Triptanophobia in migraine: A case-control study on the causes and consequences of the non-use of triptans in chronic migraine patients.

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Abstract

Background

Triptanophobia is the excessive and inadequately justified concern about the potential risks of triptans. In this study we evaluate the possible causes of non-use of triptans in chronic migraine patients and the possible consequences.

Results

We included 941 patients, 86.2% female with a mean age of 39.9 years. Mean number of headache days per month was 24.1. The number of patients using triptans was 247 (26.2%). Triptans had been discontinued due to adverse events in 116 patients (12.3%), so 578 patients (61.4%) were triptan naïve. Formal contraindications were found in 23 patients (2.4%). Frequency of vascular risk factors, contraceptive use or age did not differ between the groups ($p > 0.1$). Participants with triptans used symptomatic medication fewer days per month (13.9 vs. 17.1, $p < 0.001$), had used prior prophylactic treatment more frequently (79.4% vs. 34.8%, $p < 0.001$) and presented symptomatic medication overuse less frequently (55.1% vs. 63.0%, $p = 0.03$).

Conclusion

Triptans were not used in three-quarters of chronic migraine patients. Non-use of triptans was not justified by inadequate tolerability, frequency of formal contraindications or frequency of vascular risk factors. Triptan use was associated with a better clinical situation at the moment of referral to a headache unit.

Introduction:

Acute patient relief is a keystone of migraine management. Symptomatic treatment aims to abort migraine episodes and restore patients' normal function, minimizing migraine morbidity and impact. To date, different symptomatic treatments have been used[1], representing triptan discovery a new era with more robust studies and better clinical results[2].

Triptans are indicated in acute episodes of migraine with moderate to severe intensity, inadequate response or contraindication to other analgesics[3,4]. *Pearls* of triptans include the effective control in 9 to 48% of migraine attacks[5], avoiding emergency department visits[6]. Triptans should be prescribed in every person with migraine, in particular those with chronic migraine (CM)[4].

Pitfalls of triptans are their adverse effects, including the possibility of cardiovascular events[7]. Coronary artery diameter may decrease up to 26% in healthy subjects[8], leading to the contraindication of triptans in

patients with ischemic coronary artery disease or uncontrolled hypertension[9]. However, when used in healthy patients, they seem reasonably safe[7]. Frequency of side effects ranges from 17–72%[10], being the most frequent nausea and dizziness[11].

Even though triptans are effective, safe in selected patients, and generally well tolerated[12], up to a fourth of CM patients have never used them[13,14]. The possible reasons for the non-use of triptans seem multifactorial, including formal contraindications, cost, and *triptanophobia*, among others. Contraindications seem infrequent in most people with migraine[12]. Cost should not be the reason, as Spanish healthcare system subsidizes them[15]. Therefore, *triptanophobia* could be an important reason for not using triptans. *Triptanophobia* could be defined as the excessive and inadequately justified concern of health professionals about the potential risks of triptans.

In the present study, we evaluated causes and consequences of the non-use of triptans in CM sufferers. We analyzed frequency of triptan use in CM patients. We compared, between triptan users and triptan naïve patients, the presence of contraindications, frequency of vascular risk factors, and differences in management prior to the referral to a headache unit.

Material And Methods:

We conducted an observational analytic study with a case-control design, following the STrengthening the Reporting of OBservational Studies in Epidemiology (STROBE) statement[16]. The study took place in the Headache Unit of Valladolid University Hospital, a third-level academic hospital with a reference population of 280.000 people. It receives patients from both specialized care and primary care. We recruited patients between May 2013 and May 2019, using a non-probabilistic sampling method, screening all consecutive patients.

We included patients that were: 1) Firstly referred to our headache unit, 2) Definitely diagnosed of CM according to the International Classification of Headache Disorders (ICHD) operating at the time, either 2nd version (ICHD-2)[17], beta 3rd version (ICHD-3b)[18] or 3rd version (ICHD-3)[19]; 3) Diagnosed of CM for the first time; 4) Older than 14 years old; 5) Agreed to participate in the study and signed the informed consent form. Patients were considered cases if they were triptan naïve and controls if they had previously used triptans.

Patients were excluded if they had: 1) Hypersensitivity to triptans 2) a serious systemic disease with higher impact than migraine that could be life-threatening 3) severe psychiatric disorders, including bipolar and related disorders; dissociative disorders, schizophrenia spectrum and other psychotic disorders; drug abuse; addictive disorders, or intellectual disability 4) concurrent administration of a monoamine oxidase inhibitor[9] 5) pregnancy or breastfeeding status.

Objectives:

The first endpoint of the study was to analyze if non-use of triptans was justified by the presence of formal contraindications or previous adverse events. The second endpoint was to compare if triptan naïve patients had a higher frequency of vascular risk factors (hypertension, hyperlipidemia, diabetes, smoking or prior smoking or obesity), use of contraceptive drugs or older age. The third endpoint was to compare the clinical situation of patients and previous management in triptan naïve and current triptan users. In this analysis, we excluded patients that discontinued triptans due to inadequate tolerability. The compared variables included age, age of onset, sex, months of CM prior to the consultation, number of headache days per month, migraine days per month, number of acute medication days per month, frequency of medication overuse headache (MOH), and prior use of prophylactic drugs. Figure 1 depicts the study design.

Intervention:

For the first endpoint, every first visit we assessed the presence of contraindications to triptans, including chronically uncontrolled hypertension, coronary artery disease, history of stroke and peripheral vascular disease.

Concerning the second objective, presence of vascular risk factors was systematically evaluated, including hypertension (systemic blood pressure higher than 140/90 mmHg in at least two prior determinations), hyperlipidemia (total cholesterol > 220 mg/dl, LDL > 150 mg/dl or HDL < 40 mg/dl, triglycerides > 200 md/dl), diabetes (fasting blood glucose level > 126 mg/dl on two separate tests, HbA1c > 6.5%, blood glucose level > 200 mg/dl with diabetes symptoms or blood glucose level > 200 mg/dl after oral glucose overload), current smoking habit, prior smoking habit (if the smoke cessation occurred > 3 months before) and obesity (Body Mass Index > 30). As in some studies, older age[20] and the use of contraceptive drugs[21] have been associated with a higher frequency of vascular events in migraine patients, we also compared mean age, frequency of patients older than 50 years old and frequency of patients older than 65 years. We compared frequency of patients under contraceptive therapies in both groups.

With regards to the third endpoint, we compared triptan naïve patients and patients using triptans at that moment. We gathered information about demographic data, including referral source considering primary care or secondary care, gender, age of onset of migraine, and age when CM started. We analyzed the clinical situation of the preceding month, in terms of number of headache days per month, migraine days per month and number of days using acute medication. We evaluated if patients fulfilled MOH criteria according to ICHD-3 criteria[19], by calculating it mathematically based on the number of acute medication days, as 10 or more days of triptan, opioids or combination analgesics use per month; or more than 15 days of analgesics or non-steroidal anti-inflammatory drugs (NSAIDs) days per month. We also studied the use of prior prophylactic migraine treatments, defined according to the local guidelines[22]. We analyzed time in months since the patient experienced > 15 headache days per month and > 8 migraine days per month.

This study was approved by the local research ethics committee with the number PI 14–152 and was conducted in accordance with the Declaration of Helsinki. All patients were informed prior to the study and signed an informed consent form.

Statistics:

We present qualitative data as frequency and percentage and quantitative data as mean and standard deviation or median and interquartile range if the distribution was not normal, according to Kolmogorov-Smirnov test. In the first endpoint, we describe frequency and percentage of contraindications in both triptan naïve patients and triptan users, differentiating current and former triptan users.

For the second and third endpoints, we employed the Chi-Squared test to compare qualitative variables and the Student-t test to compare qualitative and quantitative variables, providing degrees of freedom. We did a logistic and linear regression analysis. We considered an alpha error of 5%. We corrected for multiple comparisons by using Bonferroni method. We also did a survival analysis through a Kaplan-Meier analysis and Cox regression log-rank test, presenting the pertinent graphic representation. We anticipated as potential confounder in frequency of MOH the prior use of prophylactic drugs and adjusted for it. We also anticipated that patients being referred earlier to our headache unit might have essayed preventive medications less frequently. Missing data was managed by complete-case analysis. We did not estimate sample size in advance. Statistical analysis was conducted with SPSS v.26 (IBM Corp., Armonk, NY).

Results:

During the study period, 4138 patients were screened, fulfilling inclusion/exclusion criteria 941 of them (22.7%), being 811 of them (86.2%) female. Mean age of migraine onset was 19.2 years (9.7), mean age at the moment of the first visit was 39.9 years (13.9), duration of CM prior to diagnosis were 36.4 (50.4) months in mean and 12.0 months in median [6–36]. Referral source was primary care in 574 patients (61.0%) and general neurology or other specialties offices in 367 (39.0%).

Mean number of headache days per month was 24.1 (5.2), being 15.0 [9–20] of them migraine headaches in median. Patients were taking acute medications 16.6 (9.1) days per month in mean. In the total sample, 247 patients were under triptan use (26.2%) and 694 (73.8%) were not. Triptans had been previously used and stopped due to adverse events in 116 (12.3%) patients, leading to a total of 578 triptan naïve patients (61.4%). Triptans were used 9.6 (7.0) days per month in mean.

MOH criteria were fulfilled in 593 patients (63.0%). In 493 patients (52.3%) NSAIDs or paracetamol were overused, in 117 (23.8%) triptans, in 35 (3.7%) ergot derivates, and in six patients (0.6%) opioids were overused. Preventive drugs had been previously used in 476 patients (50.6%). Beta-blockers had been used by 233 patients (24.7%), topiramate by 201 (21.3%), amitriptyline by 192 (20.4%), flunarizine by 181 (19.2%) and other drugs by 73 patients (7.7%).

Contraindications for triptan use:

Formal contraindications for triptan use were found in 23 patients in the whole sample (2.4%), being one of those patients under triptan use. Frequency of contraindications was 22/694 subjects, leading to 3.2% of all triptan naïve patients and former triptan users. The contraindications included uncontrolled hypertension in fourteen cases, severe peripheral artery disease in four cases, antiphospholipid syndrome with associated peripheral vascular disease in three cases, and prior stroke in two patients. One of the patients with severe peripheral artery disease was under triptan treatment.
Vascular risk factors, contraceptive use and old age:

We found no statistically significant differences in the frequency of vascular risk factors between triptan users and triptan naïve patients (all corrected $p > 0.1$). Table 1 shows the relative frequency of each vascular risk factor in triptan users vs. triptan naïve patients.

Table 1
Frequency of vascular risk factors in triptan users compared with triptan naïve patients. Frequency and percentage within each group.

	Triptan users (n = 247)	Triptan naïve patients (n = 578)	p-value[a]
Hypertension	12 (4.9%)	44 (7.6%)	0.15
Hyperlipidaemia	12 (4.9%)	23 (3.6%)	0.41
Diabetes	2 (0.8%)	10 (1.7%)	0.31
Current Smoker	54 (19.7%)	114 (21.9%)	0.48
Former Smoker	31 (12.6%)	62 (10.7%)	0.45
Obesity (BMI > 30)	15 (6.1%)	32 (5.5%)	0.76

Frequency of contraceptive treatment was also similar between both groups, being used by 11 triptan users (4.5%) and 40 triptan naïve patients (6.9%), ($p = 0.17$). Proportion of patients aged 50 or older was 66/247 (26.7%) in triptan users and 146/578 (25.3%) in triptan naïve patients (Chi-squared test, 1 df, $p = 0.66$); and proportion of subjects aged 65 or older was 7/247 (2.8%) in triptan users and 28/578 (4.8%) in triptan naïve subjects (Chi-squared test, 1df, $p = 0.19$).

Clinical situation and previous management.

Table 2 summarizes demographic and clinical variables between triptan users and triptan naïve patients. After adjusting for multiple comparisons ($p = 0.004$), we found statistically significant variables related with age ($p < 0.001$), acute medication days per month ($p < 0.001$), and frequency of prior prophylactic use ($p < 0.001$), but frequency of MOH ($p = 0.008$) loss statistical signification.

Table 2
Comparison of demographic and clinical variables between triptan users and triptan naïve patients.

Item	Triptan users (n = 247)	Triptan naïve (n = 578)	OR (95% CI)	*p*-value[a]
Age (years)	42.2 (11.6)	38.6 (14.9)	1.018 (1.008–1.029)	< 0.001
Age of onset (years)	17.8 (8.6)	19.7 (10.2)	0.978 (0.96–0.995)	0.005
Female sex	219 (88.7%)	493 (85.3%)	1.349 (0.85–2.13)	0.197
Months of CM	38.8 (62.1)	35.8 (60.5)	1.001 (0.998–1.003)	0.511
Headache days per month	23.5 (4.9)	24.4 (5.1)	0.967 (0.939–0.995)	0.021
Migraine days per month	14.1 (6.9)	14.6 (7.7)	0.992 (0.973–1.012)	0.449
Acute medication days per month	13.9 (9.8)	17.1 (8.8)	0.963 (0.94–0.98)	< 0.001
Medication Overuse Headache	136 (55.1%)	364 (63.0%)	0.72 (0.53–0.97)	0.033
MOH not attributed to triptans (n = 483)	123 (52.6%)	360 (62.7%)	0.659 (0.48–0.89)	0.008
MOH in patients with prior prophylactic use (n = 397)	115 (58.7%)	136 (67.7%)	0.67 (0.45–1.02)	0.063

Item	Triptan users (n = 247)	Triptan naïve (n = 578)	OR (95% CI)	*p*-value[a]
Prior preventive treatment	196 (79.4%)	201 (34.8%)	7.21 (5.07–10.25)	< 0.001

We did not find statistically significant differences in the evolution time of CM before consultation in patients treated with triptans (HR: 38.8 months, 95% CI: 31.0-46.6) or without triptans (HR: 35.8 months, 95%CI: 30.8–40.7, p = 0.176). Prior use of preventive drugs was associated with a lower evolution time of CM before consultation (HR: 0.84, 95% CI: 0.73–0.98). Figure 2 shows the time of CM evolution in patients treated with triptans compared with triptan-naïve patients.

Discussion:

In this study, we evaluated if the non-use of triptans was justified by the presence of contraindications or prior adverse events. We analyzed if triptan naïve patients had a higher frequency of vascular risk factors associated with stroke or cardiovascular conditions. Finally, we analyzed differences in clinical situation and previous management between the groups of triptan users and triptan naïve patients. We specifically studied CM patients because in that population, there is no doubt on the need of a triptan prescription[3,4].

The main results of our study were that the percentage of triptan naïve patients was surprisingly high (74%), that the frequency of formal contraindications was sparse (3%), that the percentage of patients that discontinued triptans because of adverse events low (12%), and that the non-use of triptans was associated with a worse clinical situation and worse previous management, indicated by a higher frequency of acute medication use, a higher frequency of MOH and a lesser prior use of prophylactic drugs.

Headache disorders are the second cause of years lived with disability worldwide[23]. CM patients are frequently underdiagnosed and undertreated, not only in primary care, but also at the specialized level[13]. Only 40.8% of CM patients have a consultation with a healthcare professional for headaches, and 4.5% receive adequate diagnosis and treatment[24].

The main options in the acute treatment of migraine attacks are NSAIDs, ergots and triptans[25], although recently ditans and gepants have been used[26,27]. Although NSAIDs are the most widely used treatment in migraine attacks[28], triptans are more migraine specific and its efficacy rate is overall higher than NSAIDs or ergots[29,30]. In our sample, only a fourth of all CM patients were under triptan use. National studies conducted in Spain showed a frequency of use of 17%-48%[14,15], compared to 14 to 25% in other countries [13, 31]. It is also surprising that opioids, which are not specific migraine treatments and have

more frequent and serious adverse effects, are frequently used in migraine[32], showing that *opioidophobia* seems uncommon.

Triptans are 5-hydroxytriptamine (5-HT) agonists with several mechanisms of action. First, they decrease the diameters of systemic and intracranial arteries, by 5-HT_{1B} receptor stimulation[33]. Second, they inhibit axonal transmission acting on trigeminal 5-HT_{1B} and 5-HT_{1D} receptors[33]. Third, they might diminish neurogenic inflammation, targeting presynaptic 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F} receptors, decreasing Calcitonin Gene-related Peptide (CGRP) and Substance P[34].

Adverse events of triptans are related with their effect on 5-HT_{1B} receptors[35], being contraindicated in subjects with coronary artery disease, coronary vasospasm, prior cerebrovascular events, peripheral arteriopathy or uncontrolled hypertension[7]. Despite its potential risks, serious cardiovascular effects occur in < 1/1.000.000 exposures, the most severe events being stroke and myocardial infarction[36,12]. In our sample, only a minority of patients without triptan use presented contraindications (3.2%), so contraindications seem insufficient to explain the non-use of triptans.

The main vascular risk factors associated with both stroke and ischemic coronary disease are hypertension, hyperlipidemia, diabetes, smoking or obesity[37]. Therefore, we analyzed if the non-use of triptans could be associated with an excessive concern for vascular events. Nonetheless, frequency of vascular risk factors was similar between the two groups, without significant differences. Evidence suggests that migraine patients have increased vascular risk[38], and especially those with aura, those who smoke, those treated with contraceptives, and those older than 40 years old[21]. Therefore, some authors do not recommend triptans in old patients[39]. Nevertheless, we could not find differences in age, use of oral contraceptives, or seniority.

Triptan non-use was not justified by a worse efficacy compared with NSAIDs or ergots, presence of contraindications, or an increased frequency of vascular risk factors. Two other explanations seem possible: a worse tolerability profile or treatment expense. Concerning tolerability, frequency of adverse is estimated around 17–41% in ergots[40], 5–28% in NSAIDs and 40% in triptans[7]. In our sample, adverse events led to triptan discontinuation in 12% of patients. Adverse event profiles differ: NSAIDs typically cause gastrointestinal AE[11], and ergot derivatives cause nausea or vomiting[41]. The most frequent triptan AE are nausea (10%), dizziness (4%), fatigue (3%) and feeling of heaviness (3%)[11].

Triptans can cost between 4 and 62 times higher than NSAIDs. Still, the Spanish healthcare system covers between 0%-60% of the total price[42]. Retired workers with less than 18.000 € of annual income only contribute a 10% of the total cost, with a maximum amount of 8.23 € per month[42]. The total annual cost of CM is estimated to be 12,922 € per patient. Only 43% corresponds to the direct cost[15]. Despite the higher cost of triptans, they have proven to be cost-effective, due to the decrease of direct costs related with emergency department[6] consultations and indirect costs[13,43]. Therefore, neither tolerability nor cost seem to fully explain the underutilization of triptans.

All CM patients should be under prophylactic medication[44]. In our sample, only 51% of the patients were under preventive treatment, in line with comparable series (49%)[15] and more than primary care-based series (1.6–14%)[13]. One of the most remarkable findings of our study was the significant difference of prior prophylactic treatment in patients treated with triptans compared with triptan naïve subjects, being almost twice as frequent (79% vs. 35%).

We examined whether differences in triptan use were related with a delayed referral to Headache specialized care. In our setting, general practitioners can refer patients directly to our Headache Unit without prior consultation with a general neurologist, reducing the wait time. In our sample, we could not explain differences in time prior to the referral by the use or non-use of triptans, being 36 and 38 months in both groups.

We used the term *triptanophobia* to define the excessive and inadequately justified concern of health professionals about the potential risks of triptans. It should not be interpreted in a pejorative or dismissive way. The reasons for the non-use of triptans seem multifactorial; however, in the present study we observed that the relative weight of many of them seem insufficient, so there must be some degree of *triptanophobia*.

Causes of *triptanophobia* can be related to education on headache medicine. Headache education is not an obligatory rotation during neurology residence curriculum. The lower percentage of preventive use in triptan naïve patients may also suggest this worse management of CM patients. It could also be motivated by the atypical commercial presentation, in blisters of two to nine pills, unlikely for a medication that should be used frequently.

Our study had several limitations: it is a single-center study with an unusual referral pathway. In some patients, there could exist some degree of memory bias, but we reviewed referral charts and double-checked prescription history in every case. The study could fail to detect differences in the frequency of vascular risk factors, given that the sample was not sized primarily for that, but all the relative frequencies were similar with the sole exception of hypertension (4.9 vs 7.6%). Prior use of preventive medications could also influence the results, but all included patients met CM criteria when included, suggesting that almost all preventive drugs failed in them. *Triptanophobia* is a new term that may not fully correspond to the classic definition of phobia. We use this concept in a practical way to try to explain the underutilization of triptans, without assuming the negative connotations of phobia. Among the strengths of our study, we analyzed an important subject not previously studied in detail. Our study design allowed us to study multiple effects and multiple exposures, given the high prevalence of migraines. The large sample size also gave robustness to the analysis. Patients were diagnosed in an experienced setting and quality of information was high. More research on this subject is needed to definitely demonstrate some of this hypothesis. Future studies should analyze the presence of *triptanophobia* in larger samples and different settings, specifically analyzing if triptan use might change the clinical situation.

Conclusion:

Triptans were not used in up to three-quarters of CM patients despite the absence of formal contraindications, prior adverse events, or prior adverse events.

Frequency of vascular risk factors, old age, or contraceptive use were not different between groups of triptan users and triptan naïve patients.

Triptan use was associated with a lesser percentage of MOH, a lesser frequency of acute treatment medications per month and a higher percentage of prior prophylactic use.

Abbreviations

CM
Chronic Migraine
ICHD
International Classification Headache Disorders
MOH
Medication Overuse Headache
NSAIDs
non-steroidal anti-inflammatory drugs
5-HT
5-hydroxytriptamine
CGRP
Calcitonin Gene-Related Peptide

Declarations

Clinical Research Ethics Committee of East Valladolid Area approved the study. All the patients read and signed informed consent.

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Enrique Martínez-Pías drafted the manuscript, analyzed and interpreted the data. David García-Azorín analyzed and interpreted the data and drafted the manuscript. Ane Minguez-Olaondo drafted the manuscript. Javier Trigo, Álvaro Sierra and Marina Ruiz collected the data. Ángel L. Guerrero supervised the manuscript.

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References

1. García-Azorin D, Yamani N, Messina LM, Peeters I, Ferrili M, Ovchinnikov D (2018) et. al. A PRISMA-compliant systematic review of the endpoints employed to evaluate symptomatic treatments for primary headaches. J Headache Pain 19(1):90
2. Charles A, Migraine (2017) N Engl J Med 377(6):553–561
3. Marmura W, Silberstein SO, Schwedt TJ (2015) The acute treatment of migraine in adults: the american headache society evidence assessment of migraine pharmacotherapies. Headache 55(1):3–20
4. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A (2009) et. al. EFNS guideline on the drug treatment of migraine–revised report of an EFNS task force. Eur J Neurol 16(9):968–981
5. Hou M, Liu H, Li Y, Xu L, He Y, Lv Y (2019) et. al. Efficacy of triptans for the treatment of acute migraines: a quantitative comparison based on the dose-effect and time-course characteristics. Eur J Clin Pharmacol 75(10):1369–1378
6. Adelman JU, Adelman LC, Freeman MC, Von Seggern RL, Drake J (2004) Cost considerations of acute migraine treatment. Headache 44(3):271–285
7. Ferrari MD, Goadsby PJ, Roon KI, Lipton RB (2002) Triptans (serotonin, 5-HT1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. Cephalalgia 22(8):633–658
8. Goldstein JA, Massey KD, Kirby S, Gibson M, Hettiarachchi J, Rankin AJ (2004) et. al. Effect of high-dose intravenous eletriptan on coronary artery diameter. Cephalalgia 24(7):515–521
9. Electronics medicine compendium
   Sumatriptan 50 mg Tablets
   accessed 28 January 2020)
   Electronics medicine compendium. Sumatriptan 50 mg Tablets, https://www.medicines.org.uk/emc/product/524/smpc#CONTRAINDICATIONS. (2018, accessed 28 January 2020)
10. Tfelt-Hansen P (2018) Optimal balance of efficacy and tolerability of oral triptans and telcagepant: a review and a clinical comment. J Headache Pain 12(3):275–280
11. Tajti J, Majláth Z, Szok D, Csáti A, Vécsei L (2015) Drug safety in acute migraine treatment. Expert Opin Drug Saf 14(6):891–909
12. Weatherall MW (2015) Drug therapy in headache. Clin Med (Lond) 15(3):273–279
13. Katsarava Z, Mania M, Lampl C, Herberhold J, Steiner TJ (2018) Poor medical care for people with migraine in Europe – evidence from the Eurolight study. J Headache Pain 19(1):10
14. Gracia-Naya M, Alarcia-Alejos R, Modrego-Pardo PJ (2008) Importancia de la migraña crónica en una consulta general de neurología. Rev neurol 46:577–581
15. Garrido Cumbrera M, Gálvez Ruiz D, Braçe O, Nieblas Rosado MI, Delgado Domínguez CJ, Colomina I, et. al. Impacto y situación de la migraña en España: Atlas 2018. 1st. Ed. Universidad de Sevilla

16. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP (2007) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS Med 4(10):e296
17. Headache Classification Subcommittee of the International Headache Society (2004) The International Classification of Headache Disorders: 2nd edition. Cephalalgia 24(Suppl 1):9–160
18. Headache Classification Committee of the International Headache Society (HIS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018; 38(1):1-211
19. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013; 33(9):629–808
20. Buse DC, Reed ML, Fanning KM, Kurth T, Lipton RB (2017) Cardiovascular Events, Conditions, and Procedures Among People With Episodic Migraine in the US Population: Results from the American Migraine Prevalence and Prevention (AMPP) Study. Headache 57(1):31
21. Sacco S, Merki-Feld GS, Ægidius KL, Bitzer J, Canonico M, Kurth T (2017) et. al. Hormonal contraceptives and risk of ischemic stroke in women with migraine: a consensus statement from the European Headache Federation (EHF) and the European Society of Contraception and Reproductive Health (ESC). J Headache Pain 18(1):108
22. Ezpeleta D, Pozo-Rosich P (2015) Guías diagnósticas y terapéuticas de la Sociedad Española de Neurología. Guía oficial de práctica clínica en cefaleas. Editorial Luzan 5, Madrid vol. 53
23. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators (2018) Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 392(10159):1789–1858
24. Dodick DW, Loder EW, Adams AM, Buse DC, Fanning KM, Reed ML (2016) et. al. Assessing Barriers to Chronic Migraine Consultation, Diagnosis, and Treatment: Results From the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study. Headache 56(5):821–834
25. Charles (2018) The pathophysiology of migraine: implications for clinical management. Lancet Neurol 17(2):174–182
26. Kuca B, Silberstein SD, Wietecha L, Berg, Dozier G, Lipton RB (2018) et. al. Lasmiditan is an effective acute treatment for migraine: A phase 3 randomized study. Neurology 91(24):e2222–e2232
27. Dodick DW, Lipton RB, Ailani J, Lu K, Finnegan M, Trugman JM (2019) et. al. Ubrogepant for the Treatment of Migraine. N Engl J Med 381(23):2230–2241
28. Lipton RB, Munjal S, Alam A, Buse DC, Fanning KM, Reed ML (2018) et. Al. Migraine in America Symptoms and Treatment (MAST) Study: Baseline Study Methods, Treatment Patterns, and Gender Differences. Headache 58(9):1408–1426
29. Cameron C, Kelly S, Hsieh SC, Murphy M, Chen L, Kotb A (2015) et. al. Triptans in the Acute Treatment of Migraine: A Systematic Review and Network Meta-Analysis. Headache 55(Suppl 4):221–235

30. Xu H, Han W, Wang J, Li M (2016) Network meta-analysis of migraine disorder treatment by NSAIDs and triptans. J Headache Pain 17(1):113
31. Schwedt TJ, Alam A, Reed ML, Fanning KM, Munjal S, Buse DC (2018) et. al. Factors associated with acute medication overuse in people with migraine: results from the 2017 migraine in America symptoms and treatment (MAST) study. J Headache Pain 19(1):38
32. Woolley JM, Bonafede MM, Maiese BA, Lenz RA (2017) Migraine Prophylaxis and Acute Treatment Patterns Among Commercially Insured Patients in the United States. Headache 57(9):1399–1408
33. Andrew H, Ahna, Allan I (2005) Basbaum. Where do triptans act in the treatment of migraine? Pain 115(1–2):1–4
34. Moreno-Ajona D, Chan C, Villar-Martínez MD, Goadsby PJ (2019) Targeting CGRP and 5-HT1F Receptors for the Acute Therapy of Migraine: A Literature Review. Headache 59(Suppl 2):3–19
35. Rubio-Beltrán E, Labastida-Ramírez A, Villalón CM (2018) MaassenVanDenBrink. Is selective 5-HT1F receptor agonism an entity apart from that of the triptans in antimigraine therapy? Pharmacol Ther 186:88–97
36. Dodick D, Lipton RB, Martin V, Papademetriou V, Rosamond W, MaassenVanDenBrink A (2004) et. al. Consensus statement: cardiovascular safety profile of triptans (5-HT agonists) in the acute treatment of migraine. Headache 44:414–425
37. D'Agostino RB, Grundy S, Sullivan LM, Wilson P, CHD Risk Prediction Group (2001) Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 286(2):180–187
38. Mahmoud AN, Mentias A, Elgendy AY, Qazi A, Barakat AF, Saad M (2018) et. al. Migraine and the risk of cardiovascular and cerebrovascular events: a meta-analysis of 16 cohort studies including 1 152 407 subjects. BMJ Open 8(3):e020498
39. Mathew S, Ailani J (2019) Traditional and Novel Migraine Therapy in the Aging Population. Curr Pain Headache Rep 23(6):42
40. Meyler WJ (1996) Side effects of ergotamine. Cephalalgia 16(1):5–10
41. Silberstein SD, McCrory DC (2003) Ergotamine and dihydroergotamine: history, pharmacology, and efficacy. Headache 43(2):144–166
42. de Trabajo M, Migraciones y Seguridad Social. Guía Laboral - Prestaciones del Régimen General de la Seguridad Social. http://www.mitramiss.gob.es/es/Guia/texto/guia_14/contenidos/guia_14_29_2.htm (accessed 29 January 2020)
43. Lipton RB (2015) Risk Factors for and Management of Medication-Overuse Headache. Continuum (Minneap Minn) 21(4 Headache):1118–1131
44. Lipton RB, Silberstein SD. Episodic and chronic migraine headache: breaking down barriers to optimal treatment and prevention. Headache 2015; 55 Suppl 2:103 – 22; quiz 123-6

Figures

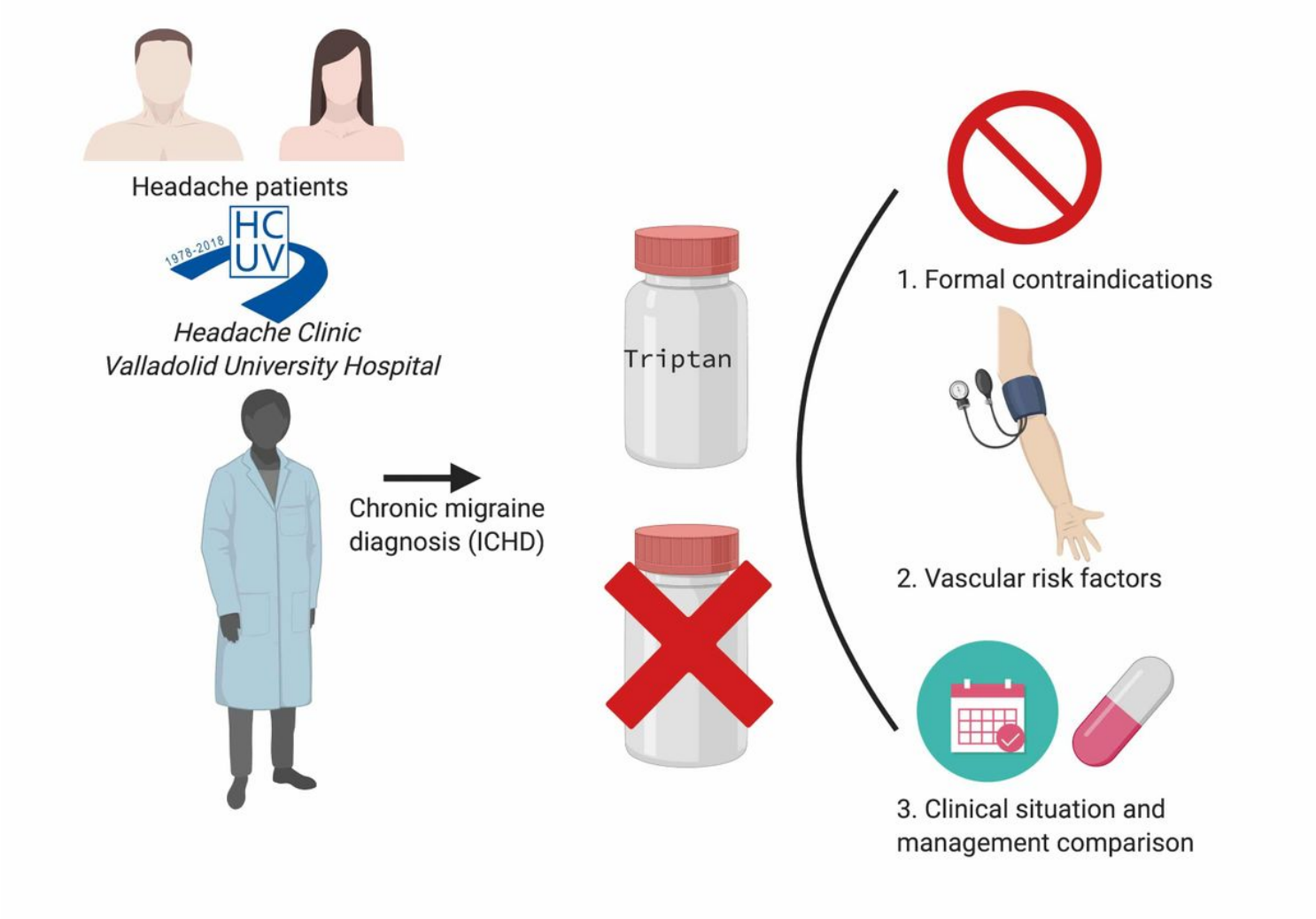

Figure 1

Study design: Diagnosis of patients with chronic migraine in Headache Unit. Evaluation of contraindications and vascular risk factors. Comparison of clinical situation and management of triptan users and triptan naïve patients.

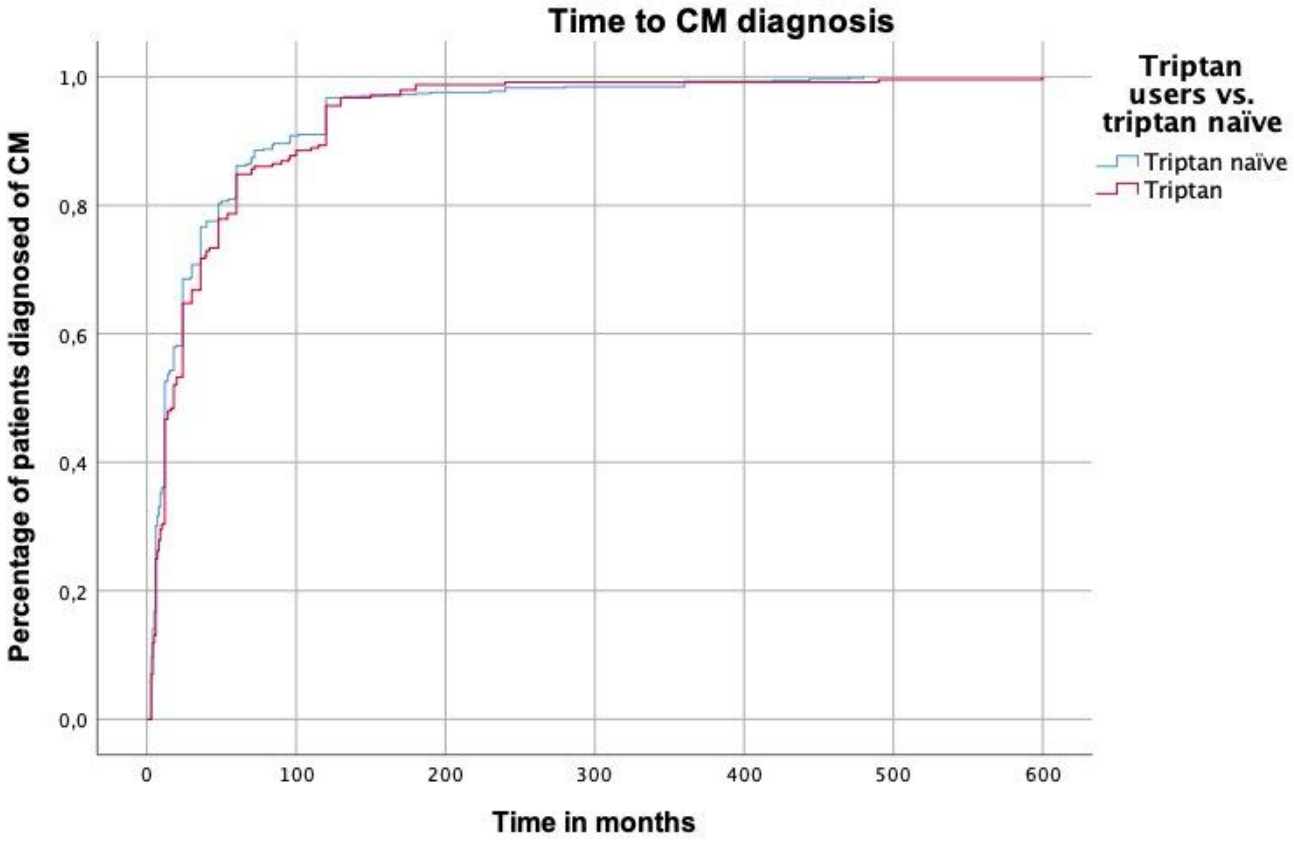

Figure 2

Comparison of time to chronic migraine diagnosis in triptan users and triptan naïve patients. CM (Chronic Migraine).

Supplementary Files

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