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Review Articles

Wine and Headache

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Background.—The notion of migraine attacks triggered by food and beverages has been posited for centuries. Red wine in particular has been acknowledged as a migraine trigger since antiquity when Celsus (25 B.C.-50 A.D.) described head pain after drinking wine. Since then, references to the relationship between alcohol ingestion and headache attacks are numerous. The most common initiator of these attacks among alcoholic beverages is clearly wine. The aim of this review is to present and discuss the available literature on wine and headache.

Methods.—A Medline search with the terms headache, migraine, and wine was performed. Data available on books and written material about wine and medicine as well as abstracts on alcohol, wine, and headache available in the proceedings of major headache meetings in the last 30 years were reviewed. In addition, available technical literature and websites about wine, grapes, and wine making were also evaluated.

Results.—Full papers specifically on headache and wine are scarce. General literature related to medicine and wine is available, but scientific rigor is typically lacking. The few studies on wine and headache were mostly presented as abstracts despite the common knowledge and patients' complaints about wine ingestion and headache attacks. These studies suggest that red wine, but not white and sparkling wines, do trigger headache and migraine attacks independently of dosage in less than 30% of the subjects.

Discussion.—Wine, and specifically red wine, is a migraine trigger. Non-migraineurs may have headache attacks with wine ingestion as well. The reasons for that triggering potential are uncertain, but the presence of phenolic flavonoid radicals and the potential for interfering with the central serotonin metabolism are probably the underlying mechanisms of the relationship between wine and headache. Further controlled studies are necessary to enlighten this traditional belief.

Key words: migraine, headache, wine, red

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The idea of dietary migraine or the triggering of migraine attacks with food and beverages has long been disseminated. In 1778, Fothergill first described headache attacks after the ingestion of specific dietary factors, but the variability of clinical presentations among and within migraine and non-migraine sufferers has cast doubts about the real existence of such entity.[1,2]

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Particularly with regards to wine, medicine has been imaginative in correlating its consumption with bad and good consequences throughout the centuries, with the first references about a possible relationship between wine and medicine in Mesopotamia 7000 years B.C.[3,4]

When wine making arrived in ancient Greece, it was enjoyed by the whole spectrum of society, and became a popular theme in literature, religion, leisure, medicine, and mythology. Hippocrates promoted wine as part of a healthy diet. He also claimed that wine was good for disinfecting wounds, as well as a liquid in which medications could be mixed and

Conflict of Interest: None.

taken more easily by patients. Hippocrates said wine should be used to alleviate pain during childbirth, for symptoms of diarrhea, and even lethargy.[3-5] Around 1863, a French Corsican chemist called Angelo Mariani developed a beverage containing Bordeaux wine and cocaine (approximately 6 mg of cocaine per fluid ounce of wine). This beverage named Vin Tonique Mariani was suggested as a substitute for opiates and was awarded a Vatican Gold Medal by Pope Leo XIII in addition to an endorsement of its use.[6]

Wine's intrinsic link with the practice of medicine was also featured prominently in the first printed book on wine written by Arnaldus de Villa Nova (circa. 1235-1311 A.D.), a physician, who wrote at length on wine's benefits for the treatment of many illnesses and conditions, including sinus problems and dementia.[5]

For triggering migraine and/or headache attacks, red wine is well known as a trigger and has been so since antiquity when Celsus (25 B.C.-50 A.D.) described pain contracted by drinking wine. Six centuries later, Paul of Aegina (625-690 A.D.) also described drinking wine as a trigger of headache, possibly of migraine etiology.[1,7]

Although the term headache trigger has rarely been consistently defined,[8] the current version of the International Headache Society[9] defines in its group of headaches attributed to a substance use or exposure, the so-called alcohol-induced headache. It can be caused immediately, or after a delay, by the ingestion of alcoholic beverages. If the headache occurs within 3 hours of alcohol ingestion and resolves within 72 hours after alcohol ingestion has ceased, the headache is classified as immediate alcohol-induced headache (8.1.4.1 of the International Classification of Headache Disorders [ICHD]-III beta). If it has developed within 5-12 hours after alcohol ingestion and has resolved within 72 hours of onset, it is known as delayed alcohol-induced headache (8.1.4.2 of the ICHD-III beta).

The alcohol-induced headache has a bilateral and pulsating quality, aggravated by physical activity, and the commonest initiator of headache attacks among alcoholic beverages is definitely wine.[7,9] Although not without dispute, in some countries at least, by far the most notorious headache trigger is red wine. This is certainly the case in the United Kingdom.[10] White wine and champagne may also trigger attacks.[11] However, red wine is a proven traditional headache trigger even in non-migraineurs,[7,12-16] despite the work of a French neurologist from Bordeaux, Dr. Pierre Henry, who lectured extensively on the fact that white wine was a bigger trigger for migraine than the red wine.[17]

The reasons why alcohol may induce headache and even hangover syndrome were studied by Maxwell et al, who demonstrated in animal models (rats) that not only ethanol induced delayed trigeminal hypersensitivity, 4 to 6 hours after administration, but also acetate, rapid forming from acetaldehyde, are in fact the responsible for a suggested induced headache-like pain using a dietary trigger.[18,19]

Specifically with wine triggering headache, it was discussed in depth by Panconesi, who competently dissected the possible substances responsible for initiating an attack.[7]

Histamine.—Starting with histamine, which can certainly provoke migraine, it was hypothesized that in patients suffering from histamine intolerance, the high content observed in red wines (20- to 200-fold more than in white wine) could be held responsible for headache occurrence regardless of the existence of migraine. However, a review of studies did not demonstrated differences in headache-attack occurrence between different wine types, beer, and even foods containing high content of histamine. In addition, other symptoms occurring in patients with histamine intolerance do not occur in headache sufferers after the ingestion of wine, as well as no difference was found in the level of plasma diamine-oxidase between red wine sensitive and nonsensitive migraineurs.[20-24]

Tyramine and phenylethylamine were also suggested as responsible substances for headache and migraine triggering after wine consumption.[7] However, in addition to the negligible content of these amines in wine (1-2 mg/L), studies performing oral challenges in sensible and non-sensible migraineurs were inconclusive regarding this possible relationship.[25]

Sulfites.—Sulfites were once linked to headache after wine ingestion.[26] However, most of this belief is either speculative or in fact wrong, since the food and

wine preservative sulfur dioxide (SO2), called generically sulfite, although present in wines, is much more existent in common foods that do not trigger headache attacks, such as dried fruit. While red wines contain around 160 parts per million (ppm) of sulfites, white wines reach 210 ppm and dried fruit up to 1000 ppm. Moreover, recently produced organic wines contain lower levels of sulfites or, indeed, have none at all, but the persistence of the headache triggering potential remains.[26] In addition, published literature has not yet established any links between the presence of sulfite and headache.[7]

Flavonoid Phenolic Compounds.—The flavonoid phenolic compounds are probably the most likely contender responsible for red wine induced headache either for migraineurs or non-migraineurs.[15] These compounds – natural phenol and polyphenols – include a large group of several hundred chemical radicals that affect the taste, color, and mouth feel of the wine. It includes phenolic acids, stilbenoids, flavonols, dihydroflavonols, anthocyanins, flavonol monomers (cathecins) and polymers (proanthocianins), which can be separated into two categories – flavonoids and non-flavonoids. The flavonoids include the anthocianins and tannins which contribute to the color and mouth feel of the wine, while the non-flavonoids include the thestilbenoids such as resveratrol and the phenolic acids such as benzoic, caffeic, and cinnamic acids.[27-30]

Phenols are the substrate for the enzyme phenosulphotransferase (PST), which exists in the forms of PST-M (inactivates phenolic monoamines such as tyramine and dopamine) and PST-P (degradates phenol itself and p-cresol) in the gut. Extracts of red wine contain high amounts of flavonoids able to potently inhibit PST, particularly its P form, and red wine may present up to 50 times more flavonoid when compared to white wine.[20] Catechin, quercetin, narigin, anthocyanin, and others are the flavonoid molecules absorbed through the gastrointestinal tract able to inhibit PST-P.[10] The inhibition of conjugation of PST-P carried out by phenolic flavonoids could result in buildup of free phenols in the circulation, which may be toxic in several ways.[13] In addition, the inhibition of PST-P by red wine is much more potent than previously thought, with 2000-fold dilution even with dealcoholized red wine having the ability to inhibit the process of sulphation by at least 50%. These facts, observed in *in vitro* studies, and confirmed by measurements of p cresol in urine after oral challenges using red and white wine, as well as beer, suggest that the presence of flavonoid radicals are responsible for the red wine capacity of triggering migraine and perhaps headache attacks in non-migraineurs.[2,7,12,15,20]

5-Hydroxytryptamine (5-HT).—Red wine is a powerful releaser of 5-HT from the platelet. Even in dilutions of 1:20 and in different types of wine or samples of the same wine type, this unique releasing ability seems to lie mainly in two flavonoid fractions with molecular weight greater than 500 Da.[2,31] Interestingly, neither white wine nor beer have any releasing effect on 5-HT.[32] Despite the existence of sensitivity to red wine among migraineurs and non-migraineurs, red wine, but not white wine, causes an increase of whole blood 5-HT levels even in controls.[31,33] In addition, wine inhibits 5-HT and noradrenaline reuptake as well as mono amine oxidase (MAO) activity, through its polyphenolic component resveratrol and through an action on 5-HT receptors. Moreover, red wine strongly inhibits the binding of 5-HT to 5-HT1 receptors, and no conclusive results were demonstrated regarding a mediation of induced headache through 5-HT2 receptors.[20] Therefore, the release of 5-HT, possibly from central stores and due to the flavonoid content of red wine, is a plausible mechanism for wine-induced headache.[7]

Studies on Headache and Wine.—Several studies have been conducted to explore the relationship between headache and wine ingestion. One of the first studies on headache and wine, specifically red wine, was performed by Kaufman, who tested the prophylactic ingestion of acetylsalicylic acid (ASA) to prevent the so-called red wine headache syndrome (RWH).[34] Although poor in details, the small study observed that red wine indeed provoked a headache attack and ASA had little or no effect in altering headache evolution once it already began (Table 1).

Kaufman and Starr also studied 12 patients (9 women and 3 men) who examined previous attacks of headache after red wine ingestion. Following a 4-hour fasting period, patients consumed 90 mL of red wine. After being closely observed every 10 minutes and

Table 1.—Summary of Studies on the Relationship of Headache and Wine

	N	Objectives	Procedures	Results
Kaufman[34]	n/d	To assess the efficacy of ASA to prevent RWH.	n/d	1. Red wine provoked attacks. 2. ASA showed little or no effect to treat established headache.
Kaufman and Starr[35]	12	To assess the efficacy of three IPS in preventing RWH.	1. Participants ingested 90 mL of red wine after 4-hour fasting. 2. Use of one capsule of an IPS or placebo followed (after 60 minutes) by 180 mL of red wine. 3. Blinded assessments.	1. RWH happened in all participants within 2 hours. 2. Two subjects using placebo still had RWH within 2 hours. 3. Two acetaminophen patients had RWH between 6–12 hours.
Peatfield et al[10]	6†	To compare RWH and blood levels of PST-P and -M after ingestion of 2 types of red wine.	1. 5 mL/kg of Valpolicella and Chianti were given 2 weeks apart. 2. Blood levels were collected 2 and 3 hours after wine ingestion.	1. RWH happened in 10 out of 12 participants. 2. No difference was seen between wine types. 3. PST-P significantly decreased after 2 hours compared to PST-M

n/d = not disclosed.
†Three migraineurs without aura and 3 migraineurs with aura.
ASA = acetylsalicylic acid; IPS = inhibitors of prostaglandin synthesis; PST-P or -M = phenosulphotransferase types P or M; RWH = red wine headache syndrome.

after a total period of 120 minutes, patients were discharged and oriented to return 1 week later, maintaining the same fasting time. All 12 patients presented a headache within 2 hours[35] (Table 1).

The second step of the study was performed with the same 12 patients, who were randomized to take one capsule of 650 mg ASA or 500 mg acetaminophen or 400 mg ibuprofen or placebo and 180 mL of red wine after 60 minutes. None of the patients receiving an active drug developed a headache within 2 hours contrarily to the 2 patients who received placebo. Two of the 4 patients who received acetaminophen developed a headache within 6-12 hours after the red wine ingestion (Table 1).

Peatfield et al tried to compare the headache triggering potential of two types of red wine.[10] Testing what the study authors nominated as wine-sensitive patients, the authors gave 5 mL/kg of Valpolicella and Chianti red wines to 6 migraineurs. Blood was collected immediately and after 2 and 3 hours. A headache attack developed on 10 of the 12 occasions, but no difference was found between wine types. Platelet PST type P was significantly decreased when compared to PST type M, after 2 hours on all occasions (Table 1).

Valpolicella wines are generally composed of 3 red-wine grape varieties grown in the Veneto region, of the Italy's northeast. Corvina, Rondinella, and Molinara grapes are the trio primarily constituting the blend, but Valpolicella DOC (Denominazione di Origine Controllata) also allows for up to 15% of other red-wine varieties grown in the province of Verona, including Rossignola, Negrara Trentina, Barbera, and Sangiovese.[36] The Corvina plays the starring role in Valpolicella (up to 75%) and is regarded as the blend's central element. It is known more for its acidity and sour-cherry flavors than for its depth. The Rondinella grape, used primarily to add color and body to the blend (up to 35%), offers some herbal notes and further accentuates the gentle spiciness of Corvina. Additional tannins and fresh acid are provided by the grape Molinara, though it is the least regarded of the three main grapes, and its use is on the decline.

The Chianti wine type refers to any wine produced in the Chianti region of central Tuscany. It is composed of 70% Sangiovese, 15% Canaiolo, and up to 20% Cabernet Sauvignon, Merlot, or Shiraz.[37] Theoretically, sangiovese wines have more tannins than Valpolicella wines, but in truth its content is

similar especially if the Chianti is not purely made with a variety called sangiovese grosso. High acidity and light weight, thus the need to blend with other grapes to give it a bit more structure, defines Chianti wines. In general wines are lower in tannins, especially if the grapes are picked before becoming fully ripe (which can be mid-October in Tuscany). Sour cherry, plum, and even blackberry notes, if fully ripe, are possible. Otherwise, notes of spice and mocha or vanilla are prevalent if aged in oak.[38] Perhaps, the study by Peatfield and colleagues did not show any difference between patients because the tannin content of both wines was, in truth, similar.[10]

Personal Experience.—The authors of this review article have compared the potential for triggering migraine attacks among different red wine types.[39] The wines studied were from South America and belonged to the varietal types: Cabernet Sauvignon, Merlot, Malbec, and Tannat, which have at least 75% of the nominal grapes. The 40 patients (28 women and 12 men, ages 32-53 years) had a diagnosis of migraine according to the ICHD-II criteria,[40] were regular patients of a tertiary center (the Headache Center of Rio) under various preventive treatments, considered themselves wine drinkers, and had self-identified a relationship between wine intake and migraine attacks. For the purposes of the study, the patients had to consume half bottles of various wines, from any kind of producer, at their discretion, with a minimum interval of 4 days between the wine types. In addition, they were asked to avoid any other kinds of alcohol through the duration of the study and to not drink more than one-half bottle at a time.

Thirty-three patients (23 women, 10 men) completed the study. Twenty-nine patients (87.8%) reported a migraine attack on at least one occasion within 12 hours of consuming the wine, and 11 (33.4%) reported migraine attacks after all 4 times in which the wine was consumed. Four patients (12.2%) drank the four wine types and didn't present any headache attack (Figure). The triggering power of each specific wine is shown in Table 2.

Tannat is a red wine grape, historically grown in South West France. It is now one of the most prominent grapes grown in Uruguay, where it is considered

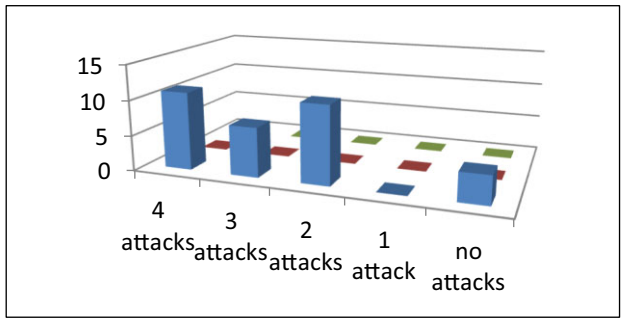

Figure.—Number of patients presenting migraine attacks after the ingestion of 4 wine types (n = 33).

the "national grape."[39] It is also grown in Argentina, Australia, Brazil, Peru, Bolivia, and in Italy's Puglia region, where it is used as a blending grape. In the US states of Maryland and Virginia, there are small experimental plantings of the vine, and plantings in California have increased dramatically in the first years of the 21st century.[41]

The Tannat wine is notable for its very high-tannin levels and is often blended with cabernet sauvignon and cabernet franc to soften the astringency and make it more approachable. In addition, modern wine making has begun utilizing oak aging to help soften the tannins.[42,43] Now, the wines typically spend about 20 months in oak prior to release. Tannats from Uruguay are particularly high in tannins and depending on the wine-making techniques may present the highest contents among South American red wines.[44,45]

Malbec is a purple grape variety with an inky dark color and robust tannins known as one of the six grapes allowed in the blend of red Bordeaux wine. It needs more sun and heat than either Cabernet Sauvignon or Merlot to mature. It ripens mid-season and can bring very deep color, ample tannin, and a particular plum-like flavor component to add complexity to claret blends. The French plantations of Malbec are now found primarily in Cahors in South West France. It is increasingly celebrated as an Argentine varietal wine and is becoming more widely grown around the world.[46] Also called Auxerrois or Côt Noir in Cahors, called Malbec in Bordeaux, and Pressac in other places, the grape became less popular in Bordeaux after 1956 when frost killed off 75% of the crop. Despite Cahors being hit by the same frost,

Table 2.—Personal Experience on the Relationship Between Wine Consumption and Headaches

	N	Objectives	Steps of the Study	Results
Krymchantowski and Jevoux[39]	40	To assess the prevalence of headaches within 12 hours of consuming different† South American red wines	375 mL of red wines were given at least 4 days apart	Rates of migraine were 1. Tannat = 51.7% 2. Malbec = 48.2% 3. CS < 30% 4. Merlot < 30%
Krymchantowski and Jevoux[49]	28	To assess the prevalence of headaches within 12 hours of consuming CS from France and from South America	375 mL of different CS were given at least 4 days apart	Rates of migraine were 1. French CS = 60.9% 2. South American CS = 39.1% ($P < .001$)

†Cabernet Sauvignon (CS), Merlot, Malbec, Tannat.

which devastated the vineyards, Malbec was replanted and continued to be popular in that area where it was mixed with Merlot and Tannat to make dark, full-bodied wines, and more recently has been made into 100% Malbec varietal wines.[47] In Argentina, Malbec becomes softer with a plusher texture and riper tannins. The wines tend to have juicy fruit notes with violet aromas. Malbec grown in the state of Washington tends to be characterized by dark fruit notes and herbal aromas.[44,46]

We then studied the potential for triggering migraine attacks between Cabernet Sauvignons from France and South America.[48] French Bordeaux from the left margin of the Gironde River are richer in tannins because they have a minimum of 75% Cabernet Sauvignon grapes. They usually are complex and very good wines with a high potential from aging. Cabernet Sauvignons from South America have also improved in quality in recent years.

In a study the authors of this review article conducted, we evaluated 28 regular patients (14 women and 14 men, ages 25 to 67 years, mean 54.5) from the Headache Center of Rio under various preventive treatments, who were also self-considered wine drinkers and reported a clear-cut relationship between wine intake and a headache attack. They were all migraineurs according to the ICHD-II.[40] The patients took two half bottles of any French and any South American Cabernet Sauvignons (minimum 4 days between wines). French wines had to be from the Medoc or Haut Medoc regions, specified in the bottle label. A detailed headache calendar had to be filled out, and any headache attack within 12 hours had to be reported. No other alcohol source and no more than 375 mL were allowed during the study.

Twenty-three patients (13 women and 10 men) completed the study. French wine ingestion triggered a migraine attack more often than reporting in the South American wines (Table 2). Four patients had no attacks, and 4 patients presented attacks with both wines. Five patients reported a migraine attack after the South American Cabernet but not with the French Cabernet. None of the patients from the last 2 studies had a headache attack not fulfilling migraine after the wine ingestions.

Cabernet Sauvignon is one of the world's most widely recognized red wine grape varieties. It is grown in nearly every major wine producing country among a diverse spectrum of climates. This grape became internationally recognized through its prominence in Bordeaux wines where it is often blended with Merlot and Cabernet Franc in amounts varying with the region in which it is produced. Although well known among wine producers and consumers, the Cabernet Sauvignon is relatively new, representing a chance crossing between Cabernet Franc and Sauvignon Blanc during the 17th century in southwestern France.[49,50]

The Cabernet Sauvignon is a very small grape with a thick skin, creating a high 1:12 ratio of seed to fruit.[50-52] This results in the high proportions of phenols and tannins observed in this wine, especially if the must is subjected to long periods of maceration (skin contact) before fermentation. In Bordeaux, the

maceration period is traditionally 3 weeks, which results in very tannic and flavorful wines that require years of aging. Reducing the maceration time to as a little as a few days, may create light and more approachable wines as with some South American wine makers. Following maceration, the Cabernet must can be fermented at high temperatures up to 30°C (86°F), which will play a role in the result, providing deeper colors and more flavor components being extracted at higher temperatures.[53,54]

In the Medoc and Haut-Medoc regions in France (left margin of the Gironde River), the wines are primarily made of Cabernet Sauvignon grapes (up to 75%), while in the right bank of the Gironde River, due to the arenous soil, the typical wines are primarily made with Merlot grapes as those from the Pomerol district, which originates the legendary Chateau Petrus.[47,50-52]

Merlot is a dark blue wine grape used as a blending grape and for varietal wines. The name *Merlot* is thought to be a diminutive of *merle*, the French name for the blackbird, probably a reference to the color of the grape. Merlot-based wines usually have medium body with hints of berry, plum, and currant. Its softness and "fleshiness," combined with its earlier ripening, makes Merlot a popular grape for blending with the sterner, later ripening Cabernet Sauvignon, which is much higher in tannins.[50]

Along with Cabernet Sauvignon, Cabernet Franc, Malbec, and Petit Verdot, Merlot is one of the primary grapes used in Bordeaux wine, and it is the most widely planted grape in the Bordeaux wine regions. Merlot is also one of the most popular red wine varietals in many markets throughout the world.[50-54] This flexibility has helped to make it one of the world's most planted grape varieties.

As a varietal wine, Merlot can make soft, velvety wines with plum flavors.[44,46,47,53] Some of the fruit notes commonly associated with Merlot include cassis, black and red cherries, blackberry, blueberry, and plum. Vegetable and earthy notes include black and green olives, nuts, leather, mushrooms, and tobacco. When Merlot has spent significant time in oak (longer than 8 months), the wine may show notes of caramel, chocolate, coconut, coffee bean, smoke, vanilla, and walnut.[46,47,53]

CONCLUSIONS

Wines, especially red wines, are very different in composition, producing processes and therefore, taste and the ability to please. Consumption habits of different grapes and varietal wines are very peculiar among countries and people. For the good or bad, wine has been linked to headache and migraine attacks as a traditional trigger. Tannins and the phenolic flavonoid components of the red wine, with its ability to interact with the metabolism of certain monoamines as well as its capacity of mobilizing 5-HT, are probably related. However, the methodology of most of the studies discussed in this review and the analysis of the available literature do not allow definitive conclusions regarding the real role of wine in headache. We believe that red wine is indeed a migraine trigger, at least for a percentage of migraineurs, even under regular preventive treatment. In addition, red wines with more tannins are probably worse in triggering migraine attacks. Controlled studies with well-known wines are important to clarify this common belief.

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