



# Odorant substances that trigger headaches in migraine patients

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## Abstract

**Objectives:** Our objective was to determine odorants that trigger migraine attacks and the time of onset of headache after exposure.

**Methods:** Migraine or tension-type headache patients, diagnosed according to the criteria of the International Classification of Headache Disorders-II, were interviewed about lifetime prevalence of headaches triggered by odors and time of onset of pain, after exposure of the patient to the odor.

**Results:** We studied 200 migraine patients and 200 tension-type headache patients. There were odor-triggered headaches after  $25.5 \pm 1.9$  minutes of exposure in 70.0% (140/200) of migraine patients and none with tension-type headache, which ran at low sensitivity (70.0%, 95% CI 63.1–76.2) and high specificity (100.0%, 95% CI 97.6–100.0). Odor-triggered headaches are distributed in the following order of frequency: perfumes (106/140, 75.7%), paints (59/140, 42.1%), gasoline (40/140, 28.6%) and bleach (38/140, 27.1%). There was significance in the association of odor-triggered migraine, especially among perfume with cleaning ( $\phi = -0.459$ ), cooking ( $\phi = 0.238$ ), beauty products ( $\phi = -0.213$ ) and foul odors ( $\phi = -0.582$ ).

**Conclusions:** Odorants, isolated or in association, especially perfume, may trigger migraine attacks after a few minutes of exposure.

## Keywords

Migraine, odors, osmophobia, migraine triggers

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## Introduction

In general, odors are a result of the action of volatile molecules, either organic or mineral, with distinct physicochemical properties that, acting as a stimulus to the olfactory system, trigger impulses that are transmitted to the brain (1,2).

There are three known characteristics of odors: the character or quality, corresponding to a rating scale of measurement in which a person recognizes the odor as similar to one of his or her own repertoire; the intensity and concentration, which are equivalent to the strength of the perception of odor; and the hedonic tone assessment, defined as the measurement of the pleasantness of odor (3).

Odorant substances well tolerated by the general population may trigger headache attacks in migraine patients (4–8), even in low concentrations.

This fact is relevant because in migraine, a chronic neurological disease with 15.2% prevalence in Brazil (9), headaches are associated with nausea or vomiting,

photophobia, phonophobia, dizziness and osmophobia (4,10,11), with an intensity that may incapacitate the patient from performing daily activities.

The migraine attacks may be triggered by various factors, including odors. However, odors as migraine triggers have been insufficiently studied. This is the first study to specifically determine the odorant substances that trigger migraine attacks and the time of onset of headache after exposure.

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## Patients and methods

### Study design and patients

This was a retrospective study with comparison of groups. The study population comprised a nonrandom and convenience sampling, consisting of the first 200 migraine patients and 200 tension-type headache patients (comparison group) treated at a headache clinic in the city of Teresina in northeastern Brazil. Data for this study were collected from August to December 2011.

### Inclusion and exclusion criteria

Patients aged between 18 and 60 years, with migraine or tension-type headache, according to the diagnostic criteria of International Classification of Headache Disorders, second edition (ICHD)-II (12), and presence of headache in the last six months at a frequency less than 15 days per month were included in the study.

In order to obtain consistent and valid data, the study excluded patients without a headache in the last six months, association between migraine and tension-type headaches, concomitantly or at different times, the presence of other primary or secondary headaches, the presence of associated diseases or the use of medications that might impair olfaction, and pregnant women.

### Data collection

The patients underwent a thorough standard medical history performed by a headache specialist to record the typical characteristics of their pain over the past six months. Having met the criteria for inclusion and exclusion, patients were invited to participate in the study by signing the informed consent form. There was, then, a structured interview based on a questionnaire to investigate the research objectives; excluded at this stage were uncooperative patients or those who answered the interview incompletely.

The interview consisted of questioning the patients about odorant substances that trigger headaches at least once in a lifetime, as well as time of onset of pain after exposure. Such substances were divided into eight categories: fetid odor, perfumes, oil derivatives, insecticides, cleaning, culinary and beauty products, among others.

### Statistical analysis

Once the information was organized in the database, the Statistical Package for Social Sciences (SPSS®) version 17.0 for statistical analysis was used. The chi square test with Yates correction, Fisher's exact test

and Mann-Whitney test for differences between averages of unpaired samples were used, besides the phi coefficient of contingency for nominal variables, assuming a significance level of 0.05. Sensitivity and specificity parameters and positive and negative predictive value were determined.

### Ethical aspects

This study was approved by the Ethics in Research Involving Human Subjects Committee at the State University of Piauí, Brazil, protocol number 049/11 and the National Ethics in Research System, registry number 439715. All patients signed the informed consent form.

## Results

There were 400 patients averaging  $38.6 \pm 9.9$  in age (95% confidence interval (CI) 37.7–39.6) and ranging from 22 to 58 years old, 219 (54.7%) of whom were women, which corresponded to the sex ratio of 0.83:1 male/female.

Two hundred patients (50.0%) were diagnosed with tension-type headache and 200 (50.0%) with migraine, whose distribution differed according to sex and age, as observed in Table 1. Tension-type headache was predominant in men, with a 4.4:1.0 ratio male/female, whereas in migraine this ratio equaled 0.1:1 ratio, thus, predominantly female. These differences were significant. Regarding age, tension-type headache was present in patients age  $40.0 \pm 10.4$  years old, while migraine was diagnosed in younger patients age  $37.3 \pm 9.0$  years old, and these differences were significant.

The triggering of headaches by odors occurred in 140/200 (70.0%) migraine patients and in none of the tension-type headache patients (0/200), and it had low sensitivity (70.0%, 95% CI 63.1–76.2) and high specificity (100.0%, 95% CI 97.6–100.0). The pain occurred  $25.5 \pm 1.9$  minutes after exposure of the patient to odor. The median latency was equal to 10 minutes, meaning that in 50% patients, the pain appeared before 10 minutes and in 50%, after 10 minutes of exposure.

The odors were referred to as triggering factors for headache in the following order of frequency: perfumes (106/140; 75.7%), paints (59/140; 42.1%), gasoline (40/140; 28.6%) and bleach (38/140; 27.1%). The triggering time of the headache attacks were not statistically significant (Table 2).

The patients reported headache attacks triggered by more than one odorant substance, but this occurred at different times. Perfumes were associated with cleaning products, cooking products, beauty products and fetid odors; cleaning products were associated with oil

**Table 1.** Distribution of sex and age according to diagnosis of 200 patients with migraine and 200 with tension-type headache.

Variables	Diagnosis		<i>p</i> value
	Migraine	TTH	
Sex			<0.001 <sup>a</sup>
Female (n; %)	182 (83.1)	37 (16.9)	
Male (n; %)	18 (9.9)	163 (90.1)	
Age (years)			0.008 <sup>b</sup>
Average	37.3 (9.0)	40.0 (10.4)	
95% CI	36.0–38.6	38.5–41.4	
Mean (interquartile semi-amplitude)	39.0 (8.0)	39.0 (8.0)	
Variation	22–58	22–58	

TTH: tension-type headache; CI: confidence interval. <sup>a</sup>*p* value based on the chi square test. <sup>b</sup>*p* value by the Mann-Whitney test for average difference test between averages of unpaired samples.

derivatives, cooking products and fetid odors; oil derivatives were associated, exclusively, with cooking products; insecticides were associated with other odors, as well as the cooking products. These associations were significant (Table 3).

## Discussion

In migraine, the attacks may be triggered by many identifiable factors and, in most cases, in multiples for the same patients. Among these factors, the ones that most frequently trigger pain are stress, hormonal changes (ovulatory or premenstrual period, menopause and hormone replacement therapy), deprivation or excessive sleep, eating habits (long fasting periods or ingestion of certain foods, food additives or alcohol), physical exertion (sexual activity, coughing, sneezing, bowel movement and weight lifting) (10,13–16). Besides these factors, many patients may present with headache attacks triggered by sensorial stimulation, such as luminosity, noises or exposure to some types of odorant substances (5,7,10,17–22).

The two groups were not randomly selected. Thus, migraine occurred more often in women and tension-type headache in men. Despite the predominance of women in studies on odors (7,18,20) and evidence that women outnumber men in olfactory identification (23,24), we do not believe that this has an impact on our results because a study (25) that evaluated the role of odors in migraine exclusively in men showed that 48% have headaches triggered by odors, and mainly by perfume, similar to women.

The olfactory processing is altered during headache attacks in migraine patients, suggesting that there are specific neuronal connections between the olfactory and trigeminal nociceptive system (26) because most odors are bimodal, i.e. activating trigeminal and olfactory

nerves (27). The trigger mechanism of the headache by odors in tension-type headache patients is unknown. A study by functional magnetic resonance imaging (fMRI) during headache attacks in migraine patients and normal subjects showed increased activity of the limbic system and brainstem in response to olfactory stimulation only in migraine patients (26).

There is another hypothesis that the olfactory stimulus excites the locus coeruleus in migraine patients and causes norepinephrine release. Consequently, substance P and calcitonin gene-related peptide (CGRP) are released. These two potent and inflammatory vasodilatory substances trigger the painful phenomenon (28).

Recent studies have shown that inhalation of certain odors can cause severe attacks of headache through stimulation of transient receptor potential ankyrin 1 (TRPA1), a nonselective cation channel expressed in sensory neurons, and activation of the trigeminovascular system. Consequently, there are nociceptive responses and calcium-dependent release of CGRP from trigeminal nerve terminals in the dura mater. Furthermore, TRPA1 activation can activate dural nociceptors and lead to central sensitization and cutaneous allodynia (29,30).

It was confirmed that odorant substances triggered migraine attacks in most of the patients at least once in a lifetime. Headache was typical of migraine patients, i.e. it was associated with nausea and/or vomiting, photophobia and phonophobia. A high percentage of headaches triggered by odors was also found by other authors (31,32). However, there was disagreement in other studies in which the authors reported different percentages ranging from 25.3% to 46.0% (4,13,18).

In the literature review, we found no studies in which tension-type headache patients describe attacks triggered by odors. Tension-type headache patients may report intolerance to odors during crises, but no

**Table 2.** Distribution of odors and latency times to trigger headache, isolated or in association, in 140 migraine patients.

Groups odor	Frequency of the association of odors <sup>a</sup>		Frequency of single odor		Latency time (min)
	n	%	n = 140	%	
Perfumes	106	75.7	43	30.7	23.5 ± 2.0
Floral	21	15.0	8	5.7	
Citric	3	2.1	—	—	
Cleaning products	69	49.3	25	17.9	22.4 ± 2.3
Bleach	38	27.1	12	8.6	
Deodorizer	29	20.7	7	5.0	
Air freshener	12	8.6	3	2.1	
Detergent	6	4.3	2	1.4	
Soap	3	2.1	1	0.7	
Fabric softener	1	0.7	—	—	
Oil derivatives	46	32.9	16	11.4	21.9 ± 2.7
Gasoline	40	28.6	14	10.0	
Kerosene	5	3.6	—	—	
Diesel oil	4	2.9	2	1.4	
Kitchen gas	1	0.7	—	—	
Cooking products	21	15.0	6	4.3	15.9 ± 3.5
Fried food	3	2.1	2	1.4	
Fish	2	1.4	2	1.4	
Coffee	2	1.4	1	0.7	
Meat	2	1.4	—	—	
Garlic	2	1.4	—	—	
Cooking oil	1	0.7	—	—	
Other food	5	3.6	1	0.7	
Fetid odor	16	11.4	4	2.9	23.3 ± 4.8
Sewer	4	2.9	2	1.4	
Sweat	3	2.1	2	1.4	
Animal feces	1	0.7	—	—	
Animal carcass	1	0.7	—	—	
Other	3	2.1	—	—	
Insecticides	10	7.1	7	5.0	17.1 ± 5.6
Naftalin	2	1.4	2	1.4	
Carbamate (Baygon <sup>©</sup> )	2	1.4	1	0.7	
Any type	5	3.6	4	2.9	
Beauty products	2	1.4	2	1.4	35.0 ± 25.0
Nail polish	2	1.4	2	1.4	
Other odors	93	66.4	37	26.4	22.8 ± 2.0
Paints (varnish)	59	42.1	24	17.1	
Smoke cigarette	48	34.3	9	6.4	
Other odors	4	2.9	4	2.9	

<sup>a</sup>They were not able to describe perfumes in 82 cases (77.4%); cooking products, four cases (19.0%); fetid odors, four cases (25.0%); and insecticides, one case (10.0%).

**Table 3.** Association between odors that trigger headaches in 140 patients with migraine.

Perfumes (n = 106)			
Odors that trigger headaches	n	%	Coefficient phi
Cleaning products	38	35.8	-0.459
Oil derivatives	31	29.2	—
Insecticides	10	9.4	—
Cooking products	21	19.8	0.238
Beauty products	—	—	-0.213
Fetid odor	1	0.9	-0.582
Other odors	69	65.1	—

  

Odors that trigger headaches	Cleaning products (n = 69)	Coefficient phi	
	n	%	
Oil derivatives	30	43.5	0.223
Insecticides	4	5.8	—
Cooking products	15	21.7	0.186
Beauty products	2	2.9	—
Fetid odor	14	20.3	0.275
Other odors	46	66.7	—

  

Odors that trigger headaches	Oil derivatives (n = 46)	Coefficient phi	
	n	%	
Insecticides	3	6.5	—
Cooking products	12	26.1	0.217
Beauty products	—	—	—
Fetid odor	2	4.4	—
Other odors	28	60.9	—

  

Odors that trigger headaches	Insecticides (n = 10)	Coefficient phi	
	n	%	
Cooking products	1	10.0	—
Beauty products	—	—	—
Fetid odor	—	—	—
Other odors	3	30.0	-0.214

  

Odors that trigger headaches	Cooking products (n = 21)	Coefficient phi	
	n	%	
Beauty products	—	—	—
Fetid odor	—	—	—
Other odors	18	85.7	0.172

  

Odors that trigger headaches	Fetid odor (n = 16)	Coefficient phi	
	n	%	
Other odors	12	75.0	—

headache was triggered by odors. These findings confirmed that odors are used to differentiate migraine from tension-type headache (16,18).

Other authors (18) report that osmophobia during migraine attacks includes different odors, while the

olfactory stimuli as trigger is more individualized, since in most cases only one odor is identified.

There is a correlation between headache triggered by odors and osmophobia, both during the attack and in the period between episodes. In our experience, in the

Name: _____			
Age: _____ years	Sex: <input type="checkbox"/> female	<input type="checkbox"/> male	<input type="checkbox"/> tensional-type headache
Diagnosis: <input type="checkbox"/> migraine			
During the crisis of headache, do you present osmophobia?			
<input type="checkbox"/> yes	<input type="checkbox"/> no	<input type="checkbox"/> no information	
In the period between attacks, do you present osmophobia?			
<input type="checkbox"/> yes	<input type="checkbox"/> no	<input type="checkbox"/> no information	
Beside osmophobia, do you have those symptoms associated with pain?			
<input type="checkbox"/> nausea and/or vomiting	<input type="checkbox"/> photophobia/phonophobia		
In the period between attacks, do you present headaches triggered by odors?			
<input type="checkbox"/> yes	<input type="checkbox"/> no	<input type="checkbox"/> no information	
<b>Continue the questionnaire if answered "yes" to the previous question</b>			
How long the headache arises after exposure to the odor? <input type="checkbox"/> Hours <input type="checkbox"/> minutes <input type="checkbox"/> seconds <input type="checkbox"/> no information			
What are the smells that trigger headaches?			
<input type="checkbox"/> Perfume (which?) <input type="checkbox"/> citric <input type="checkbox"/> herbal <input type="checkbox"/> musk <input type="checkbox"/> wood <input type="checkbox"/> floral <input type="checkbox"/> no information			
<input type="checkbox"/> Cleaning products (which?) <input type="checkbox"/> bleach <input type="checkbox"/> fabric softener <input type="checkbox"/> alcohol <input type="checkbox"/> deodorizer <input type="checkbox"/> detergent <input type="checkbox"/> other <input type="checkbox"/> soap <input type="checkbox"/> air freshener <input type="checkbox"/> no information			
<input type="checkbox"/> Oil derivatives (which?) <input type="checkbox"/> gasoline <input type="checkbox"/> kerosene <input type="checkbox"/> other <input type="checkbox"/> diesel oil <input type="checkbox"/> kitchen gas <input type="checkbox"/> no information			
<input type="checkbox"/> Insecticides (which?) <input type="checkbox"/> naftalin <input type="checkbox"/> carbamate <input type="checkbox"/> any			
<input type="checkbox"/> Cooking products (which?) <input type="checkbox"/> fried food <input type="checkbox"/> fish <input type="checkbox"/> other condiments <input type="checkbox"/> cooking oil <input type="checkbox"/> coffee <input type="checkbox"/> other food <input type="checkbox"/> meat <input type="checkbox"/> garlic <input type="checkbox"/> no information			
<input type="checkbox"/> Beauty products (which?) <input type="checkbox"/> nail polish <input type="checkbox"/> hair dye <input type="checkbox"/> other <input type="checkbox"/> acetone <input type="checkbox"/> makeup products <input type="checkbox"/> no information			
<input type="checkbox"/> Fetid odor (which?) <input type="checkbox"/> sweat <input type="checkbox"/> animal feces <input type="checkbox"/> other <input type="checkbox"/> sewer <input type="checkbox"/> animal carcass <input type="checkbox"/> no information			
<input type="checkbox"/> Other odors (which?) <input type="checkbox"/> cigarette smoke <input type="checkbox"/> camphor <input type="checkbox"/> other <input type="checkbox"/> paints (varnish) <input type="checkbox"/> mint <input type="checkbox"/> no information			

**Figure 1.** Study protocol.

study we are carrying out, osmophobia is present prospectively in 86% (172/200) of migraine patients during attacks, and in 24% (48/200) in the period between attacks. Headache triggered by odors was observed in 74.4% (128/172) of those who had osmophobia during the attack, and in 87.5% (42/48) when the osmophobia occurred in the period between attacks. The patients reported intolerance to any odor.

In the present study, we observed that the olfactory stimulus was individualized. However, in many patients the headache was triggered by more than one odor, but this occurred at different times.

The characteristics of intensity, character and hedonic tone of odors were not applied as criteria to determine the onset of pain. However, the hedonic tone seems to be the most important since there was a predominance of perfume, a pleasant odor. Several authors have reported similar results when they affirm that perfumes, more frequently trigger pain, followed by oil derivatives and cleaning and cooking products (4,7,10,13,18,19).

Although most of our patients have reported perfume as the main odorant substance triggering headaches, only a minority was able to distinguish the

fragrance as being from a floral or citric source. In a similar study in which there was a detailing of fragrances, the type of perfume was also distinguished by a minority of patients (18).

It was also possible to discriminate statistically significant associations from several categories of odorant substances in the triggering of headaches, but this occurred at different times. In other studies, there were also associations with two or more odors in percentages ranging from 63.8% to 64.7% of the patients (10,18).

Many patients had headache attacks triggered by more than one odor but not concurrently. We have calculated the latency between exposure to an odor and onset of headache only for patients who cited a single odor. From these latencies, it was possible to calculate the mean latency of the group of odors.

Therefore, one single latency was recorded in the study protocol (Figure 1).

In our study, pain occurred within minutes after patient exposure to the odor. These data are confirmed by a single study conducted to determine the time of the onset of pain, in which its authors reported that 68.4% of the patients presented headache in less than 20 minutes after exposure to the odors (10).

## Conclusions

The odorant substances, isolated or in association, that triggered migraine attacks, ranked by frequency were: perfumes, paints, gasoline and bleach. Headache occurred within a few minutes after exposure to the odor.

### Clinical implications

- Odors trigger headaches in migraine but not in tension-type headache patients.
- Odors trigger migraine attacks after a few minutes of exposure.

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### Conflict of interest

None declared.

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