failure were also those reporting a less evident change in these variables, with only a minority of them moving to a less severe level than baseline at follow-up.

Our data do not enable clarifying the relation between improvement in anxiety and depression symptoms and headache outcome, as patients received different type or prophylaxis, including anxiolytics and antidepressants. So the improvement in anxiety and depression symptoms may either be an effect of drugs specifically targeting these symptoms, or be an effect of improvement in headache outcome, and a different study design would be needed to approach such a relation. Anyway, addressing symptoms of anxiety and depression may be one of the keys to success, as shown in studies who specifically address it in the treatment of CM with onabotulinumtoxin-A.[50,51] In particular, the study of Blumenfeld and colleagues[51] showed that a considerable part of subjects who showed relevant depression and anxiety at baseline significantly improved over the 108 weeks of the study (respectively, 78% of those with relevant depression and 82% of those with relevant anxiety). However, the vast majority of these patients improved by 12 weeks (respectively, 62% of those with relevant depression and 69% of those with relevant anxiety). Our results are consistent with those presented by Blumenfeld and colleagues, on the value of anxiety and disability score: however, we employed a different approach to the definition of relevant change over time, which is not based on normative data, but on the specific features of this sample.

Patients overusing NSAIDs at baseline had the worst outcome: among those for whom failure was observed, none was able to stop NSAIDs overuse; on the contrary, all of those for whom withdrawal was successful were able to stop NSAIDs overuse. Our opinion is that those with baseline NSAIDs overuse who failed withdrawal were not able to follow the recommendations provided on occasion of the structured withdrawal, that is to switch from NSAIDs to triptans, likely due to ineffectiveness of triptans or to patients' inability to engage in a new treatment.

The fact that no difference on number of intakes and total amount of consumed compounds referred to NSAIDs, triptans and opioids is likely a consequence of the features of sample, namely the kind of overused drugs. In fact, around one-third of patients were poly-overusers but, within those overusing only one drug, the consumption of more than one compound, also at different dosages, was quite common, and this was particularly true for NSAIDs overusers. A previous study from our group, in which we presented baseline features of the entire sample from which the present study was drawn together with the results of a literature review,[52] supported the idea that CM associated with MOH is not drug-specific and that all drug classes may induce migraine chronification. Such a finding is reinforced by the results herein presented that suggest that the kind of overused drug is not associated with withdrawal failure: however, caution is warranted in the interpretation of this result in reason of the small sample and overdispersion of data, especially those referred to patients undergoing withdrawal failure.

Some limitations of the study have to be acknowledged. First, sample representativeness is a concern as we studied patients attending a single centre, and with a very high frequency of headaches, a relevant consumption of symptomatic medications, and a high disability level at both baseline and follow-up. The relatively high failure rate might therefore be a direct consequence of our setting, that is a centre where the most severe patients are likely to attend. Second, the number of candidate variables for the two models was quite large in consideration of our sample size, with the risk of problems with model fit. The reason for this is the inconsistency in literature findings on predictors of negative outcome, in particular in a short-term period: to avoid model fit problem, we therefore had to reduce the amount of predictors through a pre-selection based on chi-squared test. Third, we did not include some candidate variables which were found as possible predictors of failure in previous published studies, such as specific psychological and psychiatric aspects, personality problems, history of important traumatic events; furthermore, we could not assess the influence on outcome of different types of primary headache, as our patients had all a CM diagnosis. On the other hand, we think that our study included a series of aspects possibly predicting treatment failure which were scarcely evaluated in published studies, namely history of recent withdrawal treatments, access to ER and the setting for withdrawal treatment. Fourth, 39 out of 176 patients, corresponding to 22%, did not complete the follow-up. Given the nature of study and in particular the kind of data collected (ie salary, health and health-related expenditures), we could not explore drop-out further. We may therefore hypothesize that such a high rate may be due to lack of interest in a study in which patients have to communicate their salary: we cannot in fact exclude the possibility that some of the patients we enrolled accept to participate to the study because they did not want to 'say no' to their treating neurologist during hospitalization. Other patients might have been dissatisfied with the prescribed prophylaxis and decided to interrupt it: in fact, previous studies showed that adherence to prescribed prophylaxis varies between 26% and 29% over a six-month period.[53]

5 | CONCLUSIONS

In conclusion, our findings provide clinicians with useful indications on the possible factors contributing to the failure of structured withdrawal over a 3-month period. We confirm that particular attention should be given to patients with high frequency of headaches before treatment. In addition to this, our result point out at two less investigated aspects that should be taken into account as predictors of

negative short-term outcome: treatment in day-hospital setting and ER attendance in the months before withdrawal treatment. Finally, symptoms of anxiety and depression should be systematically assessed at baseline, so that appropriate treatment can be prescribed, and monitored in the short term.

Awareness of these aspects as well as a close monitoring of patients with MOH for CM at three months after withdrawal programme are therefore of paramount importance to identify patients who are more likely not to revert to episodic migraine and to maintain overuse of symptomatic medications, with benefit for patients in terms of health improvement and for societies in terms of disease cost reduction.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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