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An exploratory questionnaire-based survey

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RESEARCH ARTICLE

Triptan treatment is associated with a higher number of red wine-induced migraine episodes: An exploratory questionnaire-based survey

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Abstract

Aim: Diet, including foods and beverages, affects migraine. Conversely, the influence of migraine therapies on dietary habits is largely unknown. This study aimed at investigating the effects of triptan intake on foods and drinks consumed by adults with migraine with and/or without aura.

Methods: An exploratory questionnaire-based survey took place online between November 2022 and June 2023. Participants were recruited through advertisements shared on social media accounts (e.g., Facebook and Instagram) and seasonal newsletters of three Danish patient associations. In addition, posters and flyers in headache and pain centers at Danish hospitals and private neurological, pain, and physiotherapeutic clinics were utilized.

Results: A total of 314 adults with migraine with and/or without aura completed the survey. Among the respondents, 236 individuals (75.2%) regularly used triptans to treat their migraines. Compared with non-triptan users, individuals using triptans were characterized by significantly more foods and/or drinks triggering migraine (74.2% vs. 56.4%, $p=0.005$). Alcoholic beverages and most specifically red wine were overreported as migraine triggers by triptan users (48.3% vs. 21.8%, $p<0.001$). In the week preceding the survey, red wine was significantly less consumed by triptan users than non-triptan users (92.4% vs. 76.9%, $p<0.001$).

Conclusions: Patients who regularly consume triptans report red wine most frequently as a migraine trigger. Triptan users are characterized by a lower consumption of red wine than non-triptan users, suggesting that a regular triptan intake may promote an increased sensitivity to red wine-induced migraine.

KEYWORDS
CGRP, headache, medication overuse headache, pain, serotonin

INTRODUCTION

Migraine is a complex headache disorder that remains challenging to prevent and treat. The contribution of dietary ingredients to migraine occurrence has been recognized, leading to personalized nutritional solutions and diet therapies.[1–3] Several individuals with migraine are sensitive to diet and report that some foods and drinks trigger migraine attacks, including chocolate, citrus fruits, alcoholic beverages, histamine, and caffeine.[4,5] The correct identification of dietary triggers is difficult because the response of an individual with migraine to a certain trigger depends on several factors, including the amount and timing of exposure.[6] Several types of diets have been proposed to be beneficial for migraine, including ketogenic, low-glycemic, and gluten-free ones.[7–9] Advancements in

personalized medicine will be useful to determine individualized dietary recommendations for migraine patients.[10]

Triptans are a group of serotonin or 5-hydroxytryptamine (5-HT) receptor agonists used as abortive medications in the treatment of migraines.[11] Triptans act by selectively binding the 5-HT_{1B} and 5-HT_{1D} receptors, leading to vasoconstriction of cranial arteries and inhibition of nociceptive transmission.[12] They are associated with specific side effects, including medication overuse headache (MOH) when used for 10 or more days per month for at least 3 months.[13] A regular use of triptans can potentially influence any aspect of human health, including dietary habits. Whether triptans influence nutrition in migraine patients is currently unknown.

This study aimed at retrospectively investigating self-reported dietary triggers, relievers, and aggravating factors in a cohort of adults with migraine with and/or without aura. In accordance with the abortive medication that was routinely used, individuals who responded to the questionnaire-based survey were divided into triptan and non-triptan users. We additionally asked their consumption of chocolate, red wine, and citrus fruits in the week prior to completing the survey.

METHODS

Participants

We included individuals aged between 18 and 70 years old recruited through posters and flyers in headache clinics and pain centers at Danish hospitals and private neurological, pain, and physiotherapeutic clinics. The advertisements were shared on the social media accounts (e.g., Facebook and Instagram) and seasonal newsletters of three patient associations (*Migræne Danmark*, *Danmarks Patientforening for Hovedpineramte*, and *Migræne og Hovedpineforeningen*). We confirmed the presence of migraine by implementing four questions designed to screen adults with migraine in the Danish population.[14] The screening questions included in the survey were as follows: (1) "Have you ever had migraine?", (2) "Have you ever had severe headache accompanied by nausea?", (3) "Have you ever had severe headache accompanied by hypersensitivity to sound and light?", and (4) "Have you ever had visual disturbances lasting 5–60 min followed by headache?". Two positive answers were considered sufficient to confirm the presence of migraine.[14] The approval from the local Ethics Committee was not required as data could not be traced to individual participants.

Data collection

The questionnaire-based survey was developed in collaboration with the Danish Headache Center (Glostrup, Denmark) and constructed by using SurveyXact software. The questionnaire-based survey collected binary variables (gender, headache location, and accompanying symptoms) and categorical variables (age, migraine frequency, and severity). Open-ended questions allowed the respondents to report their dietary habits (triggers, relievers, and aggravating factors) and medications used to treat migraine (abortive and preventive medications). For this reason, each respondent could report more than one dietary trigger, reliever, and/or aggravating factor at a time. After the survey was closed, reported foods and drinks were classified as alcoholic beverages (including red wine, white wine, beer, and spirits), sweet foods and drinks, artificial sweeteners, foods, or drinks of animal origin (including milk, cheese, and eggs), salty foods, chocolate, methylxanthine-containing products (including coffee and tea), citric fruits (including oranges, lemons, and limes), fruits and vegetables (including tomatoes, avocados, strawberries, nuts, onions, and garlic), red meat, herbs, and spices (ginger and liquorice), bakery products (including bread and gluten-free products), fish (including salmon, shrimps, and other fishes), and others (fermented foods, spicy foods, smoked foods, and foods with a strong odor). We additionally asked about the consumption of red wine, chocolate, and citrus fruits in the week preceding the completion of the survey. The survey was completed online between November 2022 and June 2023.

Statistical analysis

The statistical analysis was performed with R software (version 4.3.1). Sample size was not calculated a priori since estimates of the effect size were not available. The primary outcome was the difference in the percentage of individuals reporting dietary triggers between triptan and non-triptan users. Secondary outcomes included any difference in the consumption of red wine, chocolate, and citrus fruits between triptan and non-triptan users. All other analyses were considered exploratory. Statistical tests were performed by using the chi-square test with the Yates's correction to prevent overestimation of statistical significance. For this reason, we did not adjust for multiple testing. The 95% confidence intervals (CIs) were calculated according to the normal approximation of the binomial distribution. p-values were defined as statistically significant as <0.05.

RESULTS

A total of 314 adults completed the questionnaire-based survey online. We confirmed the presence of migraine in every respondent. Among them, 152 out of 314 individuals (48.4%) reported visual disturbances followed by headache. A total of 236 individuals (75.2%) used triptans to treat their migraines, while

the other 78 individuals (24.8%) used different medications, including paracetamol, ibuprofen, naproxen, metoclopramide, domperidone, promethazine, diazepam, morphine, and/or analgesic combinations. The baseline characteristics of all respondents are reported in Table 1. At the baseline, the use of migraine prophylactics was greater in triptan users (55.5%, 95% CI: 49.2%–61.9%) than in non-triptan users (38.5%, 95% CI: 27.7%–49.3%) ($p=0.013$).

Migraine triggers

A total of 175 out of 236 triptan users (74.2%, 95% CI: 68.6%–79.7%) reported foods and/or drinks triggering migraine, compared with 44 out of 78 non-triptan users (56.4%, 95% CI: 45.4%–67.4%) ($p=0.005$). The most common dietary triggers reported by triptan users were alcoholic beverages ($n=114$, 48.3%), chocolate ($n=44$, 18.6%), and sweets ($n=40$, 16.9%). The most common dietary triggers reported by non-triptan users were alcoholic beverages ($n=17$, 21.2%), chocolate ($n=12$, 15.4%), sweets ($n=10$, 12.8%), and herbs/spices ($n=9$, 11.5%). Compared with non-triptan users (21.8%, 95% CI: 12.6%–31.0%), alcoholic beverages were significantly more reported as migraine triggers by triptan users (48.3%, 95% CI: 41.9%–54.7%) ($p<0.001$). The number of triptan and non-triptan users reporting dietary triggers is described in Table 2. The individual dietary triggers collected under the category "alcoholic beverages" are described in Table 3.

Migraine relievers

Regarding dietary relievers, a total of 90 out of 236 triptan users (38.1%) reported foods and/or drinks alleviating migraine, compared with 29 out of 78 non-triptan users (37.2%) ($p=0.987$). The most common dietary relievers reported by triptan users were sweets ($n=69$, 29.2%) and salty foods ($n=20$, 8.5%). The most common dietary relievers reported by non-triptan users were sweets ($n=19$, 24.4%) and methylxanthine-containing products ($n=7$, 9.0%). The number of triptan and non-triptan users reporting dietary relievers is described in Table 4.

Foods and/or drinks aggravating migraine

Considering dietary aggravating factors, a total of 73 out of 236 triptan users (30.9%) reported foods and/or

TABLE 1 Baseline characteristics of respondents.

	Triptan users ($n=236$, %)	Non-triptan users ($n=78$, %)	p-Value
Age (years)			
18–39	86 (36)	37 (47)	0.112
40–59	135 (57)	40 (51)	0.435
60 or more	15 (6)	1 (1)	0.142
Gender			
Females	222 (94)	71 (91)	0.502
Headache frequency (episodes)			
Until 2/week	146 (62)	57 (73)	0.097
3–5/week	73 (31)	15 (19)	0.064
More than 5/week	17 (7)	6 (8)	0.986
Headache severity			
Mild	1 (0)	2 (3)	0.311
Moderate	99 (42)	29 (37)	0.542
Severe	136 (58)	47 (60)	0.783
Headache location			
Bilateral	85 (36)	38 (49)	0.063
Unilateral	151 (64)	40 (51)	0.063
Accompanying symptoms			
Nausea	182 (77)	53 (68)	0.142
Photophobia	214 (91)	69 (88)	0.726
Phonophobia	199 (84)	59 (76)	0.117
Preventive medications			
Yes	131 (56)	30 (38)	**0.013**

Note: Bold values represent statistically significant p-values ($p < 0.05$).

TABLE 2 Triptan and non-triptan users self-reporting migraine triggers.

	Triptan users ($n=236$)	Non-triptan users ($n=78$)	p-Value
Alcoholic beverages	114	17	**<0.01**
Sweet foods and drinks	40	10	0.493
Artificial sweeteners	25	3	0.113
Chocolate	44	12	0.630
Fruit and vegetables	25	9	0.982
Foods or drinks of animal origin	22	7	0.894
Methylxanthine-containing products	15	7	0.596
Citric fruits	17	5	0.986
Red meat	18	3	0.369
Herbs and spices	22	9	0.726
Bakery products	7	3	0.991
Fish	7	1	0.686
Others	14	6	0.776

Note: Bold values represent statistically significant p-values ($p < 0.05$).

TABLE 3 The self-reported dietary triggers collected under the category "alcoholic beverages."

	Triptan users group	Non-triptan users group
Alcohol	53	9
Wine	19	0
Red wine	45	8
White wine	5	1
Beer	3	1
Gin	1	0
Liquor	2	0
Rosé wine	1	0
Sparkling wine	1	0

drinks aggravating migraine, compared with 19 out of 78 non-triptan users (24.4%) ($p=0.336$). The most common dietary aggravating factors reported by triptan users were alcoholic beverages ($n=34$, 14.4%) and sweets ($n=20$, 8.5%). The most common dietary aggravating factors reported by non-triptan users were sweets ($n=8$, 10.3%), chocolate ($n=8$, 10.3%), and alcoholic beverages ($n=7$, 9.0%). The number of triptan and non-triptan users reporting dietary aggravating factors is described in Table 5.

Recent consumption of red wine, chocolate, and citrus fruits

In the week preceding the completion of the survey, 218 out of 236 triptan users (92.4%, 95% CI: 89.0%–95.8%) reported no consumption of red wine, compared with 60 out of 78 non-triptan users (76.9%, 95% CI: 67.6%–86.3%) ($p<0.001$). Considering chocolate, 69 out of 236 triptans users (29.2%) reported no consumption of chocolate in the last week, compared with 23 out of 78 non-triptan users (29.5%) ($p=0.919$). Regarding citrus fruits, 111 out of 236 triptan users (47.0%) reported no consumption of citrus fruits in the last week, compared with 37 out of 78 non-triptan users (47.4%) ($p=0.945$).

DISCUSSION

Food–drug interactions are commonly observed as a consequence of accidental misuse or insufficient knowledge of the molecules involved in the interaction.[15] Less frequently discussed are interactions that can go the other way around, that is, drug therapies affecting nutrition. In this retrospective study, we found that alcoholic beverages, especially red wine, triggered more migraine headaches in triptan users. In addition, triptan users consumed significantly less red wine than non-triptan users in the week preceding the survey.

Triptans do not typically treat the underlying migraine disorder but eliminate the pain until the next attack occurs. When used in excess, triptans increase the risk for MOH in individuals with a history of migraine by increasing the sensitivity of sensory pathways and generating more pain.[16] A number of animal studies showed that a persistent exposure to triptans may alter neuropeptide expression and receptor function in the trigeminal ganglion, ultimately leading to an increased sensitization to certain stimuli.[17–20] In rats, triptans administered for one week induced a state of long-lasting sensitization demonstrated by an increased responsiveness of animals to an established trigger of migraine headache in humans.[18] These persistent neural adaptations promoted an increased sensitivity to environmental stress beyond the period of treatment with triptans.[18,19] Our retrospective survey found that individuals with migraine who regularly use triptans were more sensitive to alcoholic

TABLE 4 Triptan and non-triptan users self-reporting dietary relievers of migraine.

	Triptan users ($n=236$)	Non-triptan users ($n=78$)	p-Value
Sweet foods and drinks	69	19	0.492
Salty foods	20	5	0.732
Fruit and vegetables	2	4	0.055
Methylxanthine-containing products	9	7	0.134
Chocolate	3	2	0.788
Herbs and spices	5	1	0.993

TABLE 5 Triptan and non-triptan users self-reporting dietary aggravating factors of migraine.

	Triptan users ($n=236$)	Non-triptan users ($n=78$)	p-Value
Alcoholic beverages	34	7	0.298
Sweet foods and drinks	20	8	0.803
Chocolate	17	8	0.534
Fruit and vegetables	5	5	0.134
Foods or drinks of animal origin	8	1	0.565
Methylxanthine-containing products	13	3	0.778
Citric fruits	8	3	0.869
Red meat	5	2	0.833
Herbs and spices	6	2	0.686
Bakery products	4	1	0.788
Others	6	2	0.686

beverages than non-triptan users. Considering the self-reported dietary triggers collected under the category "alcoholic beverages," triptan users were particularly sensitive to red wine, a well-known trigger of migraine (Table 3).[21]

In the week preceding the completion of the questionnaire-based survey, triptan users consumed significantly less red wine than non-triptan users. 218 out of 236 triptan users reported no use of red wine in the week before survey, compared to 45 out of 236 triptan users reporting red wine as migraine trigger. This discrepancy may be due to several reasons, including an inaccurate or incomplete recollection of events by the respondents and the generation of similar answers ("alcohol," $n=53$; "wine," $n=19$) accentuated by the open-ended question related to migraine triggers. Similarly, 60 out of 78 non-triptan users reported no use of red wine in the week before survey, compared to 8 out of 78 non-triptan users reporting red wine as migraine trigger. Red wine contains a plethora of substances besides the alcohol itself that may trigger migraine, including histamine, tyramine, sulfites, and flavonoid phenols.[22] In a provocation study, 19 migraine individuals suspecting themselves to be sensitive to red wine were treated with a Spanish red wine (300 mL) or a vodka–lemonade mixture (300 mL) of equivalent alcohol content.[23] About 9 out of 11 individuals developed a migraine-like episode after red wine compared with none out of 8 individuals consuming the mixture of vodka–lemonade, suggesting that the migraine-provoking agent in alcoholic beverages is neither alcohol nor tyramine.[23,24] In contrast to white wine and beer, red wine is a powerful releaser of 5-HT from human platelets.[25–27] The released 5-HT may activate endothelial 5-HT_2 receptors in the cerebral vasculature, promoting the release of nitric oxide and provoking headache.[28] Despite a role of 5-HT_2 receptors in red wine-induced migraine has not been excluded,[29] the precise mechanism is still unclear.

The 5-HT receptors located in the trigeminovascular system are involved in migraine pathophysiology.[30,31] The complexity of serotonergic signaling is attributed to 7 main families (5-HT_1 to 5-HT_7) comprising 14 distinct receptors. The abortive activity of triptans prevents the release of vasoactive peptides through $5HT_{1B/1D}$ receptors expressed on presynaptic trigeminal afferents.[32] Other receptors, like 5-HT_2, are expressed at the vascular level and may mediate opposing effects. Fenfluramine and m-chlorophenylpiperazine are serotonergic agents binding to 5-HT_2 receptors that provoke migraine attacks in individuals with migraine.[33,34] We hypothesize that a regular intake of triptans may sensitize the vascular 5-HT_2 receptors involved in red wine-induced headache. In mice, chronic administration with a 5-HT_1 agonist (8-hydroxy 2-(di-n-propylamino) tetralin or 8-OH-DPAT) enhanced the activity of 5-HT_2 receptors in the hindbrain.[35] 8-OH-DPAT acts at presynaptic receptors rather than terminal sites, which is similar to

how triptans function.[36] Nowadays, no studies documenting a similar effect at the trigeminovascular level are available. Mechanistic studies in animals may clarify the effects of a chronic administration of 5-HT_1 agonists on trigeminovascular 5-HT_2 receptors.

Study limitations

Our retrospective study was exploratory, supporting a potential relationship between regular a consumption of triptans and an increased ability of red wine to induce migraine. However, a true causal relationship can only be established by properly conducted prospective studies. In addition, the baseline characteristics of triptan and non-triptan users were similar but not identical. The use of prophylactic drugs was greater in triptan users than in non-triptan users, with the most common medications being candesartan and β-blockers (Table S1). We cannot exclude those prophylactic medications affected the dietary habits of triptan users. The frequency of migraine attacks might have influenced our results, as more triptan users reported a frequency of 3–5 migraine attacks per week than non-triptan users (31% vs. 19%, $p=0.064$). Nonetheless, patients with chronic migraine are not more likely to report a migraine trigger than patients with episodic migraine.[37,38] Infusions of calcitonin gene-related peptide, a recognized trigger of migraine, induced similar proportions of migraine-like attacks in patients with episodic and chronic migraine (67% vs. 65%, respectively).[39] In the future, powered studies controlling for confounding factors may validate our observations.

CONCLUSION

In conclusion, triptan users reported alcoholic beverages, especially red wine, as more relevant migraine triggers than non-triptan users in a cohort of adults with migraine with and/or without aura. Red wine was less consumed by triptan users than non-triptan users, suggesting that the habitual use of triptans may exacerbate the migraine-triggering abilities of red wine.

AUTHOR CONTRIBUTIONS

LP conceived the idea. LP, LN, MCM, and MDBC planned and disseminated the survey. LP analyzed the data and took the lead in writing the manuscript. LN, MCM, and MDBC contributed to the interpretation of the results and drafted the manuscript. All authors provided critical feedback and helped shape the research, analysis, and manuscript.

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CONFLICT OF INTEREST STATEMENT

LP has been employed by Lundbeck in the past 2 years. LN, MCM, and MDBC report no conflict of interest.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Table S1.

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