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Differences in pharmacological migraine treatment across different levels of clinical headache care – a cross-sectional study

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Abstract

Background Migraine significantly impairs quality of life, reduces workplace productivity, and imposes a substantial socio-economic burden. The severity of migraine correlates with its impact on quality of life and healthcare costs, emphasizing the need for adequate management. In the past, primary care services often faced issues of inadequate treatment. This study evaluates differences in pharmacological recommendations for acute and preventive migraine treatments across primary, secondary, and tertiary care settings.

Methods This cross-sectional study involves patients with confirmed migraine (with or without aura) visiting the tertiary headache center at Charité Berlin between 12/2015 and 01/2023 for the first time. Data on headache characteristics and prior treatments for acute and prophylactic treatments at primary/secondary and recommendations from tertiary level of care were retrieved from medical letters written after first consultation.

Results Among 1,047 migraine patients (42 years, 84% women), 99% had received treatment for acute migraine attacks by primary/secondary care facilities, and 96% were using it at their first consultation, with 63% advised to use a triptan. The average number of triptans tested prior to referral was 1 ± 0.99. Prophylactic treatment was prescribed to 52% of patients by primary/secondary care facilities, with an average of 1.2 ± 1.6 prior prophylactic attempts per patient, and 44% were actively using it at the time of consultation. More than two thirds of patients with over four monthly migraine days were not using prophylactic treatment at referral. Tricyclic antidepressants, beta-blocker and, anticonvulsants were prescribed significantly more often in primary/secondary care settings while Onabotulinumtoxin-A and Calcitonin Gene-Related Peptide(-receptor) antibodies were more commonly initiated in tertiary care. Treatment recommendations from primary/secondary settings were revised in 77% of patients following consultation at the tertiary headache clinic.

Conclusion Compared to previous studies, the overall prescription of acute and prophylactic therapies in primary and secondary care facilities has improved. Further progress is needed in expanding the range of triptans and prophylactic treatments tested before referring patients to specialized centers. However, given the selected study population, the findings may not be fully applicable to all patients treated in primary/secondary care, especially those already receiving adequate care without being referred to specialized settings.

Keywords Treatment recommendation, General practitioners, Triptans, CGRP

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Background

Migraine is one of the most common neurological disorders, ranking as the third leading cause for years lived with disability worldwide [1]. Characterized by recurring headache attacks, it not only impairs the quality of life [2], but also significantly impacts workplace productivity [3]. Over two-thirds of those affected report that their condition adversely affects their careers, with 32% fearing long-term financial security due to their migraine [4]. Migraine is one of the most common reasons for medical consultations with general practitioners (GPs) or emergency services, which collectively leads to a significant socio-economic burden [3, 5]. In 2011, the financial cost of migraine in Europe was estimated to range between 50–111 billion Euro [6]. More recently, a Spanish study reported an annual cost of €8,894 per migraine patient, with €894 (10.1%) attributed to direct costs and €8,000 (89.9%) to indirect costs associated with absenteeism and presenteeism [7]. Additionally, migraine has a negative effect on social aspects, including partner relationship and child care [8, 9].

Both quality of life and financial burden on the healthcare system correlate with the severity of migraine [10–12], highlighting the importance of providing adequate care for those affected. This involves pharmacological treatment of migraine consisting of acute therapies to manage individual attacks and preventive therapies to reduce the frequency and severity of attacks. Acute medication should be offered to every migraine patient [13]. Nonsteroidal anti-inflammatory drugs (NSAIDs) and other analgesics are suitable for mild migraine attacks, while triptans, serotonin 5-HT1B/1D agonists, are recommended for severe migraine headaches or if NSAIDs taken at appropriate doses and early during the attack lack in response [13]. At the time the study was conducted, other specific acute therapies such as lasmiditan and gepants were not yet available for acute therapy in Germany. Patients experiencing severely debilitating, frequent or prolonged migraine attacks should be additionally considered for preventive treatment [14]. Further, prophylactics should be discussed in the event of lack of response, overuse, intolerance or contraindications to acute migraine treatment. In Germany, recommended treatment of first choice include beta-blockers, amitriptyline, flunarizine, topiramate, and Onabotulinumtoxin- A for chronic migraine [15]. In addition, three monoclonal antibodies (mAbs) targeting Calcitonin Gene-Related Peptide (CGRP) or its receptor (CGRP-R) are available on the market since 2018, the fourth (Eptinezumab) was approved in Germany in 2022 [14, 16]. Until October 2022, these specific treatments were only accessible to patients who had experienced lack of efficacy, intolerable side effects, or contraindications with all non-specific first-choice preventatives. However, since October 2022, erenumab can now be prescribed in Germany to patients who have failed or not tolerated at least one prior preventive treatment [17], simplifying access to this targeted therapy compared to other CGRP mAb [18].

With an estimated 594 million people aged 19–39 years affected by migraine in 2021 [19], specialized headache centers alone cannot manage all migraine patients. In many European countries, headache care is therefore structured into multiple levels. GPs make up the first tier, providing primary care services. Across Europe, around 90% of headache patients are managed by GPs [20]. The second level comprises specialists in pain and headache management, such as neurologists or anesthesiologists. A recent Spanish study revealed that neurologists treat between 29% and 88% of migraine patients, depending on the severity of their condition [21]. The third tier involves specialized headache centers, which are designed to treat patients with particularly severe or complex cases. According to the recommendations from a collaboration between the European Headache Federation and Lifting the Burden, the Global Campaign against Headache, these centers should care for approximately 1% of all headache patients [20]. In Europe, these centers, often affiliated with universities, see approximately 10% of all patients [20]. In Germany, headache patients are managed according to this tiered system. Primary care is provided by GPs, secondary care involves specialists such as neurologists or anaesthesiologists, and tertiary care is offered by specialized headache clinics affiliated with universities. Prior to referral to our tertiary headache center, patients must have first received treatment at least at the primary, preferably also at the secondary care level. Despite their critical role in headache management, primary care services often face issues of misdiagnosis and inadequate treatment [8]. Transnational studies have shown a misdiagnosis rate of over 70% in primary care, and a significant under-prescription of migraine prophylaxis by GPs in Austria, France, and the UK to less than 10% of eligible patients [8, 22]. In a recent study of patients with confirmed or probable migraine visiting a tertiary headache center, after all 67% had previously been diagnosed with migraine in primary or secondary care settings [23]. Globally, there are still major barriers to adequate headache management, including inequalities in access to treatment, reimbursement for novel acute and preventive treatments, and regional availability of drugs and knowledge [24]. In response to these challenges, various headache societies have intensified efforts to improve migraine care by developing diagnostic and treatment guidelines and offering training for primary care physicians [25–27].

To evaluate the effectiveness of these initiatives this study aims to assess differences in pharmacological recommendations for acute and prophylactic migraine treatment between primary/secondary level of headache care and our tertiary headache center. By understanding the current state of pharmacological recommendations, we can identify gaps and areas for improvement.

Methods

Study design, setting and participants

This is a sub-study of a cross-sectional study among patients visiting our tertiary headache center Charité – Universitätsmedizin Berlin between December 2015 and January 2023 for the first time. For detailed methods please refer to the primary publication [23]. Unlike the first publication, this study included only patients with confirmed migraine (with or without aura, episodic and chronic) according to the ICHD-3 criteria [28]. In addition to migraine, patients may also have experienced other types of headache disorders, such as tension-type headache (TTH) or cluster headaches.

In summary, data on headache characteristics as well as acute and prophylactic migraine treatment prescription from primary/secondary level of care (corresponds to the referring GPs, neurologists or anesthesiologists) and treatment recommendation from tertiary level of care (corresponds to Charité headache clinic) were retrieved from the doctor's letter written after their first consultation at the headache outpatient clinic of Charité Berlin. Although patients were treated at the headache center for an extended period, this study only includes data from their first appointment and does not follow up beyond that. We excluded patients in which the doctor's letter was unavailable. Further variables obtained from the doctor's letters for this study included: Migraine frequency in headache days per 28 days (monthly migraine days—MMDs), headache onset, occurrence of migraine aura, attack duration, and headache intensity measured using the numerical rating scale (NRS) on a scale from one to ten. A differentiated analysis of the recommendations from primary and secondary levels of care was not possible as we considered all previous recommendations and had no information on where they originally came from.

Endpoints

The primary endpoint of the study was the frequency with which acute medication and/or migraine prophylaxis was prescribed in the primary/secondary headache level compared to treatment recommendation from the tertiary level of headache care in people with confirmed migraine. As secondary outcomes, we looked in detail at the medications recommended and the differences between the different headache care levels. Exploratory endpoints included reasons for possible treatment switching.

Statistical analyses

For statistical analysis we used IBM SPSS Statistics (IBM SPSS Statistics ©; 23.0, for Mac). Missing values are indicated for each analysis or can be derived from the adjusted overall sample size (fewer than $n=1047$). We conducted descriptive analyses for demographic and headache characteristics as well as questions on treatment recommendations. Categorical variables are reported as absolute numbers (n) and percentages (%), whereas numerical variables are displayed as mean values ± standard deviation. To analyze differences in the frequency of treatment recommendations between primary/secondary level of care and tertiary level of care, we performed a fisher-exact test. For multiple-choice questions, the percentages indicated represent the proportion of the respective cases (responses). Accordingly, the total value may exceed 100%.

Results

Study population and headache characteristics

Between December 2015 and January 2023, 3264 patients visited our tertiary headache center for the first time. We excluded 280 (8.6%) cases due to missing doctor's letters and another 32 (1.0%) due to non-headache related consultations, e.g. visual snow syndrome or facial pain. Of the remaining 2,952 patients, 1,047 patients (mean age 42 years, 84% women, 81.5% with more than 4 MMDs) were diagnosed with migraine and included in the following analyses. Demographics are summarized in Table 1.

Recommendations for the acute treatment of migraine headaches

Primary and secondary level of care

Within our study population the vast majority (1031/1041 (98.5%), 6 missing) were recommended acute medication at some point in their migraine history and were using acute pain medication against migraine headache (986/1027 (96.0%), 4 missing) prescribed by their GP or registered neurologist at the time of referral (Fig. 1). This comprised predominantly NSAIDs and triptans: At some point in their migraine history, 81.9% of patients (844/1031) used at least one NSAID, while 47.6% (469/986) were using one at the time of referral. Similarly, 74.4% (767/1031) had used at least one triptan in the past, with 63.4% (625/986) still using one at the time of referral. Among the prescribed NSAIDs (one patient could have used multiple), ibuprofen (540/1007) was the most commonly used. Among the triptans (one patient could have tested multiple), sumatriptan (all forms of administration) (445/1191),

Table 1 Study population and headache characteristics

	n (%) or mean ± SD Total, 1047 (100)	Missing n (%)
Female sex	879 (84.0)	-
Age at referral (years)	42 ± 13.3	-
Age at onset (years)	20.1 ± 11.9	7 (0.7)
Disease duration (years)	22.3 ± 14.4	7 (0.7)
Chronic migraine	290 (27.7)	-
Migraine with aura	388 (37.1)	-
NRS (1–10)	7.5 ± 1.4	40 (3.8)
Attack duration (in h)		
min	34.3 ± 52.7	5 (0.5)
max	64.6 ± 103.0	5 (0.5)
Number of prophylactic drugs[a]	1.2 ± 1.6	-
0	500 (47.8)	-
1	201 (19.2)	-
2	143 (13.7)	-
3	77 (7.4)	-
4	53 (5.1)	-
5	73 (7.0)	-
MMD	11.4 ± 7.5	27 (2.6)

[a] incl. current and previous –*NRS* numerical rating scale, *MMD* monthly migraine days

followed by rizatriptan (277/1191) and naratriptan (188/1191) were the three most frequently used compounds. A total of 1.7% of patients (18/1031) received a prescription for opioids at some point of their migraine history to cope their migraine headache. Of those who were recommended a triptan at some point in their migraine history, 30.0% (308/1025; 6 missing) had already discontinued at least one triptan for various reasons (i.e. lack of efficacy or intolerance).

The average number of triptans tested (including the current preparation) was 1 ± 0.99 (range 0–6) and the number of all acute medications (including triptans and the current preparation) tested amounted to 2 ± 1.4 (range 0–7).

Tertiary level of care

After the first consultation at our tertiary headache clinic, 94% (941/998, 49 missing) of patients received a treatment recommendation for the therapy of an acute migraine attack (Fig. 1). Among these, we recommended at least one triptan (all forms of administration) to 92.1% (858/932, 9 missing). Rizatriptan was suggested most frequently (401/932 (43.0%)), followed by zolmitriptan (366/932 (39.3%)) and sumatriptan (282/932 (30.3%)). The average number of triptans prescribed at the tertiary headache center was 1.3 ± 0.7 (range 0–3, $n = 998$, 49 missing) (Table 2). Of those receiving a recommendation for acute migraine treatment, we advised 25% (236/932, 9 missing) to use NSAIDs, with the most common compound being naproxen (84/932 (9.0%)). Thus, triptans were prescribed significantly more often (92.1% vs. 74.4%, $p < 0.001$) while NSAIDs were prescribed significantly less often (25.3% vs. 81.9%, $p < 0.001$) in a tertiary headache center compared to primary/secondary level of care. It should be noted that the recommendations regarding acute medication from primary/secondary level of care include both the current and all previous recommendations.

The most common recommendation (714/932 (76.6%), 9 missing) from the tertiary headache clinic was to switch to another substance or, in the absence of any acute medication, to start treatment (Table 2). In slightly more than a third of patients (326/932 (35.0%), 9 missing) we suggested the continuation of the previously recommended preparation. A total of 35 patients (3.8%)) were advised to change the dosage of the previously recommended preparation (usually dose increase). We recommended a different pharmaceutical form (including dose change) in 18 patients (1.9%).

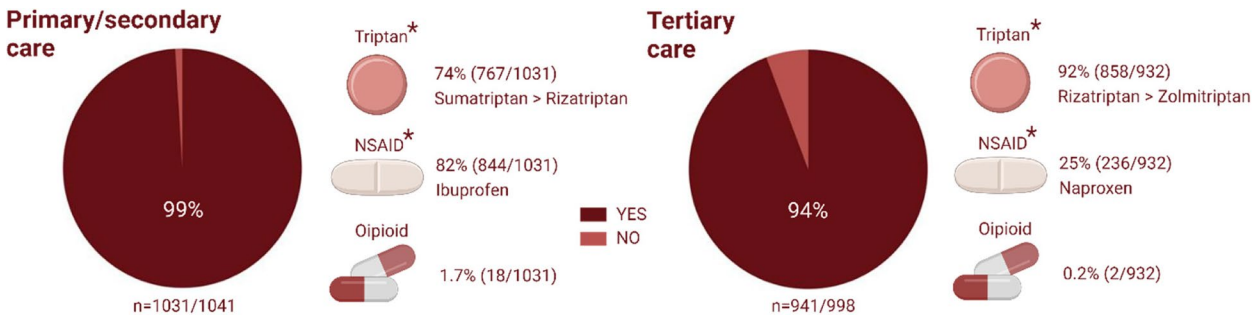

Fig. 1 Prescription of acute migraine treatment from primary/secondary (at some point in their migraine history) and recommendation from tertiary level of care (after first consultation). The reported prescription frequencies for triptans, NSAIDs, and opioids represent the number of patients who received at least one medication from each drug class. The frequency with which at least one triptan and NSAID were prescribed by primary/secondary care centers differed significantly (*) from that of the tertiary headache center. *Figure generated with biorender.com*

Table 2 Acute treatment recommendation from tertiary level of care

Recommendation	n (%) Total, 941	Missing n (%)
Switch/start	**714 (76.6)**	**9 (1.0)**
Antiemetic	78 (8.4)	
Pyrazolone derivate	38 (4.1)	
NSAID	93 (10.0)	
Triptan	652 (70.0)	
Continue	**326 (35.0)**	**9 (1.0)**
Pyrazolone derivate	16 (1.7)	
NSAID	89 (9.5)	
Triptan	255 (27.4)	
Change dosage	**35 (3.8)**	**9 (1.0)**
Pyrazolone derivate	6 (0.6)	
NSAID	12 (1.3)	
Triptan	18 (1.9)	
Change pharmaceutical form[a]	**18 (1.9)**	**9 (1.0)**
Triptan	8 (0.9)	
Restart previously tested	0 (0)	**9 (1.0)**

[a] If applicable with associated change in dosage

Recommendations for the prophylactic treatment of migraine headaches

Primary and secondary level of care

Before visiting our tertiary headache center for the first time, 53.3% (547/1026, 21 missing) of patients had already tested a pharmacological migraine prophylaxis. Of those 43.9% (238/542; 5 missing) had ongoing prophylactic treatment (Fig. 2). The average number of preventatives tested (including the current preparation) was 1.2 ± 1.6 (range 0–5). The most frequently prescribed migraine prophylactics in primary/secondary care included antidepressants, beta-blockers, and topiramate, given at least once to 54.7% (299/547), 55.4% (303/547), and 51.9% (284/547) of patients, respectively. Of the 368 prescribed antidepressants (with some patients having previously tried more than one), amitriptyline accounted for 72.3% (266/368). Onabotulinumtoxin A was prescribed to 12.1% of patients (66/547). While the other preventatives were available to all patients, CGRP(R) mABs became accessible in Germany starting in 2018, limiting their availability to a subset of 69.5% (728/1047) of patients. Among this subgroup, 52.7% (384/728) had

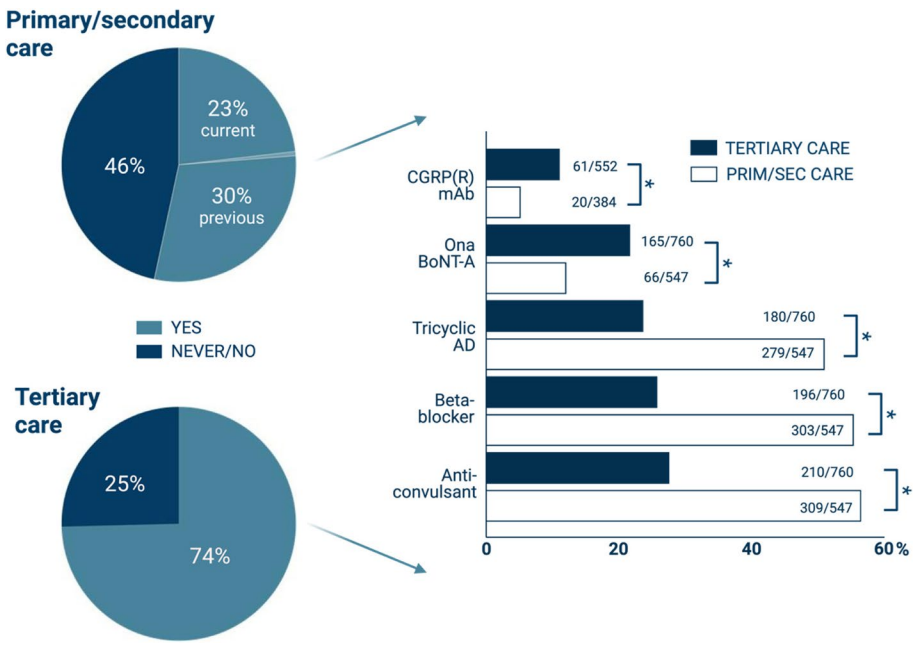

Fig. 2 Prescription of prophylactic treatment for migraine headaches in primary/secondary (at some point in their migraine history) and recommendation from tertiary level of care (after first consultation). The data on tricyclic antidepressants (AD) and anticonvulsants should not be equated with the data on topiramate and antidepressants in general reported in the main text. The frequency with which CGRP(R)mAb, onabotulinumtoxin-A, AD, beta-blockers and anticonvulsants were prescribed by primary/secondary care centers differed significantly ($p < 0.001$) (*) from that of the tertiary headache center. While the other preventatives were available to all patients, CGRP(R)mAB became available in Germany starting in 2018, making them accessible to only a subgroup of 69.5%. Regarding CGRP-directed therapy, the numbers refer to the proportion of patients with prior prophylactic treatment who received CGRP-directed therapy in primary/secondary care between January 2018 and January 2023, as well as the subset of patients from tertiary care centers who were recommended prophylactic treatment and advised to start CGRP(R)-directed therapy. *Figure generated with biorender.com*

already tested a pharmacological migraine treatment, with 5,2% (20/384) having used CGRP(R)-mAb. Of those who already tested prophylactic treatment, a total of 46.5% (252/542; 5 missing) had already discontinued the treatment due to lack of efficacy, 38.4% (208/542, 5 missing) due to side effects and 14.9% (81/548, 5 missing) had discontinued the prophylaxis due to a combination of side effects and poor efficacy. Of the patients suffering from more than 4 MMDs ($n=831$), 26.7% (125/468; 363 missing) had ongoing prophylactic migraine treatment at the time of consultation at our tertiary headache clinic and 73.3% (343/468; 363 missing) had tried prophylactic treatment in the past.

Tertiary level of care

After the first consultation at our tertiary headache clinic, we recommended a pharmacological migraine treatment in 73.8% (767/1039, 8 missing) of patients (Fig. 2). Among them, we advised at least one antidepressant to 28.6% of patients (217/760, with 7 missing), prescribing amitriptyline in 86.2% of those cases (187/217). We recommended topiramate to 24.6% (187/760, with 7 missing) and beta-blocker to 25.8% (196/760, with 7 missing) of patients. Onabotulinumtoxin-A was suggested in 21.7% (165/760; 7 missing) of patients. In the subgroup of patients (728/1047) for whom CGRP(R)-mABs were accessible, 555 (76.2%) were recommended preventative pharmacological treatment, with 11.1% (61/552, 3 missings) being advised to begin CGRP(R)-mAb. Thus, Onabotulinumtoxin-A (21.7% vs. 12.1%, $p<0.0001$) and CGRP(R)-mABs (11.1% vs. 5.2%, $p=0.002$) were prescribed significantly more often in the tertiary headache center compared to primary/secondary care facilities in the period between December 2015 and January 2023 (for Onabotulinumtoxin-A) and January 2018 and January 2023 (for CGRP(R)-mABs), respectively. In contrast, antidepressants (28.6% vs. 54.7%, $p<0.0001$), topiramate (24.6% vs. 51.9%, $p<0.0001$) and beta-blocker (25.8% vs. 55.4%, $p<0.0001$) were prescribed significantly less often in the tertiary headache center (Fig. 2). As with the acute treatment recommendations, it is important to note that the recommendations for preventative treatment from primary and secondary levels of care encompass both current and all previous recommendations.

The most common recommendation (654/763 (85.7%), 4 missing) from the tertiary headache clinic was to switch to another prophylactic substance or, in the absence of a migraine prophylaxis, to start treatment (Table 3). In about 10% of patients, we advised to continue the drug already prescribed by colleagues at primary/secondary level unchanged (74/763 (9.7%), 4 missing) or to change the dosage of this drug (76/763, 4 missing (9.7%)). A total of 3.7% (28/763, 4 missing) received the recommendation to stop the previously started preventive treatment and to not start any further pharmacologic migraine prevention.

Table 3 Prophylactic treatment recommendation from tertiary level of care

Recommendation[a]	n (%) Total, 767	Missing n (%)
Switch/start	**654 (85.7)**	**4 (0.5)**
Anticonvulsants	176 (23.1)	
Betablocker	141 (18.5)	
Calcium-Channel- Blocker	49 (6.4)	
CGRP(R)-mAb	53 (6.9)	
Onabotulinumtoxin-A	157 (20.6)	
Tricyclic AD	156 (20.4)	
SSRIs/SNRIs	43 (5.6)	
Continue	**74 (9.7)**	**4 (0.5)**
Anticonvulsants	9 (1.2)	
Betablocker	23 (3.0)	
CGRP (R)-mAb	10 (1.3)	
Onabotulinumtoxin-A	8 (1.0)	
Tricyclic AD	13 (1.7)	
Change dosage	**76 (10.0)**	**4 (0.5)**
Anticonvulsants	19 (2.5)	
Betablocker	26 (3.4)	
CGRP (R)-mAb	1 (0.1)	
Tricyclic AD	28 (3.7)	
Restart previously tested	**1 (0.1)**	**4 (0.5)**
Tricyclic AD	1 (0.1)	
End without replacement	**28 (3.7)**	**4 (0.5)**
Anticonvulsants	7 (0.9)	
Betablocker	10 (1.3)	
Tricyclic AD	5 (0.7)	

[a] multiple answers permitted

Discussion

In this retrospective, cross-sectional study, 1047 migraine patients who visited the tertiary headache center at Charité Universitätsmedizin Berlin for the first time in the period from December 2015 to January 2023 by referral from their GP or practicing neurologist/anesthesiologist were examined with regard to differences in pharmacological recommendations between different levels of headache care. Overall, our study reveals a generally good level of pharmacological care for migraine patients, with room for improvement in certain areas.

Significantly enhanced pharmacological management of acute and prophylactic treatment for migraine patients at primary and secondary care levels

Almost all patients (99%) had received a prescription for acute migraine treatment at some point in their migraine history and were using acute pain medication (96%) at time of their first consultation in our headache center, with 63% advised to use a triptan. Prophylactic treatment was recommended to more than half of the patients (53%), and 44% were actively using it at the time of their first consultation. These figures are notably higher than those reported in previous studies. In 2018, population-based studies of 2,364 migraine patients showed that only 3.4–11.0% had used a triptan for acute treatment, and just 1.6–6.4% of eligible patients received preventive medications [29]. Among those primarily treated by GPs, the figures were only slightly higher, with 13.6–24.5% using triptans and 4.4–9.1% using preventives [29]. Similarly, a population-based study in Germany from 2011 [30] revealed that only 8% of migraine patients used a triptan and 2.3% received prophylactic treatment. In our study population, triptans were used (currently or at some point in their migraine history) by 74% of patients. These substantial improvements are likely attributable to the specific population presenting at a tertiary headache center, where most patients are already aware of their migraine diagnosis and many have received care from neurologists or pain specialists in secondary settings [23]. Additionally, these improvements may reflect the impact of extensive educational programs implemented by various headache societies [25, 26]. Evidence of a positive global trend supports this notion [21]. A Danish study on headache management in general practice from 2024 [31], involving a cohort of 161 migraine patients, revealed that almost all (98%) received acute migraine treatment, with 79% using triptans. However, 9% were treated with opioids, higher than the 1.7% in our population. This discrepancy might be due to Denmark's higher overall opioid use, ranking fifth globally [32]. Opioids are not recommended as part of migraine treatment [33]. Accordingly, in our study population following consultation with the tertiary headache center, only 0.2% of patients were recommended opioids, and solely for tapering off high initial doses, which were too high to discontinue directly.

Potential for improvement in acute treatment of migraine headaches

The average number of triptans tested prior to referral to the tertiary headache center was only one. At the same time however, 30% of patients also reported to have discontinued a triptan due to ineffectiveness or intolerance among other reasons. A Danish population-based study [34], which surveyed both triptan-naïve and triptan-experienced migraine patients regarding treatment recommendations from their primary care providers, mirrored these findings, showing that 77% of triptan-experienced participants had only tried one single triptan. Similar to our study the most common compound was sumatriptan, followed by rizatriptan. As patients may respond differently to various triptans differing in time to onset and duration of action, it is important to try multiple types and formulations [35]. As a matter of fact, according to the latest guidelines of the European Headache Federation, triptan resistance is defined as the failure of at least two triptans, while triptan refractoriness can be diagnosed when at least three triptans, including subcutaneous formulations, have failed [36]. Even though the proportion of patients who had already been prescribed a triptan in the primary and secondary care centers was high compared to the past, triptans were still prescribed significantly more often in the specialized headache center. Further education programs, also with regard to reimbursement options, could be useful and further improve the care of migraine patients with triptans.

Treatment of acute migraine headaches in a tertiary headache center

We advised 92% of patients a triptan after the first consultation at our tertiary headache center. Among the triptans recommended, rizatriptan was the most frequently prescribed, followed by zolmitriptan and sumatriptan. According to meta-analyses rizatriptan ranks amongst one of the most effective oral triptans available [37]. Zolmitriptan offers an intranasal formulation, providing a faster onset of action, which likely contributed to its frequency of use. Sumatriptan, the third most commonly prescribed triptan, is often chosen by patients seeking longer-lasting effects. On average, patients received 1.3 triptans during their first visit. We typically prescribe one fast-acting triptan and one with longer-lasting effects for patients to try, aiming to optimize treatment outcomes. According to the guidelines, antiemetic therapy should be included in the acute treatment of migraine headaches with accompanying nausea. Surprisingly, we recommended an antiemetic therapy in only 8% of cases. In addition to potential underreporting in the relevant records, this may reflect that antiemetic treatment is still not prescribed frequently enough. Therefore, during consultations, we should make a more active effort to consider and prescribe accompanying antiemetic therapy.

Potential for improvement in prophylactic treatment of migraine headaches

Although our cohort included particularly severe cases, with an average of 11 MMDs and a headache intensity of 8/10 on the NRS, more than 70% of patients with more than four MMDs – who are eligible for migraine prophylaxis according to international guidelines [38, 39] – were not using prophylactic treatment at the time of referral. This is concerning, given the clear benefits of early intervention in mitigating the burden of migraine [18]. While the specific reasons for the lack of prophylactic treatment at referral were not investigated, it is noteworthy that 73% of patients with more than four MMDs had previously tried prophylactic treatments but discontinued them due to ineffectiveness or side effects amongst others. In some cases, the discontinuation of migraine prophylaxis might have been intended to allow for new treatment options at the specialized headache center. Nonetheless, given the range of effective and cost-efficient options available for prophylactic treatment [40, 41], the average number of prior prophylactic treatment attempts per patient, at 1.2, prior to referral to the tertiary headache center appears insufficient indicating potential for improvement. This issue is particularly relevant given the extended waiting times at tertiary headache centers, which average 3.7 months for an initial visit and 2.5 months for follow-ups [42]. These delays not only postpone the initiation of migraine treatment, which is associated with poorer responses to prophylactic therapies [18], but also contribute to significant socio-economic costs [11]. Addressing this gap in care before referral to specialized centers could enhance treatment outcomes and reduce the burden on both patients and healthcare systems.

Differences in treatment recommendation between primary/secondary and tertiary level of headache care

While non-specific migraine prophylactics, such as tricyclic antidepressants, beta-blockers, and anticonvulsants, were more commonly prescribed in primary and secondary care settings, the opposite was true for Onabotulinumtoxin-A and CGRP(R)-mAbs. This could be due to patients having already attempted prophylactic treatments before their referral. If those treatments were ineffective or caused side effects, the next logical step would be to consider other prophylactic options, such as CGRP(R)-mAbmonoclonal antibodies and Onabotulinumtoxin-A. If we'd focus on patients starting prophylactic treatment for the first time, we wouldn't expect Onabotulinumtoxin-A and CGRP(R) mAbs to be the first treatment choices in tertiary headache centers either.

Onabotulinumtoxin-A is approved for prevention of chronic migraine, alongside topiramate and CGRP(R) targeted agents [43–45]. Its lower recommendation rate in primary/secondary care settings compared to the tertiary headache center may be attributed to several factors. Firstly, in Germany Onabotulinumtoxin-A is fairly expensive, compared to other unspecific migraine preventatives, with a single vial of 200 units priced at €984, and GPs as well as other outpatient clinics have a quarterly budget for medications based on their patient numbers. Exceeding this budget means physicians may need to cover the costs themselves. Additionally, there is currently no option to bill for Onabotulinumtoxin-A treatment as an additional service, even though this was already recommended by the Joint Federal Committee (G-BA) [46] as early as 2018. Secondly, administering Onabotulinumtoxin-A requires specialized skills not typically found in GPs but that could be expected of practicing neurologists. Thirdly, the administration process is time-consuming. GPs, who spend an average of eight minutes per patient [47], might not had the necessary time and resources. Addressing these barriers—such as revising reimbursement policies, providing better training, and allocating additional time for such procedures—could help improve access to Onabotulinumtoxin-A treatments in primary and secondary care.

For CGRP(R)-targeted preventatives, their limited use across all care settings may be partly due to strict prescription regulations in Germany. All CGRP(R) medications, with the exception of erenumab since October 2022 [17], require the failure, intolerance or contraindication of all non-specific prophylactics before they can be prescribed. It should also be noted that CGRP(R)-directed prophylactics were available to only 69.5% of the studied population, as they were introduced in Germany only in 2018. The reported prevalence's refer to this subgroup solely. Accordingly, during part of the observation period, the CGRP-targeted medications were not available. However, this applies equally to primary, secondary, and tertiary care centers. Differences in recommendation behavior for CGRP(R)-mAbs between primary/secondary and tertiary care centers may arise from GPs being either uninformed about this relatively new treatment option or hesitant to prescribe these newer medications due to concerns about potential financial penalties. Given the changes in reimbursement policies and the subsequent education efforts for practicing colleagues, including those by pharmaceutical representatives, an investigation of patients treated from 2023 to the present would be of particular interest.

Lastly, our data show that treatment recommendations for acute and prophylactic care in primary and secondary settings are often revised upon referral to a tertiary headache center. In our study, 77% of patients received modified treatment plans. The reasons for these changes were

not assessed, which limits our ability to draw definitive conclusions. Potential factors for these adjustments could include the lack of effectiveness of previous tested therapies. It is important to note that patients who already received adequate treatments might not have been referred to a tertiary headache center and may therefore be underrepresented in this study. Nevertheless, the average of 1.2 prior prophylactic treatment attempts suggests that the study population was not primarily therapy-refractory and may also include cases that could potentially be effectively managed under optimal conditions at primary or secondary care facilities.

Analyzing the results of this study, it is important to consider several limitations. One key limitation is the potential for recall bias, as patients may not fully remember or accurately report their previous treatments and reasons for changing them, especially if these were far in the past. To mitigate this, we ask patients to bring all relevant medical records and physician letters when possible. Unlike survey-based studies, our method of extracting information from physician letters offers an advantage by reducing reliance on patient memory and minimizing social desirability bias, potentially yielding more accurate and detailed medical histories. This study did not consider medication contraindications such as depression or obesity, which could have influenced treatment recommendations. However, these factors would likely have impacted all levels of care equally. While they may affect the absolute number of recommendations for specific treatment regimens, they would not alter the comparisons between the different levels of care. While the sample size of 1,047 patients strengthens the study's reliability and generalizability, reporting bias is another potential concern. As there is no standardized approach for collecting and reporting information on previous treatment attempts, different physicians at our headache center might have prioritized different pieces of information, which can lead to inconsistencies in the documentation of patient histories and treatment outcomes. It therefore cannot be excluded that previous treatment attempts might have been overlooked due to failure to inquire, inadequate reporting, or incomplete documentation, which could affect the completeness and uniformity of the data. Additionally, our sample may not reflect the broader population of migraine patients treated in primary and secondary care settings. The patients included in the study were referred to a specialized headache clinic, which inherently introduces selection bias. These patients likely represent a subset of individuals who, for various reasons, had a need for additional support that could not be met by their primary / secondary care providers. Moreover, they were persistent enough to seek care at our headache clinic, despite long wait times and multiple delays. Therefore, the findings from this study may not be generalizable to all migraine patients. Those who had already received effective treatment might not have been referred to our headache clinic and are therefore underrepresented in this study. Although the cross-sectional design enabled efficient measurement of treatment prevalence across different levels of care without requiring extended follow-up, a longitudinal study could offer deeper insights into treatment outcomes and long-term effectiveness. It would also allow for the assessment of causal relationships, such as the factors influencing treatment change recommendations, making it a valuable direction for future research. Finally, we were unable to distinguish between primary and secondary levels of care, as we only considered previous prescriptions without knowing their original source.

Conclusion

This comprehensive retrospective study demonstrates that the majority of patients (74%) had used at least one triptan, and over half (54%) hat tried at least one prophylactic treatment. While this reflects progress in migraine management, there is still room for improvement, particularly in the number of triptans and various migraine prophylaxis options trialed before the referral to specialized centers. Due to the costs, necessary resources, and the expertise required, it is likely that Onabotulinumtoxin-A will remain primarily within the domain of specialized centers in the German healthcare system. In contrast, the recommendation of CGRP(R)-targeted prophylactic treatments by GPs and neurologists in private practice still has potential for improvement and should be further encouraged to enhance migraine care, particularly in the outpatient setting.

Abbreviations

CGRP	Calcitonin Gene-Related Peptide
CGRP-R	Calcitonin Gene-Related Peptide receptor
GPs	General practitioners
mAb	Monoclonal antibody
MMDs	Monthly migraine days
NRS	Numerical rating scale
NSAIDs	Nonsteroidal anti-inflammatory drugs
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TTH	Tension-type headache

Authors' contributions

Authors' contributions MF: Investigation; Formal Analysis; Writing – Original Draft Preparation. LHO: Investigation; Data curation; Writing – Review & Editing. MU: Investigation; Writing – Review & Editing. JBH: Investigation; Writing – Review & Editing. CLH: Writing – Review & Editing. KSL: Investigation; Writing – Review & Editing. UR: Supervision; Writing – Review & Editing. YS: Writing – Review & Editing. BR: Conceptualization; Investigation; Project Administration; Writing – Review & Editing.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was approved by the ethics committee of Charité – Universitätsmedizin Berlin (EA4/246/23). Data were kept confidential and were not disclosed unless for study purposes. This study is reported in accordance with the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) statement for cohort studies [48].

Consent for publication
As this was a retrospective analysis, written consent from the participating patients was not required according to local regulations.

Competing interests
MF reports personal fees from Novartis and Teva. KSL reports personal fees from Organon and Teva. UR reports no personal fees; institutional fees from Amgen, Abbvie, Lilly, Lundbeck, Novartis, Medscape, Pfizer, StreaMedUp, and Teva, and research funding from Novartis. UR is the vice-president of the EHF and associate editor of JHP. BR reports research grants from Lundbeck, Novartis, German Research Foundation, German Migraine and Headache Society, Else Kröne-Fresenius-Stiftung and personal fees from Abbvie/Allergan, Eli Lilly, Lundbeck, Novartis, Organon, Perfood and Teva. BR is an Editorial Board Member of The Journal of Headache and Pain. LHO, MU, JBH, CLH and YS have nothing to disclose.

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