Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

Cephalalgia
2023, Vol. 43(5) 1–11

DOI: 10.1177/03331024231174855
journals.sagepub.com/home/cep

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What do patients' efficacy and tolerability ratings of acute migraine medication tell us? Cross-sectional data from the DMKG Headache Registry

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Abstract

Background: Most migraine patients need an effective acute medication. Real-world data can provide important information on the performance of acute migraine medication in clinical practice.

Methods: We used data from the German Migraine and Headache Society Headache Registry, where patients rate efficacy and tolerability of and satisfaction with each of their acute headache medications.

Results: A total of 1756 adult migraine patients (females: 85%, age: 39.5 ± 12.8 years, headache days per month: 13.5 ± 8.1) were included. Of these, 93% used acute medication, most frequently triptans (59.3%) and/or non-opioid analgesics (56.4%), and 58.5% rated efficacy as good or very good. This was more frequent for triptans (75.4%) than for non-opioid analgesics (43.6%, $p < 0.001$). Among non-opioid analgesics, naproxen was rated most effective (61.9% very good or good, $p < 0.001$ compared to ibuprofen, acetylsalicylic acid and paracetamol). Patient-rated efficacy significantly declined with higher headache frequencies ($p < 0.001$), and this effect remained significant after omitting patients overusing acute medication.

Conclusion: In the present population recruited at specialized headache centers, patients rated triptans as more effective than non-opioid analgesics, naproxen as more effective than ibuprofen, and acute medication efficacy decreased with increasing headache frequency.

Trial registration: The German Migraine and Headache Society Headache Registry is registered with the German Clinical Trials Register (DRKS 00021081).

Keywords

Registry, headache, migraine, Germany, acute headache treatment, triptans, non-opioid analgesics, patient-reported outcome measures

Date received: 10 March 2023; revised: 17 April 2023; accepted: 19 April 2023

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Introduction

Finding and appropriately using an effective acute medication is one of the mainstays of migraine therapy. Clinical trials have demonstrated efficacy of various non-opioid analgesics, triptans, combination analgesics and, most recently, of ditans and gepants for treatment of the acute migraine attack (1–4). Real-world data focusing on the patients' perspective such as data from headache registries are essential to complete the picture. In addition, within the limits of real-world evidence, they may allow comparisons between drugs and drug classes which are scarcely available from clinical trials.

The Deutsche Migräne- und Kopfschmerzgesellschaft (DMKG) Headache Registry has been initiated by the German Migraine and Headache Society and includes patients since June 2020 (5). Before their physician appointment, participating patients provide information on their headache via a web portal. This also includes current acute headache medication and subjective ratings of the efficacy and tolerability of and satisfaction with each drug. During the physician appointment, essential information such as type and dose of medication and medication days per month is confirmed and a headache diagnosis is provided. The registry includes patients at headache centers and private practices with a special interest in headache, therefore representing a rather severely affected and difficult-to-treat population entering specialized care.

Here, we used data from 1756 migraine patients enrolled in the DMKG Headache Registry to investigate the following questions:

- How many patients report having a subjectively effective and tolerable acute migraine medication?
- Is satisfaction with acute medication mainly driven by efficacy or by tolerability?
- Are there significant differences in patient-rated efficacy and tolerability ratings between groups of acute medications (e.g. between non-opioid analgesics and triptans) and between drugs within these groups?

It has been proposed that acute medication could lose efficacy when used too often, especially within the context of medication overuse (6), maybe in relation to trigeminal sensitization (7). However, in clinical practice patients without medication overuse also often complain about reduced acute medication efficacy with higher headache frequencies. An additional research question therefore was:

- Is there is a link between patient-rated efficacy and headache frequency independent of acute medication overuse?

Methods

The DMKG Headache Registry is conducted in accordance with the Declaration of Helsinki and has been approved by the ethics committee of the Ludwig-Maximilians-University Munich (leading ethics committee, 20-004), and by the responsible ethics committee of every participating headache center. It is conducted according to European and German Data Protection laws and registered with the German Clinical Trials Register (DRKS 00021081).

The DMKG Headache Registry started recruitment in June 2020. At the time of the present analysis (data closure 6 December 2022), 23 DMKG-accredited centers had contributed data (15 private practices, 8 clinic-based), and 1915 patients had at least one completed physician visit, with a total of 4419 completed physician visits. Before their first appointment at the center and before each follow-up appointment, patients provided detailed information about their headache and concomitant disorders via a web application, supplemented by a mobile application headache diary (DMKG-App). During the appointment, treating physicians provided the International Classification of Headache Disorders (ICHD-3) diagnosis (8) and confirmed or corrected some of the central patient entries (e.g. headache and medication days per month, current acute and preventive medication). Detailed methods have been published (5).

For the present analysis, we included all adult patients having a completed first physician visit within the registry with an ICHD-3 diagnosis of migraine without or with aura or chronic migraine before 6 December 2022.

Data

For the present analysis, demographic and general headache data (as described by Ruscheweyh et al [5]) were used in addition to data on acute headache medication (described below). Only data from the first visit within the DMKG Headache Registry was analyzed. Due to the nature of data collection, there were no missing data.

Before their first visit, patients provided information on their current acute headache medication. This included the drug name(s), and for every drug indicated: dosage, frequency of use (days per month, average of the past three months) and a subjective rating of the drug's efficacy against headache, the drug's tolerability and the patient's satisfaction with the drug. Efficacy, tolerability and satisfaction were rated on a 6-point Likert scale ranging from 1 "very good" to 6 "none" for efficacy, from 1 "very good" to 6 "very poor" for

tolerability and from 1 "very satisfied" to 6 "very unsatisfied" for satisfaction.

Analysis

Some patients used more than one acute medication, or more than one medication from a specific group (e.g. triptans). In this case, to obtain the patient's average efficacy, tolerability and satisfaction scores within the respective medication group (e.g. triptans), we calculated average ratings of the medications used by the patient from this group, weighted by frequency of use.

Only the two largest medication groups, triptans and non-opioid analgesics, were analyzed as subgroups, and only drugs used by >50 patients were included in the single drug comparisons.

To analyze the relation between efficacy ratings and headache frequency we used bins with a width of five headache days/month, and added a group for daily headache, resulting in seven groups.

For comparison of efficacy, tolerability and satisfaction ratings between medication groups, Kruskal Wallis analysis of variance (ANOVA) was used, followed by Bonferroni-corrected Mann Whitney U tests where appropriate. For comparison of efficacy between headache or medication frequency groups, efficacy was aggregated into two groups (very good/good and moderate or worse) and χ^2 tests were used, followed by Bonferroni-corrected Fisher Exact tests where appropriate.

We chose to use ANOVA to compare headache day/medication day bins and efficacy groups (instead of using correlations on ordinal data) because this allowed better visualization of the results within clinically relevant groups.

Spearman's ρ was used to test for correlations, and the magnitude of correlations was compared using a bootstrap method (9).

Statistical analysis was performed with R (version 4.2.1). Descriptive statistics include mean ± standard deviation, and numbers and percentages as appropriate. Two-sided tests were used, and $p < 0.05$ was considered significant.

Results

The present analysis includes data from 1756 patients with a migraine diagnosis. See Table 1 for demographic and headache characteristics.

Table 1. Characteristics of the study population (n = 1756)

Age	39.5 ± 12.8
Sex	
– Female	1493 (85.0%)
– Male	261 (14.9%)
– Diverse	2 (0.1%)
Diagnosis[a]	
– Migraine without aura	834 (47.5%)
– Migraine with aura	349 (19.9%)
– Migraine with and without aura	129 (7.3%)
– Chronic migraine	444 (25.3%)
Headache days per month[b]	13.5 ± 8.1
Acute medication days per month[b]	7.5 ± 5.8
Headache intensity [0–10][b]	6.4 ± 1.8
Headache duration [years]	19.2 ± 14.0
MIDAS score [0–279]	45.4 ± 48.2
– Grade 1 (0–5)	171 (9.7%)
– Grade 2 (6–10)	150 (8.5%)
– Grade 3 (11–20)	323 (18.4%)
– Grade 4 (>20)	1112 (63.3%)
DASS depression score [0–21]	5.5 ± 5.2
DASS anxiety score [0–21]	3.7 ± 3.9
DASS stress score [0–21]	7.8 ± 5.1
VR-12 Mental component score (MCS)	41.9 ± 11.2
VR-12 Physical component score (PCS)	41.1 ± 9.1
Current general health state [0–100]	53.5 ± 22.8

Values are mean ± SD or numbers and percentages.
[a]90.0% of the patients had only a migraine diagnosis, 3.5% had an additional diagnosis of medication overuse headache, 6.3% had an additional diagnosis of tension-type headache (episodic or chronic) and 0.2% had both.
[b]average of past 3 months. MIDAS, migraine disability assessment score; DASS, depression anxiety stress scales; VR-12, veterans RAND 12-item health survey.

Types and dosages of acute medications used

Most of the patients (n = 1633, 93.0%) used at least one acute headache medication, 24.3% used two and 13.8% used three or more different drugs. Triptans (n = 1042, 59.3%) and non-opioid analgesics (n = 990, 56.4%) were most common (Table 2, Online Supplementary Table 1), with sumatriptan (22.6%), rizatriptan (18.1%), ibuprofen (34.6%) and naproxen (12.7%) being the most frequent triptans and non-opioid analgesics, respectively. Combination analgesics without opioid component were used by 6.5%. Antiemetics were used by 6.0%. Opioids (including combination analgesics) amounted to 0.9%.

For triptans and non-opioid analgesics, dosages and percentages of subjects using low doses (with respect to those recommended in the German guideline [4]) are listed in Table 3. Use of low doses was frequent for metamizole, paracetamol and acetylsalicylic acid (ASA).

Patient-rated efficacy

In total, 58.6% of the patients rated their acute medication efficacy as "very good" or "good". Efficacy ratings were higher for triptans (75.5% very good/good) than for non-opioid analgesics (43.6% very good/good, Kruskal Wallis $H = 261.4$, $p < 0.001$, Figure 1a, b, Online Supplementary Table 2).

Table 2. Acute medication used by the study population (n = 1756).

	Number of patients	% of patients
Triptans	**1042**[a]	**59.3%**
– Sumatriptan[b]	380	21.6%
– Rizatriptan	317	18.1%
– Naratriptan	220	12.5%
– Zolmitriptan[b]	178	10.1%
– other	61	3.5%
Non-opioid analgesics	**990**[a]	**56.4%**
– Ibuprofen	591	33.7%
– Naproxen	223	12.7%
– Metamizole (dipyrone)	181	10.3%
– Paracetamol (acetaminophen)	98	5.6%
– Acetylsalicylic acid (ASA)	78	4.4%
– other	19	1.1%
Ergotamins	0	–
Opioids (and combination analgesics with opioid)	**16**	**0.9%**
Antiemetic drugs	**105**	**6.0%**
Combination analgesics without opioid	**114**[a]	**6.5%**
– ASA + paracetamol + caffeine	92	5.2%
– other	28	1.6%
Other drugs[c]	**55**	**3.1%**
No acute medication	**123**	**7.0%**

Single drugs are listed only when used by >50 patients (see Supplementary Table 1 for complete list).
[a]Using at least one drug of the respective class.
[b]Includes oral, nasal and (only sumatriptan) subcutaneous formulations.
[c]Included corticoids, magnesium, cannabinoids, neuroleptics, COX-2 inhibitors, benzodiazepines, z-drugs, oxygen, dexketoprofen, muscle relaxants, diphenhydramine, caffeine, non-specified drugs. ASA, acetylsalicylic acid.

Sensitivity analysis #1: We hypothesized that part of this difference might be due to use of low doses within the non-opioid analgesics. However, after eliminating data from low doses, the difference was virtually identical (triptans: 75.0% very good/good, n = 1023; non-opioid analgesics: 43.7% very good/good, n = 829; $H = 228.0$, $p < 0.001$).

Sensitivity analysis #2: We tested if the superiority of triptans might be due to the inclusion of parenteral formulations of sumatriptan and zolmitriptan. There were no significant differences among formulations apart from nasal sumatriptan being rated less effective than oral and subcutaneous sumatriptan, but numbers were low (Online Supplementary Table 3). After omitting data from parenteral formulations, the difference between triptans and non-opioid analgesics was virtually unchanged (triptans: 75.7% very good/good efficacy ratings, n = 975, non-opioid analgesics 43.6%, $H = 250.2$, $p < 0.001$).

Patient-rated efficacy: Comparison between different triptans

Within the group of triptans (Figure 2a, Online Supplementary Table 4), Kruskal Wallis ANOVA indicated significant differences ($H = 8.4$, $p = 0.039$), and post-hoc analysis revealed significantly better efficacy of zolmitriptan compared to rizatriptan (79.8% vs. 71.3% very good/good ratings, $p = 0.028$).

Sensitivity analysis: After omission of data from the nasal formulation of zolmitriptan (n = 64), zolmitriptan efficacy ratings were slightly reduced (to 79.2% very good/good ratings), and the difference to rizatriptan was no longer significant ($p = 0.267$).

Table 3. Dosage of frequently used triptans and non-opioid analgesics.

	n[a]	Dosage (mg)	Low dose: definition	Low dose: number of patients (%[b])
Triptans				
– Sumatriptan (oral/nasal/s.c.)	396	68.4 ± 32.8	<50/10/3 mg	14 (3.5%)
– Rizatriptan	318	8.9 ± 2.6	<5 mg	1 (0.3%)
– Naratriptan	220	2.6 ± 0.5	<2.5 mg	4 (1.8%)
– Zolmitriptan (oral/nasal)	184	4.3 ± 1.2	<2.5/5 mg	1 (0.5%)
Non-opioid analgesics				
– Ibuprofen	608	560 ± 179	<200 mg[c]	0
– Naproxen	223	485 ± 95	<500 mg	20 (9.0%)
– Metamizol (dipyrone)	181	696 ± 243	<1000 mg	120 (66.3%)
– Paracetamol (acetaminophen)	99	635 ± 286	<1000 mg	69 (69.7%)
– Acetylsalicylic acid (ASA)	79	621 ± 280	<900 mg	57 (72.1%)

Values are mean ± standard deviation unless indicated otherwise. Low dose definitions are according to the doses recommended in the German guideline (4).
[a]Number of observations may exceed number of patients as given in Table 2, because some patients used the same drug at more than one dose or formulation.
[b]% of patients using the drug.
[c]10 patients (1.6%) used 200 mg, the remainder used ≥400 mg.

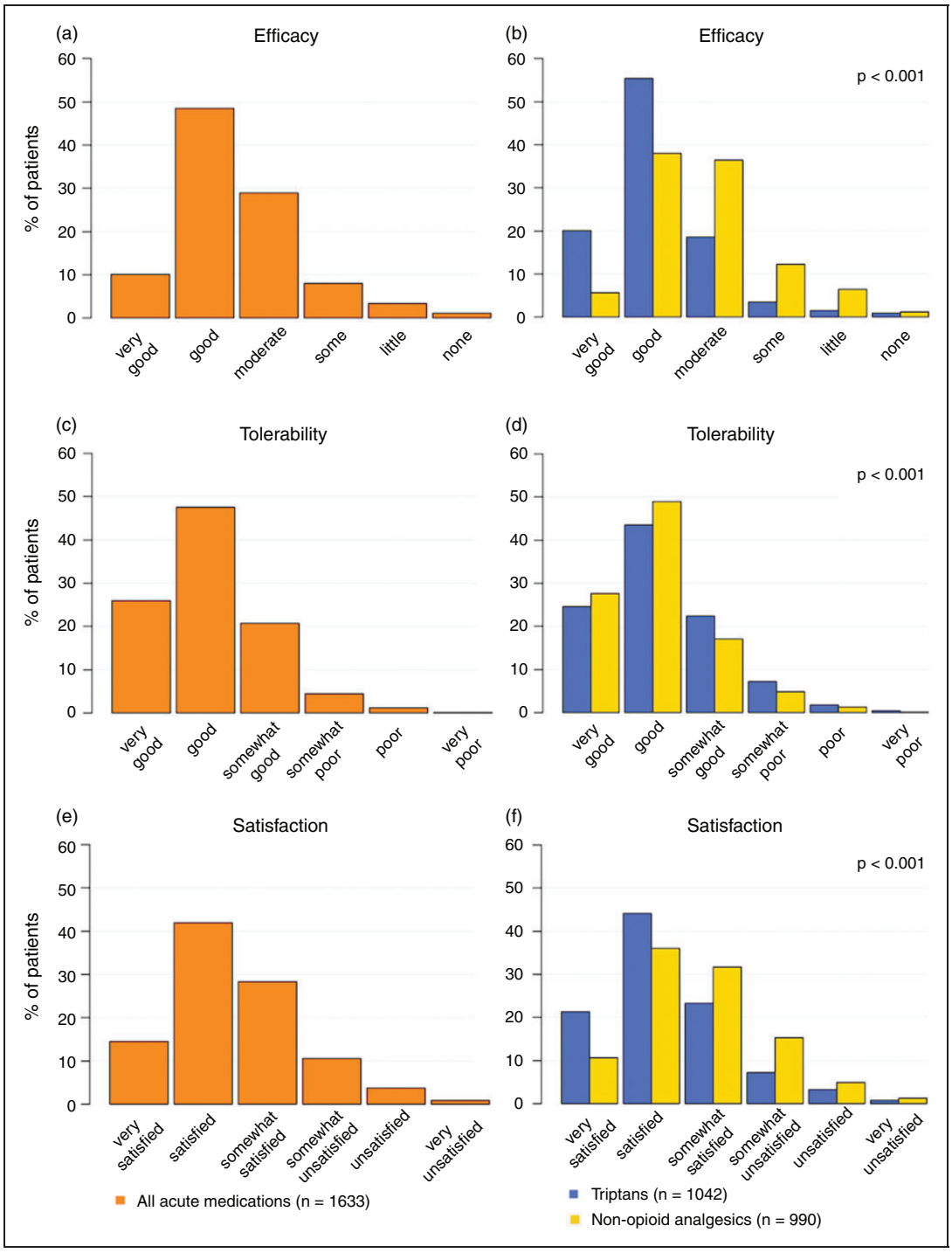

Figure 1. Efficacy, tolerability and satisfaction ratings. Panels on the left display ratings for all acute medications, panels on the right compare triptans and non-opioid analgesics (A. Kruskal-Wallis ANOVA $H = 261.4$, $p < 0.001$; B. $H = 13.7$, $p < 0.001$; C. $H = 94.0$, $p < 0.001$). Raw data are listed in Supplementary Table 1.

Patient-rated efficacy: Comparison between different non-opioid analgesics

Among the non-opioid analgesics (Figure 2b, Online Supplementary Table 4), there were significant differences in efficacy ($H = 64.5$, $p < 0.001$), with naproxen being the most effective (61.9% very good/good ratings), followed by metamizol (51.4%), ibuprofen (36.4%), ASA (30.8%) and paracetamol (27.6%). Naproxen was rated significantly more effective in comparison with ibuprofen, ASA and paracetamol

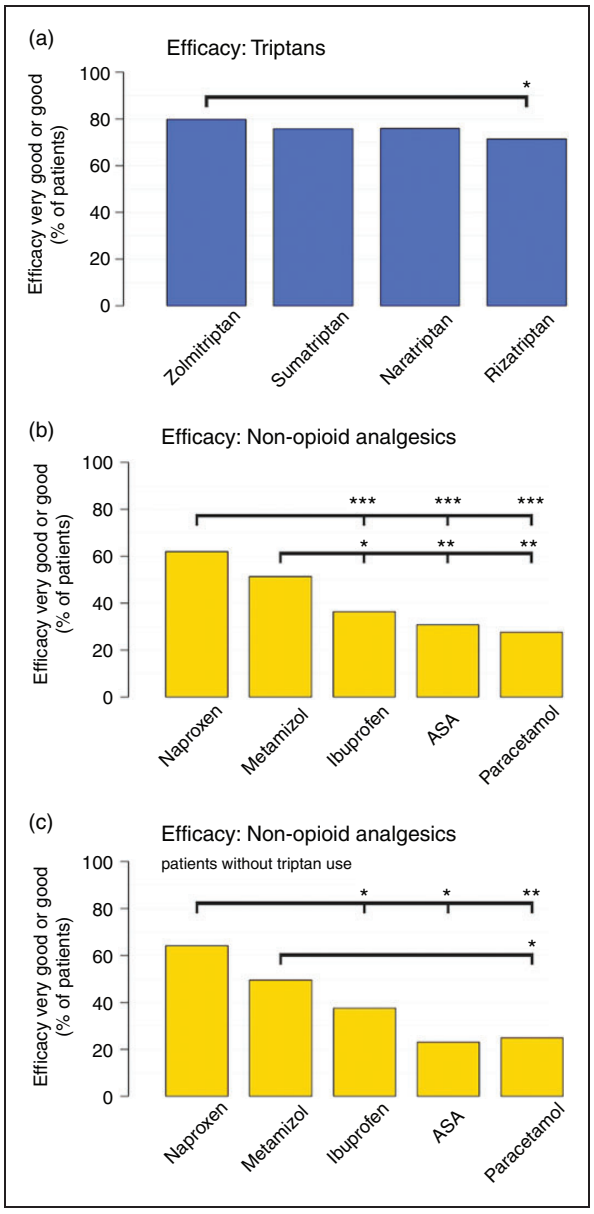

Figure 2. Efficacy ratings: comparisons within acute medication classes. Only acute medications being used by > 50 patients were included. Percentage of patients rating efficacy as very good or good are given. Kruskal Wallis ANOVA was significant for group comparison in all 3 panels. (a) Triptans (1104 observations), (b) Non-opioid analgesics (total sample; 1171 observations), (c) Non-opioid analgesics (patients without triptan use; 593 observations). Asterisks indicate results of the statistical comparison with the leftmost drug under the respective bracket; ***, $p < 0.001$; **, $p < 0.01$; *, $p < 0.05$ in the Bonferroni-corrected Mann Whitney U test.

(all $p < 0.001$), and the same was true for metamizol (all at least $p < 0.05$).

Sensitivity analysis #1: It was considered that the common practice of combining naproxen with a triptan might have biased results. However, limiting analysis to patients without triptan use ($n = 593$, Figure 2c) still found a significant difference ($H = 23.6$, $p < 0.001$) and naproxen (64.1% very good/good ratings) continued to be significantly superior to ibuprofen (37.6%), ASA (23.1%) and paracetamol (25.0%, all at least $p < 0.05$).

Sensitivity analysis #2: It was further considered that the frequent use of low doses of ASA and paracetamol might have biased the analysis. When eliminating low doses, efficacy of the two medications nominally increased (ASA: from 29.4% to 33.3%; paracetamol: from 28.0% to 41.4%), but numbers within these groups became low (ASA $n = 21$, paracetamol $n = 29$) so that a statistical comparison was not attempted. Naproxen continued to be superior to ibuprofen ($p < 0.001$).

Patient-rated tolerability and satisfaction

In total, 73.5% rated their acute medication tolerability as very good or good. Vice-versa from efficacy, tolerability ratings were higher for non-opioid analgesics (76.7% very good/good) compared to triptans (68.1% very good/good, $H = 13.7$, $p < 0.001$, Figure 1c, d, Online Supplementary Table 2).

Furthermore, 56.5% rated satisfaction with their acute medication as very good or good. Similar to efficacy, satisfaction ratings were higher for triptans (65.5% very good/good) compared to non-opioid analgesics (46.8% very good/good, $H = 94.0$, $p < 0.001$, Figure 1e, f, Online Supplementary Table 2).

Differences within triptans and within non-opioid analgesics are shown in Online Supplementary Table 4.

Satisfaction was more closely related to efficacy ($\rho = 0.728$, $p < 0.001$) than to tolerability ($\rho = 0.477$, $p < 0.001$) and the difference between the two correlations was statistically significant ($p < 0.001$).

Patient-rated efficacy: Relation to headache frequency

Patient-rated efficacy decreased with increasing number of headache days per month (Figure 3a, Online Supplementary Table 5, $\chi^2 = 75.6$, $p < 0.001$), with a significant reduction of efficacy first seen in the 20–24 headache days per month group (compared to the 0–4 headache days per month group). Reduction of efficacy happened at lower headache frequencies in non-opioid analgesics ($\chi^2 = 33.6$, $p < 0.001$, significant differences starting at 15–19 days per month) compared to triptans ($\chi^2 = 66.9$, $p < 0.001$, significant differences only in the daily headache group, Figure 3b).

Efficacy also significantly decreased with increasing acute medication frequency ($\chi^2 = 22.7$, $p < 0.001$, Figure 3d, Online Supplementary Table 5, upper

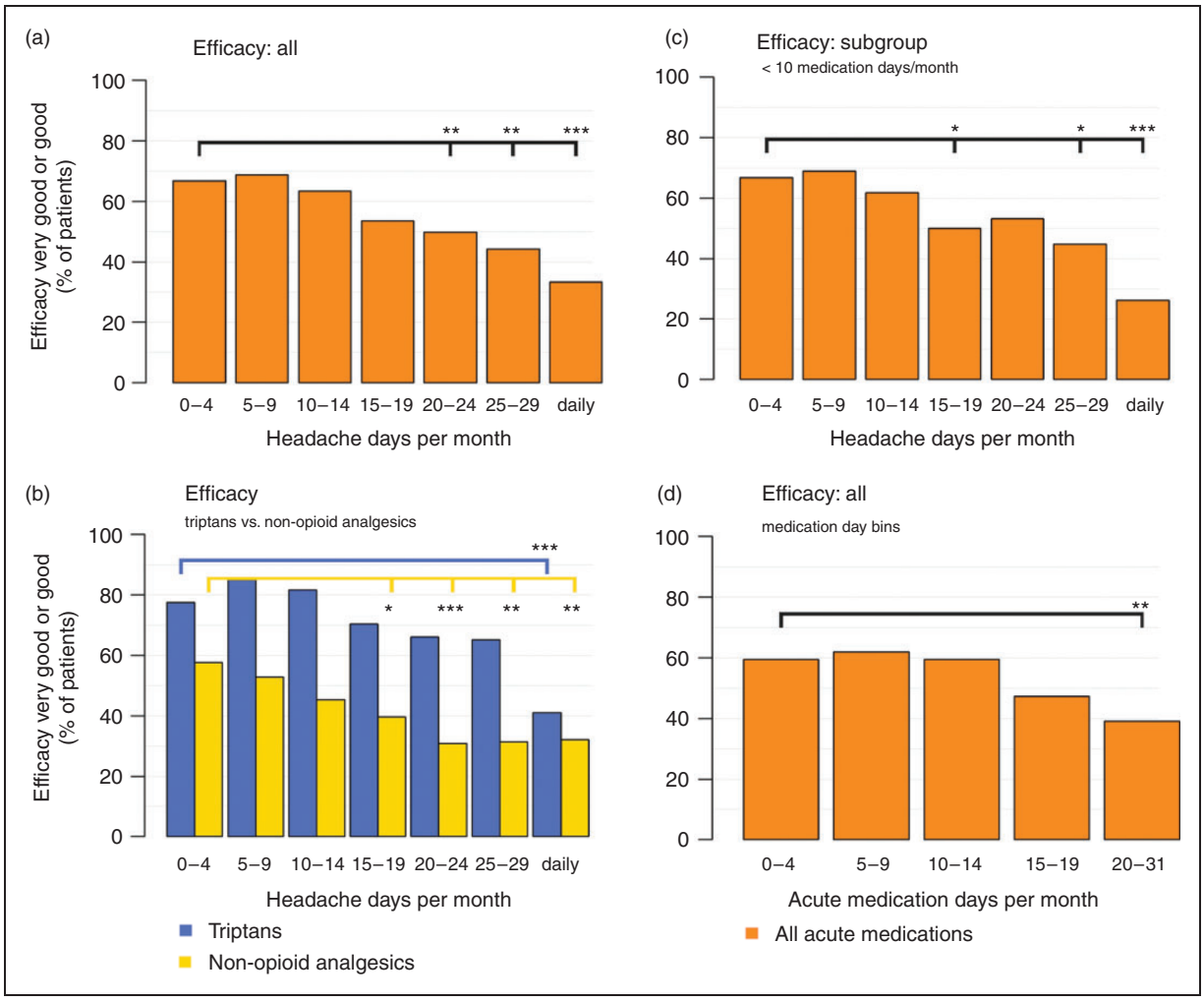

Figure 3. Efficacy ratings in relation to headache frequency and acute medication frequency. Percentages of patients rating efficacy as very good or good are given as bars. A, B and C display relation of efficacy to headache days per month, D displays the relation of efficacy to acute medication days per month. (a) All patients (n = 1633); (b) Triptans (n = 1042) vs. non-opioid analgesics n = 990); (c) Subgroup with <10 medication days per month (n = 1118); (d) all patients (n = 1633). Asterisks indicate results of the statistical comparison with the leftmost drug under the respective bracket; ***, $p < 0.001$; **, $p < 0.01$; *, $p < 0.05$ in the Bonferroni-corrected Fisher Exact test comparing the respective category with the 0–4 days per month category.

three categories merged because of low numbers). A significant reduction was detected only in the 20 to 31 medication days group.

We further investigated if the decrease of patient-rated efficacy with increasing headache frequency can be attributed to medication overuse. We considered using linear regression to test for independent influence of headache and medication frequency on efficacy ratings. However, apart from efficacy ratings being ordinal, residuals were not normally distributed and Cook's distance and leverage analysis found a number of outliers that represented clinically plausible cases. Therefore, we used Spearman's correlations followed by a bootstrap method. The correlation between efficacy and headache frequency was larger ($\rho = 0.219$, $p < 0.001$) than that between efficacy and acute medication frequency, which did not reach significance ($\rho = 0.036$, $p = 0.147$). Please note that the correlations are positive because efficacy was rated on a scale from 1 = "very good" to 6 = "very poor". The difference between the two correlations was significant ($p < 0.001$). Second, we limited analysis to patients with less than 10 acute medication days per month (n = 1118). There was still a significant relation between efficacy and headache frequency ($\chi^2 = 50.3$, $p < 0.001$, Figure 3c). In summary, results favor a relation between efficacy and headache frequency independent of medication overuse.

Discussion

Key results of the present study were: 58.6% of the patients rated efficacy of their acute headache

medication as "very good" or "good" and 73.5% rated tolerability as "very good" or "good". Satisfaction was more strongly determined by efficacy than by tolerability. Efficacy ratings of triptans were better than those of non-opioid analgesics. Naproxen and metamizol were rated significantly more effective compared to ibuprofen. Efficacy ratings decreased with increasing headache frequency, also in patients without medication overuse.

Efficacy, tolerability and satisfaction ratings of acute migraine medications

In general, the analyzed sample seemed to be well supplied with acute medication (> 93% used acute medication and almost 60% used triptans). This differs from international and German general population samples (10,11) and is likely due to the specialized headache care setting. Nonetheless, with 41.4% of the patients rating efficacy less than good and 26.5% rating tolerability less than good, there is room for improvement. For comparison, in US general population samples, 38.4% reported poor or very poor acute migraine treatment optimization (10) and 48.0% reported quick return to function in < 50% of the time after acute medication use (12). Guidelines and reviews provide guidance on escalation of acute migraine therapy (1–4). It may be necessary to try several drugs from one pharmacological group, and adequate dosages must be used. In the present study, use of dosages below those recommended by the guideline (4) was frequent for metamizol, ASA and paracetamol (see Table 3). This shows that patient education on effective dosages is important, especially with over-the-counter (OTC) drugs. If the effect of non-opioid analgesics is insufficient, triptans should be tried (1,2,4) as also supported by the present study. The present results suggest that high headache frequency may also contribute to poor acute medication efficacy, emphasizing the importance of headache preventive measures. New acute migraine medications as ditans and gepants have the potential to further improve acute migraine therapy (2). In summary, physicians should carefully assess acute medication efficacy and optimize treatment accordingly.

The present analysis also revealed that patient satisfaction with acute migraine medication was determined more closely by efficacy compared to tolerability. This likely reflects the fact that tolerability is generally fair, while efficacy needs more improvement. Another hypothesis would be that migraine patients are prepared to accept side effects if a medication is effective.

Triptans vs. non-opioid analgesics

In the present study, patients rated triptans as more effective than non-opioid analgesics. This corroborates clinical experience and previous observational data (12), while the few direct comparison studies did not show a clear superiority of triptans (13–17). It has been discussed that the choice of the primary endpoint in these studies (pain relief at 2h) may not have reflected patient overall efficacy perception (15), which may also encompass onset and completeness of headache relief, effect on accompanying symptoms, or more complex endpoints such as ability to function (18). Indeed, some secondary endpoints significantly favored triptans in the comparison studies (13–15). On the other hand, patient expectations may have biased the present data. Triptans are often perceived as strongly acting and expensive, and are mostly prescription drugs, which may have led to an increased placebo effect. Patient selection may also play a role. Present data suggest that non-opioid analgesics work best in subjects with relatively low headache frequencies, while triptans seem to remain effective also at higher headache frequencies, prevalent in the present sample. The frequent use of low doses of metamizol, ASA and paracetamol did not explain the difference between triptans and non-opioid analgesics.

For tolerability, patient ratings were significantly better for non-opioid analgesics compared to triptans. This is in line with the results of comparison studies (15). It must be emphasized that patient-rated tolerability is not equivalent to safety, as negative effects on renal function, blood pressure and a risk of gastrointestinal bleeding are associated with some non-opioid analgesics when taken on a frequent basis.

Comparison within groups: Non-opioid analgesics

Within the group of non-opioid analgesics, naproxen and metamizol were rated significantly more effective than ibuprofen, ASA and paracetamol. The superiority of naproxen is, at first sight, surprising as migraine studies have found higher number needed to treat (NNT) values for pain relief at two hours for naproxen (NNT 6–7 [19,20]) than for ibuprofen (NNT 3.2–6.3 [21]), ASA (NNT 4.9 [13]) or paracetamol (NNT 5 [22]), although direct comparisons have not been performed. Maybe other features such as the long plasma half-life of naproxen (12–15 hours) compared to ibuprofen (2–3 hours) contributed to the higher efficacy ratings of naproxen (23). While the frequent use of low doses might have biased the comparison with ASA and paracetamol, this was not the case for ibuprofen. Combination of naproxen and triptans, such as

frequently used to increase efficacy and duration of triptan action (24), did also not explain the superior efficacy of naproxen. An additional factor could be that naproxen (although available OTC in Germany for other indications) is usually prescribed by a physician when used for migraine, likely together with an adequate education. This again emphasizes the importance of educating patients on their acute migraine medication. Regarding etamizole, a frequently used prescription analgesic in Germany, NNTs from clinical migraine studies are equivalent to those of ibuprofen 400 mg (NNT 3.4 vs. 3.2) but study data are scarce for the oral form (25). In conclusion, the present data show that migraine patients in our sample perceived naproxen and metamizol as highly effective acute medications.

Efficacy of acute migraine medications decreased with headache frequency

The present study also explored the relation of patient-rated acute medication efficacy to headache frequency and acute medication frequency. Acute medication efficacy was rated significantly lower by patients with higher headache frequencies. This relation was stronger than that with acute medication frequency, and also present in patients with less than 10 acute medication days/month. Therefore, while loss of efficacy due to some form of drug tolerance during overuse may be one factor (6,7), another factor seems to be headache frequency itself. This could suggest that pathophysiological factors linked to headache frequency, such as increasing and persisting sensitization (26), may also reduce the efficacy of acute medication. Alternatively, or additionally, co-factors such as depression or anxiety may influence both headache frequency and acute medication efficacy ratings. Another factor may be that patients with high headache frequency tend to use acute medication later in the attack, trying to avoid overuse. The relation between acute migraine treatment optimization and headache frequency has also been investigated in the American Migraine Prevalence and Prevention (AMPP) study. Consistent with our results, poor acute treatment optimization was associated with chronic compared to episodic migraine (12) and ineffective two-hour pain freedom was associated with headache frequency, but not with medication overuse (27).

Interestingly, effective migraine prevention improves the efficacy of acute medication (28,29), which is also an often-cited goal of preventive treatment (2). The present data suggest that this might be a direct effect of the reduction of headache frequency. On the other hand, synergy effects, e.g. between preventive medications targeting calcitonin-gene related peptide (CGRP) and triptans (that act in part by reducing the release of CGRP) have also been proposed (30).

Strengths and limitations

The present study included real-world data from a relatively large sample of thoroughly characterized migraine patients that rated their acute medication according to efficacy, tolerability and satisfaction. The fact that each drug was rated separately enabled us to perform comparisons between different drug classes and drugs. This allowed an expansion of the results of the AMPP and Migraine in America Symptoms and treatment (MAST) studies that collected comprehensive ratings over all drugs used and did not assess satisfaction (10,27). On the other hand, rather than using a validated questionnaire such as the Migraine Treatment Optimization Questionnaire (m-TOQ) (31), the present study used single item ratings, and the validity and reliability of these single items has not been tested. The advantage is high face validity and practicability in a setting where information on many aspects of headache is collected, but clearly a dedicated questionnaire provides more detailed information. In addition, it must be considered that efficacy, tolerability and satisfaction ratings were self-reported by the patients.

The DMKG Headache Registry currently focuses on patients at centers with a special interest in headache, keeping data quality high but biasing the study population towards severely affected migraine patients, not representative for the general population. Data are also real-world, and acute headache medication likely represents the result of at least some treatment optimization by the patients and previous treating physicians. Previous acute treatment failures and preventive medication might affect acute medication efficacy differently between groups and need to be considered in future studies.

The present study focused on efficacy, tolerability and satisfaction ratings. Other relevant health care data on acute medication used, such as frequency of use and overuse, will be published separately.

Conclusion

The present study provides important real-world information on acute headache medication in migraine patients. It corroborated the clinical experience that triptans are rated as more effective than non-opioid analgesics. Migraine patients in our severely affected sample perceived naproxen and metamizole as the most effective non-opioid analgesics. In addition, acute medication efficacy ratings were reduced with higher headache frequencies, also in patients without medication overuse.

Article highlights

- Patients rate triptans as more effective but less tolerable than non-opioid analgesics.
- Among non-opioid analgesics, patients rate naproxen and metamizol as most effective.
- Acute medication efficacy decreases with increasing headache frequency, also in patients without medication overuse.

Acknowledgements

First, we wish to thank all participating patients and headache centers. In addition, we thank Dirk Reinel, Johannes Drescher and Florian Wogenstein at the software development company 'smartlytic' (Hof, Germany) and Yannic Siebenhaar at the Institute for Information Systems at the University of Applied Sciences Hof (Germany) for their excellent technical development of the DMKG Headache Registry, and Beatrix Weber and Katharina Diersch at the University of Applied Sciences Hof (Germany) and Lukas Wagner (HK2 Comtection GmbH) and Jonas Jacobsen (HK2 Rechtsanwälte), both Berlin, Germany for excellent management of the legal and data protection aspects. Moreover, we wish to thank the 'Münchner Studienzentrum' at the Technical University of Munich, Germany for outstanding organizational support. Finally, we thank the pharmaceutical companies mentioned below for their financial support.

Authorship

All authors made substantial contributions to the conception and design of the work and the interpretation of the data. RR and JS performed the data analyses. RR drafted the manuscript, all other authors substantially revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Declaration of competing interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: RR has received travel grants and/or honoraria for lectures or advisory boards from Allergan/AbbVie, Hormosan, Lilly, Lundbeck, Novartis and Teva.

GG has received honoraria from Lilly, Novartis Pharma, Teva, Lundbeck, and research grants from Novartis Pharma during the last three years. She does not hold any stocks of pharmaceutical companies.

CG has received honoraria for consulting and lectures within the past three years from Abbvie, Lilly, Novartis Pharma, Hormosan Pharma, Grünenthal, Sanofi-Aventis, Lundbeck, Perfood, Reckitt and TEVA. His research is supported by a grant of the German Research Foundation (DFG). He does not hold any stocks of pharmaceutical companies. He is honorary secretary of the German Migraine and Headache Society.

AS has received honoraria for adboards and educational talks from Allergan/AbbVie, Allergosan, Hormosan, Lilly, Lundbeck, Novartis, Sanofi, Teva.

TPJ has received honoraria from Allergan/AbbVie, Grünenthal, Hormosan, Lilly, Lundbeck, Novartis, Sanofi and Teva. He served on Advisory Boards and/or consulted for Allergan/AbbVie, Hormosan, Lilly, Lundbeck, Novartis and Teva.TPJ has received honoraria from Allergan/AbbVie, Grünenthal, Hormosan, Lilly, Lundbeck, Novartis, Sanofi and Teva. He served on Advisory Boards and/or consulted for Allergan/AbbVie, Hormosan, Lilly, Lundbeck, Novartis and Teva.

JS declares no conflict of interest.

SF received honoraria for lectures or advisory boards from Allergan/AbbVie, Hormosan, Eli Lilly, Lundbeck, Novartis, Sanofi and Teva.

TD has received honoraria for consulting and lectures from Hormosan Pharma, Novartis Pharma, and TEVA.

VR received the Soyka award as a research grant from Novartis.

Availability of data and materials

The datasets analyzed during the current study are available from the German Migraine and Headache Society on reasonable request. Please note that access to data principally suitable for conducting additional analyses must be reviewed by the Headache Registry's Scientific Steering Committee.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The DMKG Headache Registry is funded by the German Migraine and Headache Society and by unrestricted grants from companies with an interest in headache research (at the time of publication, these are Lilly, Teva, Novartis, and Lundbeck). Supporting companies were given the opportunity to comment on the research protocol, and their comments were considered where judged to be scientifically relevant. Apart from that, supporting companies did not influence design of the DMKG Headache Registry. A preliminary version of the present analysis was also supported by Lilly. The company did not influence data collection, analysis, interpretation or writing of the manuscript.

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