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PSYCHOLOGICAL AND BEHAVIORAL ASPECTS OF HEADACHE AND PAIN (D BUSE, SECTION EDITOR)

The Relationship of Tobacco Use and Migraine: A Narrative Review

Andrea H. Weinberger[1,2,3] · **Elizabeth K. Seng**[1,4]

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Abstract

Purpose of Review Tobacco use is associated with significant health consequences especially for people with medical conditions. Although lifestyle strategies (e.g., sleep, diet) are commonly recommended as part of migraine treatment, tobacco-related strategies (e.g., smoking cessation) are rarely included. This review is aimed at elucidating what is known about tobacco use and migraine and at identifying gaps in the research.

Recent Findings The prevalence of smoking is higher among people with migraine, and people with migraine believe that smoking makes migraine attacks worse. There is also evidence that smoking may exacerbate migraine-related consequences (e.g., stroke). Very few studies have examined other aspects of smoking and migraine or tobacco products other than cigarettes.

Summary There are significant gaps in our knowledge of smoking and migraine. More research is needed to understand the relationship of tobacco use to migraine and potential benefits of adding smoking cessation efforts into migraine care.

Keywords Migraine · Tobacco · Cigarettes · Smoking · Smoking cessation

Introduction

Migraine is a prevalent and disabling neurologic disease characterized by attacks of head pain and associated symptoms of nausea and sensitivity to light and sound [1]. Approximately 20% of people with migraine experience sensory changes, most often visual disturbances, immediately prior to pain onset called aura. Migraine affects 12% of the population and is the leading neurological cause of years lived in disability worldwide [2, 3].

Due to the unpredictable nature of migraine attacks and the extent to which attacks interfere with role responsibilities, migraine is particularly disabling for social and occupational functioning [2–4]. Higher monthly migraine days, average attack pain intensity, and frequency of associated symptoms are associated with higher levels of headache-related disability. Approximately 2% of the population has chronic migraine, characterized by headache on 15 or more days per month, which is associated with the highest levels of headache-related disability.

Migraine is comorbid with a variety of medical conditions. Migraine, particularly migraine with visual aura, is associated with an increased risk of stroke [5]. Odds of depression are 2–4 times higher, and odds of anxiety disorder 3–5 times higher, in people with migraine compared to controls [6–8]. The presence of depression and anxiety, alone and in combination, is associated with higher levels of migraine-related disability [9].

Lifestyle recommendations are a core component of migraine management. Maintaining consistent routine life behaviors, such as a regular sleep schedule, maintaining a consistently healthy diet, aerobic exercise, and keeping stress consistently low are common lifestyle recommendations for migraine. Each of these routine life behaviors has

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✉ Andrea H. Weinberger
andrea.weinberger@yu.edu

[1] Ferkauf Graduate School of Psychology, Yeshiva University, 1165 Morris Park Ave, Bronx, NY 10461, USA

[2] Department of Psychiatry & Behavioral Sciences, Albert Einstein College of Medicine, Bronx, NY, USA

[3] Department of Epidemiology & Population Health, Albert Einstein College of Medicine, Bronx, NY, USA

[4] Department of Neurology, The Saul R. Korey, Albert Einstein College of Medicine, Bronx, NY, USA

demonstrated efficacy to reduce monthly migraine days and migraine-related disability [10–15]. Surprisingly, the cessation of tobacco use, or more specifically cigarette smoking cessation, is rarely included among the lifestyle recommendations for migraine.

Commercial tobacco use is the leading cause of mortality and morbidity in the United States (US) [16] and a leading cause of death and disability around the world [17]. The most recent data from the CDC suggest that, in 2020, 19.0% of US adults reported using a tobacco product with the most common product being cigarettes (12.5%) [18]. It is well-known that cigarettes cause a wide range of negative health consequences in general [16, 19] and cigarette use is also associated with disease-specific consequences, more complicated illness course, and impacted recovery of people with some medical diseases such as HIV, cancer, and cardiovascular disease [20].

The purpose of the current paper is to provide a narrative review of the literature evaluating tobacco use in people with migraine, including prevalence and association with migraine disease characteristics and disability. We hope to elucidate gaps in the literature evaluating tobacco use in relation to migraine and identify needs for further research.

Risk of Migraine and Smoking Onset

Only a few studies have examined the relationship between smoking and migraine onset, or migraine and smoking onset, and these studies have shown mixed results. A longitudinal study of 980 individuals in New Zealand [21] found that smoking in childhood or adolescence was not a risk factor for the development of migraine in adolescence or adulthood. However, migraine in childhood was not a risk factor for initiating smoking in adolescence but migraine in adolescence was a risk factor for the initiation of smoking in adulthood [21]. In contrast, in a recent study using genetic variant data from genome-wise association studies, the UK Biobank Study and the FinnGen Consortium [22] found evidence for a greater risk of migraine onset related to smoking but not a greater risk of smoking initiation related to migraine. More research is needed to clarify the relationship between smoking (or, more broadly, tobacco use) and migraine onset, as well as migraine and the onset of tobacco product use.

Passive smoking and smoking during pregnancy are associated with health consequences for offspring, greater odds of smoking among offspring, and greater odds of some health issues (e.g., asthma) [23••, 24–27]. Two studies examined passive smoking and migraine with mixed results. One study of children in Turkey [28] found a positive relationship between smoking at home and headache while a study of California individuals ages 15 and up [29] found no relationship between exposure to tobacco smoke and migraine. Similarly, mixed results were found in two studies about maternal smoking and migraine in offspring with a study in Finland [30] finding a significant relationship between maternal smoking while pregnant and greater odds of migraine while one study of children in New Zealand [31] did not find a relationship between maternal smoking while pregnant and migraine.

Prevalence of Tobacco Use in People with Migraine

Several national population-based studies have examined the prevalence of migraine by tobacco use status and the prevalence of tobacco use by migraine status. Regarding the relationship of tobacco use to migraine prevalence, a national sample of US individuals [32] found greater odds of past-90-day headache (defined as "severe headache or migraine") for those with current cigarette smoking versus those who never smoked cigarettes (26.4% versus 21.2%; OR—1.38, 95% CI = 1.17–1.62). The odds of headache increased with greater quantity of cigarettes smoked per day and longer smoking history measured as pack-years (p's for trends < 0.001) but did not differ for those using menthol versus non-menthol cigarettes. Similarly, a study in Sweden [33] also found a higher prevalence of recurrent headache and/or migraine among men and women with current smoking (12.9% and 29.4%) than men and women who never smoked (9.7% and 21.1%) or smoked in the past (9.6% and 21.6%; p's < 0.001 for comparison of smoking groups within each gender); a study of a national sample of twins in Denmark [34] reported a greater prevalence of migraine for those with current smoking versus former smoking (OR = 1.09, 95% CI = 1.02–1.16) or never smoking (OR = 1.14, 95% CI = 1.07–1.20); and a study of adolescents in Germany [35] found greater odds of either migraine or migraine plus tension-type headache for those with smoking versus no smoking (OR = 2.4, 95% CI = 1.5–3.9).

A number of studies published in the past few years that did not use nation-wide population-based samples also found a relationship between tobacco use and greater odds of migraine (e.g., among residents of Al-Kharj, Saudi Arabia [36], residents of Nord-Trøndelag County, Norway [37], students at the University of Aleppo in Syria [38••], Croatian adolescents [39], outpatients in Taiwan [40••], pregnant people in the USA [41] and Norway [42], and adults who had been hospitalized in the USA [43••]). In contrast, studies from Denmark [44, 45], Spain [46, 47], Japan [48], and Saudi Arabia [49] found no relationship between current smoking and prevalence of migraine or, specifically, migraine with aura. Interestingly, in a sample of patients with ischemic stroke in China [50], the percentage of people reporting current smoking was lower among those

with migraine than those without migraine (25.9% versus 38.3%, $p = 0.025$). Studies examining other tobacco products have been mixed, with a study in Bangladesh finding that migraine is associated with greater odds of both smoked and smokeless tobacco use [51], while studies in Turkey and Syria did not find evidence of higher use of smokeless tobacco among people with migraine [38••, 52] Altogether, there is evidence for greater odds of migraine with cigarette smoking in epidemiologic studies though across community-based studies, findings have been mixed.

Electronic nicotine delivery systems (ENDS) such as e-cigarettes have gained popularity over the past several years especially among adolescents and young adults [53, 54]. Among US adults [55] and adolescents [56] who reported lifetime ENDS use, 21.9–25.4% reported a headache or migraine associated with e-cigarette use and the percentage reporting headaches or migraine increased to 43.8% for adolescents with past month ENDS use. It is not yet known how ENDS relate to aspects of migraine among individuals diagnosed with migraine.

In terms of smoking across different headache types including migraine, there was no difference in odds of smoking among adults with chronic migraine versus chronic/episodic tension-type headache in a German national sample (OR = 1.81, 95% CI = 0.76–4.34) [57] while Canadian adolescents with migraine [39] were more likely to smoke than adolescents with tension-type headache (51% versus 30.9%; OR = 2.34; 95% CI = 1.73–3.14). A study of Swedish women ($n = 27$ with migraine, $n = 27$ with cluster headache) [58] found that a lower percentage of those with migraine than those with cluster headache reported current cigarette use (48.15% versus 88.89%, $p < 0.01$) and patients with migraine reported smoking fewer cigarettes per day (CPD; 6 CPD) and smoking for a shorter period of time (8 years) than patients with cluster headaches (13 CPD, 21 years; p's < 0.001).

Consequences of Tobacco Use Among People with Migraine

People with migraine who smoke cigarettes would be expected to experience the same smoking-related health consequences as other individuals who smoke cigarettes [16, 19], but there is also evidence of specific migraine-related consequences of cigarette use. For example, migraine and smoking are each independently associated with increased risk of stroke [16, 19, 59, 60] and the risk of stroke appears to be greater for those with migraine who smoke versus do not smoke. A meta-analysis examining the relationship between stroke and migraine [60] found that smoking was associated with a ninefold increased risk of stroke among people with migraine (RR = 9.03, 95% CI = 4.2–19.34). Papers published since this meta-analysis have shown mixed results: a study of adults ages 40 and older in New York found an increased risk of stroke for people with migraine and current smoking but not for people with migraine and no current smoking [61] while a study of women nurses in the USA found no differential risk of cardiovascular disease (including stroke) among people with migraine based on smoking status [62].

Among people with migraine, several studies provide early indications that smoking cigarettes is associated with worse disease status across several indicators, including central sensitization and autonomic symptoms. For example, among 1413 people with migraine across multiple headache centers, current smoking was associated with the presence of cutaneous allodynia [63]. Among 117 US patients with migraine, lifetime smoking was associated with the presence of a variety of autonomic symptoms (i.e., eyelid ptosis or droop, eyelid or orbital swelling, conjunctival injection, lacrimation, nasal congestion, or rhinorrhea; any autonomic symptom was present in 70% with lifetime smoking versus 42% without lifetime smoking, $p < 0.005$) [64].

Little is known about the association between smoking and migraine frequency or attack pain intensity. Among 58 medical students with migraine in Spain, a larger percentage of those with smoking versus without smoking reported ≥ 1 monthly migraine attack (77% versus 56%) [65]. Among 92 people with chronic migraine in Italy, current cigarette smoking was associated with increases in migraine frequency, but not attack pain intensity, during the COVID-19 lockdown [66]. In a study of 600 adults in Turkey [52] (50% with migraine), while the prevalence of smoked tobacco was higher among those with migraine than those without migraine, the prevalence of Maras powder (smokeless tobacco) use was lower among those with migraine compared to those without migraine ($p = 0.013$). Notably, those with migraine using Maras powder and using smoked tobacco reported similar frequency and pain intensity of headaches and greater frequency and pain intensity of headaches compared to those not using any tobacco products [52]. Individuals with migraine using Maras powder reported greater dependence than individuals with migraine using smoked tobacco. More research is needed with larger samples to evaluate the impact of cigarette smoking on the cardinal symptoms of migraine.

When considering the perceptions of patients with migraine, many feel smoking triggers or exacerbates their migraine disease. For example, among 100 patients at a migraine clinic in the UK, 20% reported current smoking; of these, half of the sample believed smoking increased migraine pain intensity, although fewer reported smoking as a migraine attack trigger [67]. In a more recent study of 58 medical students with migraine in Spain [65], the

majority of students with migraine who smoked cigarettes felt that smoking precipitated migraine attacks (59%) and worsened attack pain intensity (71%). These studies provide self-report evidence that some people with migraine believe that smoking cigarettes triggers migraine and is associated with more intense attack pain intensity. To our knowledge, there have not been any controlled studies (e.g., laboratory studies, diary, or EMA studies) that have examined whether smoking is related to the onset of migraine attacks or to more frequent or more severe migraine attacks.

People with migraine who smoke appear to be at risk for medication overuse. National studies of US adults have found that smoking is associated with acute migraine medication overuse ($\chi^2 = 126.13$, $p < 0.001$) [68] and with frequent use of opiate medications for migraine ($\chi^2 = 115.92$, $p < 0.001$) [69]. A study of pregnant women in Norway [42] found that greater analgesic use was associated with recent migraine attacks or migraine attacks during pregnancy and smoking was associated with analgesic use after controlling for migraine intensity and other demographics (AOR = 1.36, 95% CI = 1.03–1.79). It should be noted the metabolism of medications used to treat migraine can be impacted by smoking through common pathways of metabolism (e.g., cytochrome P450 (CYP) enzymes such as CYP1A1, CYP1A2, CYP2A6; see Zevin and Benowitz [70•] and Anderson and Chan [71] for reviews of smoking and drug interactions in general and Joshi et al. [72] for a review of drug interactions with migraine medications specifically). More research is needed to understand the relationship between smoking and medication overuse as how smoking cessation might impact the therapeutic dose of migraine-related medications and medication side effects.

Two studies have demonstrated that in people with migraine, smoking (vs. not smoking) was associated with greater negative psychological and psychosocial outcomes. In a study of 247 individuals in Saudi Arabia with migraine [73•], those with migraine who smoked cigarettes reported greater depression and stress compared to those with migraine who did not smoke cigarettes, though no differences were found for anxiety. Further, among a sample of 80 Italian people with migraine [74], smoking (versus no smoking) was associated with greater psychosocial difficulties (e.g., energy, motivation, appetite, sleep, memory), difficulties with activities (e.g., walking, self-care), sexual functioning, and pain. Many people who smoke perceive smoking as a stress or weight management tool [75, 76]. Little is known about reasons for smoking among people with migraine or beliefs about the association between smoking and migraine-related psychosocial factors such as stress, weight, and sleep.

Migraine and Smoking Cessation

Little is known about characteristics of smoking that increase difficulty of quitting among people with migraine, such as length of time smoking, cigarettes per day, and cigarette dependence [77, 78, 79]. One 1987 study of US pregnant women ($n = 508$ with migraine, $n = 3192$ without migraine) found that both White and Black women with migraine were more likely to report smoking for at least 5 years (46.2% and 36.3%) compared to White and Black women without migraine (34.2% and 20.0%, p's < 0.01) and were more likely to report smoking more than a pack of cigarette per day (White women 13.4% versus 6.42%; Black women 3.97% versus 0.60%; p's < 0.01) [80]. More research is needed to understand the extent to which characteristics of smoking that increase difficulty quitting are present in the migraine population.

Quitting smoking reduces or eliminates the negative health risks of smoking [16, 81], and quitting smoking has benefits for the course, treatment, and outcomes of medical conditions such as cancer and cardiovascular disease [20]. Little is known about how migraine symptoms may change in response to quitting smoking. An early report [82] found improvements in headaches, defined as decreases in the number of headaches, after smoking cessation. Unfortunately, people with migraine may have a more difficult time quitting smoking than others. A recent longitudinal study of individuals in New Zealand [21] found that more individuals with migraine (33.3%) or combined migraine and tension-type headache (50.0%) reported an unsuccessful smoking quit attempt than people without a headache disorder (17.4%). It is important to note that headaches are a common short-term symptom of cigarette smoking cessation and may be worse in people with migraine. In the recent longitudinal study in New Zealand, people with migraine were more likely to report that they smoked tobacco to avoid quitting-related symptoms (31.8%, 16.7%, and 15.5% respectively) and that they experienced headaches when they quit smoking (12.6% vs. 7.5%, $p > 0.05$) [21]. Both randomized and quasi-experimental clinical trials are needed to understand the short- and long-term implications of smoking cessation on migraine symptoms.

Potential Mechanisms

Little is known about why people with migraine smoke cigarettes at higher rates than people without migraine. Either causal direction is plausible or a shared underlying

mechanism. For example, the pituitary adenylate cyclase-activating polypeptide (PACAP) system has been implicated both in migraine and in animal models of nicotine dependence [83]. Similarly, stress is implicated both in severity of migraine symptoms and smoking behavior [75, 76, 84, 85]. Smoking may also be an indicator of a cluster of lifestyle factors such as poor diet quality and lack of physical activity that could be associated with increase migraine disease severity and burden [86].

Smoking could act as a risk factor for migraine, most likely through its action on the cardiovascular system. Smoking increases risk of cardiovascular disease through inflammatory mechanisms [87] that may also be implicated in migraine onset. However, genetic determinants of smoking intensity do not appear associated with headache risk as an analysis from the HUNT study found that a single nucleotide polymorphism associated with smoking intensity was not associated with the presence of headache or migraine among smokers [88].

Among people with migraine, there are a variety of plausible mechanisms for smoking increasing disease severity. Smoking may increase oxidative stress [87], a potential shared underlying factor of a variety of migraine precipitating factors [89]. Smoking also produces a strong scent which often occurs in lists of smells people with migraine report as potential precipitating factors [90].

The direction that migraine may be associated with higher rates of smoking also deserves some attention. A rather straightforward hypothesis is a stress-mediated behavioral reward channel whereby smoking reduces perceived stress, which is both an empirical and commonly perceived migraine precipitating factor. Thus, someone with migraine may seek methods of stress reduction and turn to smoking, which reduces stress in the short term but is a maladaptive coping skill in the long term. Another psychological theory that may guide inquiry in the relationship between migraine and smoking is the fear-avoidance cycle [91]. In chronic pain, smoking has been demonstrated as a pain avoidance behavior which reduces pain anxiety in the moment, but in the long run is thought to chronify pain [92]. However, other hypotheses are worthy of attention. The migraine brain is more sensitive to its surroundings, osmophobia is common during both the premonitory and pain phases of migraine, and many patients believe that strong smells trigger migraine attacks [93]. Smoking reduces the sense of smell in the moment and may have long-term consequences on smell [94]. A deeper understanding of the impact of immediate smoking on both pain and sensory sensations may elucidate behavioral pathways that lead to increased smoking among people with migraine.

Conclusions

Research investigating the link between tobacco use and migraine is emerging. Cigarette smoking appears to be more common among people with migraine than in the population, although the directionality of this relationship is unclear. Very little is known about the relationship between smoking and migraine symptoms, but a few small reports suggest that smoking may be more common in people with worse migraine symptoms and with medication overuse. Methodologically rigorous studies using controlled laboratory methods as well as ecological momentary assessment are required to understand the time-dependent relationship of smoking on migraine symptoms.

Smoking cessation holds well-established benefits for overall health and reduction of mortality risk [16, 81]. Further, in people with migraine, smoking increases the risk of stroke beyond the risk conferred by migraine alone. Therefore, it is reasonable for clinicians to include smoking cessation in lifestyle counseling among the other lifestyle factors commonly included in migraine counseling. For example, it is recommended that health professionals use the "5 As": Ask about tobacco use and document use of tobacco products, Advise the patient to quit the use of tobacco products, Assess motivation to quit the use of tobacco products, Assist in delivering or connecting the patient with smoking cessation interventions, and Arrange to follow up with the patient over time to prevent relapse to tobacco use (see [95] for more details). There are several effective and FDA-approved smoking cessation treatments, both pharmacological (e.g., nicotine replacement therapy, bupropion, varenicline) and behavioral (e.g., problem-solving and skill building such as coping with withdrawal symptoms, building social support, stress management), with better outcomes with combinations of both pharmacological and behavioral treatments [95]. While smoking cessation is effective for preventing and/or reducing smoking-related consequences, no studies to date have evaluated the impact of smoking cessation on migraine outcomes. Randomized clinical trials are needed to understand the impact of smoking cessation on migraine symptoms and burden.

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Data Availability Data sharing is not applicable to this review as no datasets were generated or analysed for the current paper.

Compliance with Ethical Standards

Conflict of Interest Dr. Weinberger has no financial disclosures to report. Dr. Seng has consulted or served on an advisory board for GlaxoSmithKline, Click Therapeutics, and AbbVie and received research funding from the NINDS (NS096107; PI: Seng), NCCIH (R01AT011005-01A1; MPIs: Seng and Shallcross), and the Veteran's Health Administration (the Headache Center of Excellence Research and Evaluation Center and VA HSR&D, IRP 20–002 PI: Damush). The authors have no conflicts of interest to report.

Human and Animal Rights and Informed Consent This review paper summarized the results of other studies and did not involve the direct participation of animal or human subjects.

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