Curr Pain Headache Rep (2011) 15:177–184
DOI 10.1007/s11916-011-0184-4

Alcohol and Migraine: What Should We Tell Patients?

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Published online: 19 February 2011

Abstract Alcoholic drinks are a migraine trigger in about one third of patients with migraine in retrospective studies on trigger factors. Many population studies show that patients with migraine consume alcohol in a smaller percentage than the general population. Moreover, research has shown a decreased prevalence of headache with increasing number of alcohol units consumed. The classification criteria of alcohol-related headaches remain problematic. We discuss the role and mechanism of action of alcohol or other components of alcoholic drinks in relation to alcohol-induced headache. In accordance with data from a recent prospective study, we believe that reports overestimate the role of alcohol, as well as other foods, in the triggering of migraine. If a relationship between the intake of alcohol and the migraine attack is not clear, a small dose of alcohol is not contraindicated either for enjoyment or its protective effect on cardiovascular disease.

Keywords Hangover · Migraine · Headache · Alcohol · Headache classification criteria · Trigger factors · Wine · Serotonin · Serotonin release · Alcohol consumption · Congeners · Vasodilatation · Lifestyle

Introduction

Three of four migraineurs spontaneously identify a triggering factor for their headache, while roughly the total (95%) identify one when asked to respond to a specific trigger list. Almost two of three migraineurs report four to nine triggers [1•]. Retrospective studies identify a wide number of dietary triggers, with about one of three migraineurs sensitive to alcohol [2, 3••]. A recent retrospective study shows that a very high percentage (40%) of patients with migraine with aura report alcohol as a trigger [4]. From these studies, it appears that known triggers have a preponderant role in migraine.

Many foods are considered capable of triggering a migraine attack, but the relationship is frequently equivocal [2, 5]. On the contrary, lists of triggers induce the migraineur to correlate their migraine attack with a food just consumed. This is similar to crediting, in an undiscriminating way, a new symptom to a drug recently taken. A food may be likely considered a trigger of a migraine attack if (a) a strict time relationship exists between the consumption and the start of headache, and (b) this correlation is frequent and not only occasional. From retrospective patient reports, it is very difficult to be sure a link exists. In fact, especially in the drug–new symptom example, a possible link to other frequent triggers must be considered. For the migraineur, a few of these triggers include stress, poststress, fear, anxiety, menstruation, sleep, exercise, and weather changes. There are no studies unequivocally showing the involvement of a food. When chocolate was studied to assess a chocolate trigger–headache link, no connection was found with migraine and tension-type headache. Perhaps only alcohol has been considered a sure migraine trigger, but its importance still is debated [3••]. Various aspects of the alcohol–migraine relationship recently were reviewed [3••]. This article discusses the problem of alcohol-induced headache, particularly regarding classification and pathogenetic mechanisms.

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How Is Alcohol Important as a Trigger of Migraine?

In retrospective studies in different countries, about one third of patients with migraine report alcohol as a migraine trigger [3••]. However, recent studies show that alcohol acts as a trigger at least occasionally in a percentage similar to the older studies, and as a frequent/consistent trigger in only 10% of patients [1•]. Curiously, in Japan and Turkey, the percentages of alcohol or wine as migraine triggers were negligible, perhaps dependent on the degree of alcohol as a habit. No sex differences exist in alcohol susceptibility, and the great majority of studies show no differences between migraine with or without aura and between migraine and tension-type headache [3••]. A recent retrospective questionnaire study shows that alcoholic beverages are a trigger in at least 40% of patients with migraine with aura [4]. A paper reports higher alcohol sensitivity (50–80% of cases) in patients with cluster headache [6••]. That alcohol is a common trigger of headache in the principal types of primary headaches may suggest that these headaches share a pathogenetic mechanism and that this trigger acts at the start of the pathway involved in headache provocation.

Recently, a prospective study in Austria examined a wide spectrum of factors related to migraine through the application of a sophisticated statistical analysis. This study provided limited evidence for the importance of nutrition (comprising alcoholic beverages) in the precipitation of migraine [7•].

Alcohol in the Headache Classification of the International Headache Society

In the 2004 International Classification of Headache Disorders (ICHD 2004), there are several references to alcohol correlation with primary headaches [8]. The ICHD 2004 states that (1) "trigger factors increase the probability of a migraine attack in the short term (usually <48 h) in a person with migraine;" and, (2) migraine may be aggravated by a number of factors including frequent intake of alcoholic beverages, which may be associated with a long-term increase in headache severity and frequency for months. In addition, commenting on cluster headache, the ICHD 2004 affirms that during the cluster period, and in the chronic subtype, attacks may be provoked by alcohol. The ICHD 2004 does not mention alcohol interference with tension-type headache.

The ICHD 2004 secondary-headaches section includes alcohol-induced headache under "Headache attributed to a substance or its withdrawal." The introduction of this chapter states that alcohol and foods have been reported to provoke or activate migraine in susceptible individuals, but this does not prove causation because these two common events happen commonly and the association may be mere coincidence. It also declares that patients with migraine and other primary headache are more susceptible than nonheadache patients. The ICHD 2004 describes two types of headache: the "immediate alcohol-induced headache" (IAIH) and the "delayed alcohol-induced headache" (DAIH). The diagnostic criteria of IAIH require the ingestion of a beverage containing alcohol and the development of headache within 3 h, with at least one of the following characteristics of headache: bilateral; frontotemporal location; pulsating quality; and/or aggravated by physical activity. The criteria do not require other migraine criteria such as nausea, vomiting, phonophobia, and photophobia, but do not exclude these. Therefore, a headache attack with the features of tension-type headache and/or migraine may correspond to these criteria. However, in 2009, a proposal for changes to the general criteria for secondary headaches requests headache of any type [9], thus correcting this artificial specification of headache characteristics.

It is written that few patients develop IAIH, that a direct effect of alcohol or the alcoholic beverage causes the headache, and that this type of headache is much rarer than DAIH, previously called "hangover headache." The diagnostic criteria for the DAIH require the ingestion of a modest amount of alcoholic beverage by a migraineur or an intoxicating amount by nonmigrainous patients. Additionally, the headache develops after the blood alcohol level declines or falls to zero. The clinical characteristics are the same for the IAIH.

The ICHD 2004 affirms that if a new headache occurs for the first time in close temporal relation to another disorder that is known to cause headache, this headache is coded according to the causative disorder as a secondary headache. However, when a preexisting primary headache is made worse in close temporal relation to another disorder that is a known cause of headache, the patient can be given either only the diagnosis of preexisting primary headache or both the primary headache diagnosis and the secondary headache diagnosis, in the last case if a very close relationship exists (e.g., very close temporal relation, marked worsening, improvement after disappearance of the causative disorder).

What Problems Exist for the ICHD-2004 Criteria of Headache Triggered by Alcohol?

If alcohol ingestion by a diagnosed migraineur causes headache meeting their usual, or at least probable, migraine criteria within a few hours (IAIH), the patient and providers of care can consider alcohol the trigger of this typical

migraine attack. But, if the IAIH in this patient corresponds to the criteria of tension-type headache, how should this headache be classified? The same observation must be contemplated for DAIH in the migraineur. This problem seems solved with the proposed changes to general criteria for secondary headache, which request headache of any type [9]. However, if we consider alcohol one of the many migraine triggers, alcohol-provoked headache (immediate and delayed) should not be classified in the secondary headaches. Theoretically, the IAIH and DAIH (that is, secondary headaches) can be surely diagnosed only in nonheadache patients. In fact, another problem is the differentiation between DAIH and a migraine attack triggered by alcohol in diagnosed migraine patients (see later). An unsolved question is whether nonheadache patients can have IAIH.

What is the Interval from Alcohol Consumption to the Start of Headache?

Generally, studies on alcohol-induced migraine have not made a distinction between IAIH and DAIH. In migraineurs, this distinction can be partially artificial and difficult to assess. As previously proffered, an onset interval may vary from a few minutes to 24 h [3••]. Furthermore, headaches appear frequently the next morning/day with the confounding effect of sleep on the interval determination [3••]. A prospective study revealed that alcoholic drinks are not a risk factor for headache when considering alcohol and other trigger factors taken from the day before onset of headache [7•].

In some migraineurs, alcohol can precipitate a migraine attack within a few (about 3) hours [10]. This should be considered the typical headache induced by alcoholic drinks, and some migraineurs can be sensitive to very small amounts of alcohol. The other type of alcohol-related headache in migraineurs is DAIH, previously named hangover headache, appearing in the morning after alcohol intake, when the blood alcohol concentration is falling and reaches zero. The differentiation between DAIH and migraine triggered by alcohol consumption may be difficult [11]. In fact, some alcohol hangover symptoms other than headache, such as nausea, anorexia, tiredness, and general malaise, are very common in a migraine attack. However, this distinction is more academic, perhaps incorrectly, than clinically useful.

DAIH can be experienced by a patient who does not have a specific headache disorder. In fact, a population study reports a high (70%) lifetime prevalence [12]. The frequencies of hangover and related symptoms depend on various factors, such as the volume and type of alcoholic drinks, drinking practice, sex, and experimental study, making this condition difficult to study. Headache is present in about two thirds of patients with alcohol hangover after a night of moderate alcohol consumption at a targeted breath alcohol level [13]. In a survey on the prevalence of hangover symptoms after drinking among college students, about two thirds report headache in the past year (occasionally in 41% and most or every time in only 8%) [14]. From another survey among university students, 28.4% experienced DAIH after high beer intake [15]. Women report DAIH more frequently than men [14, 15].

It is a common opinion that DAIH can be experienced by anyone, but traditionally, this opinion considers migraineurs more susceptible. Furthermore, patients with migraine can develop headache with the ingestion of modest amounts of alcoholic beverages. A recent study confirms that patients with migraine, but not tension-type headache, have an increased risk (OR: 6) of DAIH [15]. However, the characteristics of headache and the frequency of associated symptoms were not different among migraineurs and nonmigraineurs [15]. Therefore, hangover headache could account for a more or less large proportion of alcohol-related migraine in retrospective study reports. It seems reasonable to include DAIH (hangover headache) in the secondary headaches, even if migraineurs have an increased risk and require lesser alcohol doses. Perhaps alcohol should be considered only a possible migraine trigger if it causes headache within a few hours (IAIH), without the inclusion of this alcohol-related headache in the secondary headaches.

Alcohol Consumption in Migraine

Because alcohol can trigger a migraine attack, perhaps only a small number of migraineurs should drink alcohol. Population-based studies performed in various countries show an inverse relationship between alcohol and migraine. A smaller percentage of migraineurs consume alcohol than control patients, and drinkers have migraine and other headache less frequently. Moreover, there are significant trends of decreasing prevalence of migraine and non-migraine headache with the increasing number of alcohol units consumed [3••, 16–18•, 19–21]. Furthermore, the frequency of migraine attacks is inversely correlated with the frequency of alcohol ingestion [18•]. Some studies have shown a correlation between the type of alcoholic drink and risk of headache. A report shows a reduced prevalence of migraine and nonmigraine headache in drinkers of wine but not beer [17], while other studies report that beer reduces the risk [7•]. Conversely, in a recent survey in adolescents, researchers significantly associate a high consumption of cocktails with headache/migraine [22].

A possible explanation for the inverse association between alcohol use and headache disorders is that patients with headache abstain from alcohol because it is a trigger for their headache attacks. In this view, genetic polymorphisms of the enzymes metabolizing alcohol, alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH), were reported to be correlated with the risk for triggering a migraine attack after alcohol consumption [20, 23]. The allelic variant ADH2 His (ADH2*2) was significantly higher in patients reporting triggering of migraine by alcohol compared with those with no effect [23]. Curiously, this allelic variant has been repeatedly associated with reduced alcohol consumption and lowered risk of alcohol dependence [24]. Conversely, an Italian study seems not to support this explanation [3••]. Only a very small percentage of non–alcohol consuming female migraineurs report that alcoholic drinks were a trigger in the past. This per se does not justify the large difference in the percentage of alcohol consumers between the migraine population studied and general populations in that country [3••]. Other explanations of the inverse relationship between alcohol consumption and headache can be the development of headache tolerance in drinkers or the stress reliever activity of alcohol [20].

Is Alcohol Per Se, or a Component of Alcoholic Drinks, the Headache Trigger?

Littlewood et al. [10] show that 300 mL of red wine, but not vodka with an equivalent alcohol content, provoked headache in red wine–sensitive migraineurs within 3 h after administration, but not in nonsensitive migraineurs or control patients. They suggest that red wine contains a migraine-provoking agent that is not alcohol. Because red wine has been considered the most frequent trigger among alcoholic drinks in some countries, many studies have been conducted to characterize this agent in the years after this report. Studies in France and in Italy report white wine as the major culprit, but also list spirits, sparkling wine, and beer as triggers [3••].

Research has not yet definitely clarified the fundamental question whether it is alcohol per se or a component of alcoholic drinks that is responsible for triggering headache. It is difficult to answer this question. To provoke a migraine attack, a combination of factors may be necessary. These may include a given blood/brain alcohol level, degree of brain hypersensitivity, and the presence or absence of other triggers. Perhaps this combination activates the pathway necessary for headache to become active. Otherwise, if alcohol per se is not directly involved in the pathogenetic mechanism, a substance present in the different alcoholic drinks could be itself responsible, or, however, could facilitate the alcohol effect.

Authors and researchers have considered several components of alcoholic beverages as possible triggers of the migraine attack. Studies cogently showing the involvement of tyramine, phenylethylamine, histamine, sulphites, and flavonoid phenols are lacking or are negative [3••]. Most inferences on their possible role derive from the correlation of the different content of the various alcoholic beverages with the capability to trigger the migraine attack shown by different alcoholic drinks, although the last statement needs verification.

Histamine is an indicator of hygienic food quality and is considered in research frequently. Intravenous histamine infusion is a traditional test able to provoke a migraine attack. Various foods such as fish, aged cheese, meat (sausage, salami), and vegetables (eggplant, sauerkraut, spinach) contain much higher amounts of histamine than alcoholic drinks. In addition, many foods, including alcohol, may release histamine from endogenous deposits (mast cells). However, other than headache, many symptoms of the so-called histamine intolerance are not characteristic of the migraine attack, and antihistamine drugs do not prevent red wine headache. The same observations made on histamine are valid for sulphites because much higher amounts are found in many foods (e.g., dried fruits, chips, raisins, soy sauce, pickles, juice fruits) compared to wine, and the so-called sulphite sensitivity provokes an asthmatic response rather than headache. The relation between tyramine, which is a biogenic amine, and migraine has been studied most extensively with negative results found. In addition, the tyramine content of wine is negligible (1–2 mg/L) in comparison with the tyramine doses utilized in oral challenge studies (100–200 mg). Phenolic flavonoids, a fraction of the tannins and part of the so-called congeners, by-products of alcohol fermentation, have been suggested as responsible for triggering the migraine. Darker drinks, such as whiskey, brandy, and red wine, have more congeners than clear drinks, such as vodka, gin, and white wine. However, certain studies show white wine more frequently involved than red wine. Congeners may increase the severity of hangover [25, 26]. Recently, bourbon with 37 times the amount of congeners compared to vodka caused a worse hangover than vodka based on an increase in the hangover intensity felt. Bourbon did not appear to increase risk or incidence [13, 27••]. However, data on the different incidences of hangover headache with different drinks exist. One old study reports that headache in hangover was 9% after 2 oz of whisky and 2% after the same amount of vodka [28]. The lack of a role for congeners in hangover headache recently was suggested in an animal model of migraine [29]. Rats that received dural

stimulation followed by alcohol showed an initial analgesic effect within the first 2 h after alcohol ingestion, but 4–6 h later, their pain sensitivity increased. Similarly, experiments in humans have shown that intravenous alcohol has an analgesic effect with increased pain sensitivity found in alcohol withdrawal [30, 31].

The decisive proof of whether alcohol itself is capable of provoking IAIH and DAIH would appear from studies with alcohol administration. There is considerable intersubject variability in alcohol concentrations when the drug is consumed orally. Experiments with an "alcohol clamp," a method of infusing alcohol to achieve and maintain a target breath/blood alcohol level for a prolonged time (3 h), do not report migraine within the 8 h of the typical session study in several hundred patients [24, 32]. These studies included healthy patients who probably do not suffer from migraine, although this was not specified in the exclusion criteria. In these experiments, migraine headache was generally not reported nor, surprisingly, were other hangover symptoms, even at blood alcohol concentration above 100 mg/dL (0.1%). One dose-dependent exception occurred in a migraineur on two out of six occasions. Only a few cases (about 15%) reported very mild and transient headache in the hours after a 3-hour clamp, perhaps as a function of withdrawal (Zimmermann US, O'Connor S, 2010, personal communications). Another alcohol-clamping procedure study in 60 medically and neurologically healthy patients did not report headache among patients within 1 h [30]. Experiments with this technique in migraineurs should be of much interest.

Alcohol per se probably is the trigger of migraine, with vasodilatory action being the mechanism frequently suggested. Research suggests both endothelial nitric oxide (NO) and calcitonin gene–related peptide (CGRP) release from perivascular sensory nerve terminals as the alcohol vasodilatation mechanism [33, 34]. As seen in an animal study, alcohol provokes neurogenic inflammation in the trigeminovascular system by mimicking capsaicin and vasodilates meningeal vessels through CGRP release [35•]. Alternatively, debate exists about the role of polyphenols in NO production and arterial vasodilatation [3, 36, 37].

A hemodynamic study in humans shows a similar acute brachial artery dilatation with a single dose (1–2 drinks) of ethanol and red wine, but curiously, a significant dopamine increase in the plasma only after red wine [38•]. Contradictory data exist regarding the effect of alcohol on the vascular system, which varies with the dose and time of evaluation. One study shows a biphasic alcohol effect on systolic and diastolic blood pressure, with a decrease at 4 h followed by an increase after 13 h, and brachial artery dilatation only after 4 h [39]. High blood alcohol concentrations lead to vasoconstriction, while lower doses have both vasodilative and vasoconstrictive activity on the cerebral vessels. An increase in the cerebral blood flow (CBF), probably through vasodilatation of small arteries, occurs 30 min after ethanol administration in healthy patients as seen with Doppler ultrasonography. This supports previous studies with positron emission tomography and single photon emission computed tomography that show frontotemporal increased CBF and decreased cerebellar perfusion [40]. Therefore, vasodilatation could possibly explain the immediate headache provoked by high initial blood/brain alcohol levels. DAIH and symptoms of alcohol hangover appear when alcohol levels decline to or reach zero. Thus, alcohol may have an action similar to other strong vasodilators (e.g., histamine, CGRP, glyceryl trinitrate), which display initial cranial vasodilatation and immediate headache, but provoke migraine when vasodilatation is ended. However, studies of healthy patients found no correlation between the degree of cerebral vasodilatation and immediate headache intensity provoked by these vasodilators. Vasodilatation per se could not explain the induced headache [41]. On the other hand, we recently discussed our disagreement with cranial vasodilatation and drug-provoked headache and other observations against the vasodilatory mechanism of migraine pain [42•]. Other mechanisms than vasodilatation are possible. One paper suggests an action of alcohol in particular through serotonin release in central pain circuits [43•]. In this light, it appears of interest that population surveys report that illicit/recreational drugs such as MDMA/ecstasy (an amphetamine derivative) and the "party pill" containing benzylpiperazine/trifluoromethylphenylpiperazine (BZP/TFMPP, piperazine derivatives), both 5-hydroxytryptamine (serotonin)-releasing drugs [44], provoke headache in a high percentage of users [45, 46]. Young adults use recreational drugs very commonly in combination with alcohol (90%) [46]. In addition, controlled studies show that BZP/TFMPP provoke headache/migraine in two out of three subjects [47]. Another piperazine derivative, meta-chlorophenylpiperazine (m-CPP), the most extensively used probe to show an altered serotonergic neurotransmission, provokes migraine-like headache in about 50% of subjects [43•].

Should Migraine Patients Avoid Alcohol Consumption?

Low doses of alcohol reduce the risk of cardiovascular disease [48•]. Migraine, specifically that with aura and with high frequency, increases the risk of some cardiovascular diseases [18•, 49•]. Migraineurs with high frequency of attacks consume alcoholic drinks less frequently than control patients and those with less attack frequency [18•]. Therefore, the undiscriminating recommendation of alcohol abstinence in all migraineurs is incorrect. In

fact, if alcohol-induced headache is not responsible for the reduced alcohol consumption in those patients with high migraine frequency who have increased risk of ischemic stroke, a low dose of alcohol may be indicated in these and in other migraine patients. Certainly, alcoholic drinks may trigger migraine and tension headache in some patients, but probably in much lesser percentage than that referred to retrospectively by patients. Moreover, it frequently is necessary to consume alcohol along with other factors (e.g., anxiety, stress, emotions) to trigger a headache attack. On the other hand, avoidance results in increased sensitivity to triggers and long exposure decreases nociceptive response. A controlled exposure, which is the philosophy of "coping with triggers," seems particularly worthwhile with food triggers [50••]. Before alcohol is considered responsible for a migraine attack, the patients should review certain factors. These include careful recording of the intake of alcoholic drinks to see the amount of alcohol intake, the specific drink types, the frequency of induced headache, and any situation or stress before the alcohol intake. Subsequently, no contraindication exists to a glass of good quality wine if a correlation is found extremely rarely or not at all. As a Greek comic poet suggests: "Three bowls only do I serve for the temperate: one for health, which they drink first, the second for love and pleasure, and the third for sleep. When this bowl is drunk up, wise guests go home. The fourth bowl is ours no longer, but belongs to violence" (Eubulus, ca 375 BC) [51]. This statement is possibly the precursor of the recommendations of the American Heart Association to limit alcohol intake to no more than two drinks per day for man and one drink for women.

Conclusions

Several studies suggest that known triggers have a preponderant role in migraine. It is our opinion that when asked "Are there some factors that trigger your headache?", headache patients do not respond in the great majority of cases. Also, when asked the question "Do you consume alcohol or wine?", they very frequently give a negative response, and if asked to explain, they very frequently respond, "Because I do not like it," not "Because it triggers my headache." In accordance with our view, prospective studies based on the diary of the patients do not report alcohol as a trigger [7•] or only do so in 4% of attacks [52]. The problem of retrospective questionnaires is that they are biased by the recall of the patients. Given that, during the anamnesis, patients with headache hardly remember the frequency of attacks during the previous month, we think that referring a food as a possible migraine trigger in the previous years has a poor reliability.

In conclusion, alcohol as a migraine trigger is probably overestimated. Migraineurs have hangover headache more frequently than nonheadache patients, and probably with lower alcohol doses. It is probable that DAIH accounts for a large part of alcohol-related headaches in migraineurs. The immediate headache provoked by alcoholic drinks is not frequent, and nonheadache patients do not experience IAIH during intravenous infusion of alcohol. Studies with intravenous alcohol should be performed to definitely evaluate if alcohol itself or other components are responsible for headache induced by alcoholic drinks and to determinate the true percentage of migraineurs experiencing IAIH.

If a relationship between the intake of alcohol and the migraine attack is not clear, a small dose of alcohol is not contraindicated either for enjoyment or its protective effect on cardiovascular disease.

Disclosures No potential conflicts of interest relevant to this article were reported.

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