Aeromedical Risk of Migraine

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INTRODUCTION: Migraine is a common condition that can carry considerable risk to aeromedical duties. Because randomized controlled trials are not an appropriate method to evaluate flight safety risk for medical conditions that may cause subtle or sudden incapacitation, the determination of fitness-to-fly must be based on risk assessments informed by extrapolated evidence. Therefore, we conducted a review of current literature to provide background information to inform the aeromedical risk assessment of migraine using a risk matrix approach.

METHODS: We identified studies on topics pertinent to conducting an aeromedical risk assessment of migraine. We generated an overview of the literature synthesizing the findings of articles retrieved from searches of Scopus, Ovid, PubMed, and the Cochrane Library published in English from all years, in both general and aircrew populations. International headache and neurology guidelines, as well as headache policies from the U.S. Air Force, were also reviewed.

RESULTS: This review includes information on the following topics relevant to conducting an evidence-based risk assessment of migraine: diagnosis, prevalence, incidence, natural course, clinical presentation, triggers, comorbidities, neuroimaging, implications of family history, and efficacy of pharmacological and nonpharmacological therapies.

DISCUSSION: This review summarizes current literature on migraine for use in a risk matrix approach to the aeromedical assessment of migraine in prospective and current aircrew. Awareness of the most current epidemiological data related to a variety of migraine parameters facilitates an evidence-based risk assessment of migraine in aircrew and requires iterative updates as new information becomes available.

KEYWORDS: migraine, headache, aura, aeromedical risk, fitness-to-fly, aircrew.

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Migraine is a common condition that can carry considerable risk to aeromedical duties. In both military and commercial industries, prospective and current aircrew must undergo medical assessment to evaluate their fitness-to-fly based on their medical history, current symptoms, clinical examination, and medical testing, such as labs and imaging studies. In Canada, a risk matrix approach is used to evaluate an individual's fitness-to-fly. Risk is a concept that requires consideration of two key factors: the likelihood of occurrence of an event (in this case, migraine) and the severity of the consequences to the individual, crew, or mission, should such an event occur. An accurate risk assessment involves identifying evidence related to the prevalence, natural course, efficacy of therapies, and potential for interference with duties for the specific medical condition being evaluated. This evidence is then applied in the context of the individual being assessed, taking into consideration their disease phenotype and specific position.

Accurate estimation of aeromedical risk ultimately leads to increased aircrew and civilian safety, preservation of equipment and resources, and greater workplace productivity. Because randomized controlled trials are not an appropriate method to evaluate safety for medical conditions that may cause subtle or sudden incapacitation, the evaluation of fitness-to-fly must be based on an aeromedical risk assessment, which is often informed by extrapolated evidence. In this article, we review current literature on the topics relevant to conducting an aeromedical risk assessment of migraine.

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METHODS

A literature review was performed to identify studies on topics pertinent to conducting an aeromedical risk assessment of migraine in aircrew, including diagnosis, prevalence, incidence, natural course, clinical presentation, triggers, comorbidities, neuroimaging, and efficacy of therapies. Scopus, Embase, PubMed, and the Cochrane Library were searched to identify relevant studies published in English from all years, in both general and aircrew populations. Searches were undertaken for each topic using a variety of search term combinations to identify the greatest number of studies relating to each of the topics. Search terms and results are available upon request. International headache and neurology guidelines, as well as headache policies from the U.S. Air Force (USAF), were also reviewed. Each topic is summarized separately in the following sections.

RESULTS

Diagnosis and Differential Diagnosis of Migraine

Migraines are a type of primary headache disorder defined by the International Headache Society as a headache lasting for 4 to 72 h, with at least two of the following characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, and aggravation by or causing avoidance of routine physical activity.[82] In addition, migraines are associated with at least one of the following: 1) nausea and/or vomiting; or 2) photophobia and phonophobia.[82]

Migraineurs may experience visual, sensory, speech, motor, or brainstem auras with their headache.[82] In the context of migraine, aura is defined by the International Headache Society as a fully reversible symptom with at least three of the following six characteristics: spreads gradually over greater than 5 min; two or more aura symptoms occur in succession; each individual aura symptom lasts 5 through 60 min; at least one aura symptom is unilateral; at least one aura symptom is positive; and the aura is accompanied, or followed within 60 min, by headache.[82] Some individuals experience aura without an accompanying headache. Even when not associated with headache, an aura can pose significant risk to aeromedical duties.

When evaluating an aircrew member with headache, migraine should be differentiated from migraine variants and other types of headache disorders, because the evidence used to evaluate the aeromedical risk of migraine cannot necessarily be applied to all headache types (**Table I**).

Prevalence of Migraine

Migraine prevalence varies by age and sex. The lifetime prevalence of migraine is 14–16% in the general population, while the 1-yr prevalence is 12–15%.[15,62,91] The lifetime prevalence of migraine is two to three times higher in women than men: while the lifetime prevalence of migraine is 25–33% among women, it is 8–13% among men.[54,91]

Most population-based studies demonstrate a unimodal distribution of migraine prevalence by age. In these studies, migraine prevalence is highest from ages 25 to 44 yr in both men and women, with prevalence peaking from ages 30 to 39 yr.[9,15,113] However, one prominent study of 40,000 randomly sampled Americans found a bimodal distribution of 1-yr peak prevalence of migraine.[117] In this particular study, migraine prevalence peaked at ages 25 and 50 among women and at ages 19 and 48 among men.

Retrospective studies of American military pilots have commented on waivers granted for headache disorders. In the U.S. Army medical database, a diagnosis of migraine was recorded for 39 (1.9%) female rated aviator pilots between 2005 and 2015.[46] Of these pilots, 18 were granted a waiver for migraine, while 8 were permanently suspended. A retrospective review within the USAF School of Aerospace Medicine showed that 5.3% (N = 871) of patient cases seen by the Aeromedical Consultation Service between 2000 and 2012 had documented input from a neurologist.[41] Among all patients evaluated, 168 diagnoses of migraines were reported. An aeromedical waiver of some type was granted in 67% of neurological cases, though the proportion of waivers granted for migraine, specifically, was not reported. More recently, a study by Hesselbrock and Haynes reported that 1559 USAF aviators were assessed for or received a waiver for the diagnosis of migraine between 2002 and 2020.[39]

Permanent groundings and sudden incapacitation events due to migraine during flight have been reported. Between 2008 and 2017, five members of the Royal Canadian Air Force (RCAF) were permanently grounded due to migraine, representing 3.0% of RCAF's total groundings during that period.[38]

Table I. Diagnostic Criteria for Migraine Variants According to the International Headache Society's International Classification of Headache Disorders 3rd Edition (ICHD-3).[82]

HEADACHE TYPE	DIAGNOSTIC CRITERIA
Typical aura without headache	A. Attacks fulfilling criteria for Migraine with typical aura and criterion B below. B. No headache accompanies or follows the aura within 60 min.
Probable migraine	A. Attacks fulfilling all but one of criteria A through D for Migraine without aura, or all but one of criteria A through C for Migraine with aura. B. Not fulfilling ICHD-3 criteria for any other headache disorder. C. Not better accounted for by another ICHD-3 diagnosis.
Hemiplegic migraine	A. Attacks fulfilling criteria for Migraine with aura and criterion B below. B. Aura consisting of both of the following: 1. fully reversible motor weakness 2. fully reversible visual, sensory, and/or speech/language symptoms

Headaches accounted for 4.9% of self-reported incidents causing sudden incapacitation of pilots in an anonymous survey by the International Federation of Air Line Pilots' Association.[45] In a review of 1000 consecutive fatal general aviation accidents in the United Kingdom from 1956 to 1995, one accident occurred after a pilot, who had a history of migraine, radioed a report of visual disturbances and numbness before crashing.[21] Based on this case report, it is not possible to conclude that the pilot's sensory disturbances were, in fact, due to migraine or that the symptoms caused the aviation accident. Future research on the prevalence of migraine in aircrew would facilitate a more accurate evaluation of the aeromedical risk of migraine.

Age of Migraine Onset

Migraine most commonly presents in adolescence and early adulthood, after which incidence decreases with increasing age.[69,92,111] The American Migraine Prevalence and Prevention (AMPP) study was a longitudinal, population-based study of 162,756 individuals from the United States and evaluated numerous parameters related to migraine.[111] In the AMPP study, migraine incidence peaked between ages 20 to 24 yr among women and between ages 15 to 19 yr among men. Migraine onset occurred before age 25 in 50% of migraine cases and before age 35 in 75% of migraine cases. It can therefore be anticipated that new-onset migraines will occur in a proportion of younger aircrew who may, for a variety of reasons, underestimate the significance of symptoms or feel compelled not to declare them. Thus, direct questioning during a clinical encounter is recommended.

Natural Course of Migraine

It is difficult to accurately estimate the proportion of people with migraine who experience persistence, progression, or remission of their migraine disorder. This, in turn, makes it difficult to estimate the natural course of any aircrew member's migraine disorder. There are few longitudinal studies that evaluate patients prospectively over significant periods of time. Further, most studies define remission as being headache-free for as little as 12 mo which, in some people, may simply represent a headache-free period before migraine recurrence. Finally, few longitudinal studies are population-based, as most select patients from Neurology clinics, likely representing a more severe headache phenotype.

Persistence and progression. Longitudinal studies have followed patients for up to 40 yr to assess headache pattern (**Table II**). Among these studies, an estimated 53–90% of individuals with migraine experience persistence or progression of their migraine disorder throughout their lifetime.[12,19,105] Approximately 3% of individuals with episodic migraine (<15 headache days per month) progress to chronic migraine (≥15 headache days per month) each year.[10,98]

It is not uncommon for individuals with migraine to experience periods of remission, followed by headache recurrence. A prospective study followed 73 children with migraine for 40 yr.[12] At the 40-yr follow-up, 22% of study participants continued to suffer from migraines but had experienced one or more migraine-free periods of greater than 2 yr duration, with a total average of 10 yr of headache-free time. Migraine-free periods represent the beginning of remission in some individuals but are temporary headache-free periods in others. For organizations that use waivers for headache, this makes it difficult to determine an appropriate waiver duration.

Case reports have commented on the natural course of migraine among aircrew. Hesselbrock et al. followed 71 USAF pilot applicants who had received waivers for migraine for a mean of 6.9 yr.[39] The average age at the time of last migraine was 17 yr old. Migraine recurrence was noted in 3 of the 71 USAF pilot applicants.

Remission. Among longitudinal studies, 10–42% of individuals with migraine experience headache remission; these studies define migraine remission as being headache-free for at least 6 mo to 1 yr (Table II).[11,70,114] A longitudinal study of 77 people with migraine with aura, specifically, found that 29% of patients were migraine-free at follow-up, which the authors defined as having no migraine attacks in the prior 2 yr.[19]

Table II. Longitudinal Studies on the Natural Course of Migraine.

STUDY	STUDY POPULATION	STUDY DURATION (yr)	PARTICIPANTS WITH HEADACHE PERSISTENCE	PARTICIPANTS WITH HEADACHE REMISSION	DEFINITION OF HEADACHE REMISSION
Bille[12]	73 individuals with at least monthly migraines in childhood	40	53%	47%	Not clearly defined
Cologno et al.[19]	77 individuals with migraine with aura	10 to 20	71%	29%	No migraine in the preceding 2 yr
Dooley et al.[26]	28 individuals diagnosed with migraine in childhood	30	71%	29%	Not clearly defined
Lyngberg et al.[70]	64 adults with migraine	11	58%	42%	No migraine in the preceding 12 mo
Sillanpaa and Saarinen[105]	31 individuals diagnosed with migraine in childhood	25	90% (migraines or a different type of headache disorder)	10%	No recurrent headaches in the preceding 6 mo
Termine et al.[114]	77 individuals diagnosed with migraine with aura in childhood	11	41% (persistence), 33% (transformed headache diagnosis)	23%	No migraine in the preceding 12 mo

An individual's experience of aura may also evolve with time. An 11-yr longitudinal study followed patients whose migraine with aura started in childhood or adolescence.[114] Of those patients, 54% experienced remission of aura, but not remission of headache itself. Average migraine duration less than 12 h and presence of electroencephalogram abnormalities at baseline predicted aura remission.[114] For aircrew, this may help to distinguish between cases with lower and higher risk of recurrence.

Clinical Presentation

The population prevalence of premonitory symptoms in migraineurs is greater than 70%.[8,55,101] The most common prodromal symptoms include fatigue, difficulty concentrating, light sensitivity, and mood change, the presence of which could extend the period of disability related to a headache episode.[35,55,101]

An estimated 20–46% of individuals with migraine experience aura.[17,66,89] Aura characteristics are highly variable from individual to individual and can vary between attacks within the same person.[17] Thus, although some people have consistent presentations, one cannot assume that a subsequent episode of aura will have the same presentation. In an interview-based study of 63 individuals with migraine, the most common type of aura was visual (99%), followed by sensory (31%), aphasic (18%), and motor (6%).[94] Sensory, motor, and aphasic aura were nearly always experienced in association with visual aura. In a retrospective study of 267 people with migraine with aura, the most prevalent visual symptoms were dots or flashing lights, then wavy or jagged lines and scotoma.[37]

In addition to pain during a migraine attack, an estimated 29–35% of individuals experience concurrent vomiting, 61–90% nausea, 65–80% photophobia, and 74–76% phonophobia.[66,89] Migraineurs may also experience neck pain or discomfort, sinus pain or pressure, nasal and ocular symptoms, or cutaneous allodynia during their headaches.[29]

The postdromal phase of migraine is the period of time after resolution of the headache, and may persist for up to 48 h.[82] A study of postdromal symptoms using daily electronic diaries found that 81% of migraineurs experience at least one nonheadache symptom in the postdromal period, with the most common being fatigue (88%), difficulty concentrating (56%), neck stiffness (42%), light sensitivity (36%), and irritability (29%).[34]

Migraine is associated with significant disability globally; however, at the individual level, migraineurs report varying degrees of pain and impairment secondary to their headaches. In the AMPP study, 7% of participants reported no functional impairment during their typical severe migraines, while 39.1% reported some impairment (able to function with reduced performance) and 53.7% reported severe impairment (unable to function or requiring bed rest).[62]

When evaluating the aeromedical risk of an aircrew member's migraine, consideration should be given to an individual's premonitory symptoms, aura characteristics, and self-reported disability, as migraine phenotypes are highly variable.

Migraine Triggers

Up to 90% of individuals who experience migraines identify one or more migraine trigger.[3] In a retrospective study of 159 USAF pilots with migraine, 63% self-identified migraine precipitants, with the most common being sleep disturbances, stress, dietary factors, caffeine intake, and hormonal factors.[40]

The role of migraine triggers is often overemphasized in studies designed to assess them. Most studies on migraine precipitants are cross-sectional and retrospective, subjecting them to recall bias and potentially limiting them by reverse causality.[65] In addition, few migraine triggers have been studied in a controlled setting and, often, only one trigger can be studied at a time, which is not realistic of an individual's true environment.

When evaluating the aeromedical risk of an aircrew member's migraine, consideration should be given to reported migraine triggers, as some triggers may be more effectively mitigated in an aviation environment than others. Easily avoidable or controllable triggers represent lower risk situations.

Weather. In retrospective studies, 7–53% of people with migraine report weather as a headache trigger.[42,85] However, most prospective studies that compare objective weather data to information from headache diaries or emergency department visits for migraine do not show a positive association. For example, Prince et al., compared weather data from the National Weather Service to headache diaries of adults with migraine living within 30 miles of a weather center.[87] While 62.3% of individuals reported weather as a migraine trigger, only 50.6% were found to be sensitive to absolute mean temperature and humidity, change in temperature or humidity, or barometric pressure. Though a subgroup of individuals with migraine may be sensitive to weather, people generally overestimate weather and change in atmospheric pressure as a migraine trigger.

Menstruation. Up to 70% of female migraineurs report menstruation as a headache trigger.[118] In a retrospective study of 51 women with menstrual-associated migraines, 67% reported their headaches during menstruation to be more severe, more refractory to symptomatic therapy, or of longer duration than their nonmenstrual attacks.[3]

Physical fatigue and psychosocial stress. Of individuals with migraine, 20–84% report physical or mental fatigue as a migraine trigger, while up to 54% report excess sleep as a precipitant of migraine.[3,16,120] In retrospective studies, 31–87% of migraineurs identify psychosocial stress as a migraine trigger. In prospective studies that compare patient-reported stress levels to information from headache diaries, relaxation after stress and stress on day −1 are associated with headache onset.[51,63,102] Evidently, both mental and physical strain may trigger migraines.

Circadian disturbances. Up to 50% of individuals with migraine report sleep disturbances, including circadian rhythm changes, as a migraine trigger.[47,48,120] Individuals with migraine are less likely to be of a normal chronotype than those without a history of migraine.[116] Further, migraineurs, and particularly those

with a high headache frequency, are significantly more tired after changes in circadian rhythm.[116] Chronobiological factors likely play a role in the relationship between circadian disturbances and migraine. Eastward flight, with its resultant shift in circadian rhythm, is particularly relevant for aircrew.

Hypoxia. Though hypoxia is not commonly identified by individuals as a headache trigger, normobaric hypoxia has been shown to induce migraine in experimental conditions. In a study by Broessner et al., 77 individuals with no migraine history were exposed to a fraction of inspired oxygen of 12.6% to simulate an altitude hypoxia of 14,764 ft (4500 m).[14] There were 63 (81.2%) participants who developed a headache by hour 6 of the experiment. In a randomized, double-blind, cross-over study by Arngrim et al., 15 participants with a history of migraine with aura were exposed to either 3 h of normobaric hypoxia or sham on two separate days, while 14 controls with no history of migraine were exposed to hypoxia.[4] Eight (53%) participants with a history of migraine experienced migraine-like attacks while hypoxic, compared to one who did during the sham procedure ($P = 0.04$) and one in the control group ($P = 0.01$). During the hypoxic state, the median time to onset of headache was 105 min. Migraine may be precipitated by hypoxia in some individuals, though people are less likely to recognize this as a trigger.

Food. Up to 57% of migraineurs report missed meals, hunger, or certain foods as migraine triggers, with the most common products being alcohol, cheese, chocolate, and caffeine withdrawal.[47,73,85] Wine, chocolate, and tyramine have been studied as migraine triggers in randomized controlled trials, with inconsistent results.[33,67,119] While migraineurs commonly report food as a migraine trigger, randomized controlled trials show mixed results.

Comorbidities

Migraine has been associated with numerous psychiatric and medical conditions, including depression, anxiety, ischemic stroke, chronic pain syndrome, and sleep disorders. The relationship between migraine and depression is bidirectional. A prospective study of 496 Americans found that major depression at baseline predicted new onset migraine at the 2-yr follow-up [odds ratio (OR) = 3.4], while migraine at baseline predicted new-onset major depression at follow-up (OR = 5.8).[13] Further, depression is associated with chronification of migraine. Compared to those with no or mild depression, individuals with moderate depression (OR = 1.77), moderately severe depression (OR = 2.35), and severe depression (OR = 2.53) are at increased risk of conversion from episodic to chronic migraine.[6]

There is a strong relationship between migraine and anxiety. Individuals with anxiety have a 2.7 to 4.2 times greater risk of developing migraine than those without anxiety.[53,76,121] The strong relationship between mental health and migraines provides additional justification to screen for and address psychiatric conditions in aircrew, particularly in those with migraine.

Ischemic stroke has also been associated with migraine. The presence of migraine increases an individual's risk of ischemic stroke by 1.5 to 2.2 times.[28,107] This relationship is only significant among people who have migraine with aura, though the relationship trends toward significance in migraineurs without aura.[107] A high frequency of migraine attacks (>12/yr) and recent onset of migraine (<1 yr ago) are each associated with an increased risk of ischemic stroke.[52,71]

Migraine has been associated with chronic pain syndromes, including fibromyalgia. The prevalence of fibromyalgia is estimated to be 3–6% in the general population, while it is 10–36% among individuals with migraine.[23] Though all migraine is associated with increased odds of fibromyalgia, there is a stronger correlation with migraine with aura.[56] Further, patients with migraine and comorbid fibromyalgia are more likely to experience suicidal ideation and suicide attempts, providing additional justification to screen for chronic pain and mental health disorders during aeromedical exams.[68]

Migraine interferes with consolidative and restorative sleep and, not surprisingly, there is a bidirectional relationship between migraine and insomnia.[80,81] Furthermore, the presence of insomnia is associated with increased migraine pain intensity, attack frequency, and risk of migraine chronification.[48,49,95]

When evaluating the aeromedical risk of migraine, consideration should be given to comorbidities, particularly depression, anxiety, and sleeping disorders. This data provides additional justification for screening for and treating comorbid conditions among current and prospective aircrew members.

Family History

Though migraine is influenced by environmental factors, it does have a strong genetic component. Individuals with a family history of migraine in a first-degree relative have up to a twofold increased risk of developing migraine compared to those without a family history.[79,110] This relationship is even more significant for aura. Individuals who have a first-degree relative with migraine with aura, specifically, have up to a fourfold increased risk of developing migraine with aura compared to those without a family history.[18,86,93]

Family history of migraine is also associated with younger age of migraine onset.[27,79,86] In a retrospective study of 54 probands with migraine in Ontario, mean age of migraine onset decreased with increasing genetic load.[79] While the mean age of migraine onset was 26.1 yr among those with a one-generation family history of migraine, the mean age of onset was 21.7 yr and 17.6 yr for two-generation and three-generation families, respectively.

The prognostic impact of family history on the natural course and severity of headache is less clear. Some studies suggest that a family history of migraine is associated with increased migraine severity, persistence, and headache duration, while other studies suggest that family history is associated with a neutral or favorable prognosis.[19,78,110] Therefore, family history is of limited use in the evaluation of the aeromedical risk of migraine.

Neuroimaging in Migraine

Neuroimaging has been performed during asymptomatic and headache phases to better understand the pathophysiology of migraine and aura. Some of the earliest studies of migraine pathophysiology date back to the 1940s, when cortical spreading depression (CSD) was first observed in rabbit studies.[57,58] CSD describes a slowly propagating wave of neuronal excitation followed by inhibition and is believed to be the physiological substrate of migraine aura. The suppression of CSD by antimigraine medications in animal models has further supported the role of CSD in migraine pathophysiology.[7]

Most functional neuroimaging studies in migraineurs have been performed during asymptomatic phases. Even interictally, individuals with migraine exhibit changes in hypothalamic activity and functional connectivity networks involved in stimulus processing.[104] In numerous studies, the extent of connectivity abnormalities correlates with markers of migraine burden, such as migraine frequency or years lived with migraine.[104] Interestingly, time to next headache has been shown to be predictable using signal amplitude in the spinal nuclei on functional MRI in a research setting.[108] However, this is not yet a commonly available assessment modality and has not been applied to a clinical setting. If this information becomes more readily available, it will provide clinically objectifiable information for risk assessment purposes.

Few studies have reported on neuroimaging during the headache phase of migraine. Schulte and May followed an individual with migraine using functional MRI each day for 30 consecutive days.[103] They noted a significant activation within the ipsilateral hypothalamus and bilateral visual cortex in the 24 h preceding headache onset, as compared to activation during interictal periods. In addition, Amin et al. observed increased functional connectivity between the right thalamus and several contralateral brain regions during the acute headache phase in migraineurs.[2] It is hypothesized that ascending pain pathways are disrupted during acute headache, accounting for cognitive, emotional, and physical symptoms experienced during migraine.

To the best of our knowledge, no neuroimaging studies have been performed during the postdromal phase of migraine. Further, no neuroimaging studies have evaluated the effect of attention or cognitive load on migraine onset.

Non-Pharmacological Interventions

Modulating devices, or stimulators, have been shown to be effective in migraine prevention. Supraorbital transcutaneous stimulation, percutaneous electrical nerve stimulation, and transcranial magnetic stimulation have been shown to significantly reduce mean number of headache days in clinical trials, while noninvasive vagus nerve stimulation is nonsuperior to sham.[77,100,109] Reported adverse effects of modulating devices include light-headedness, paresthesias, tinnitus, and erythema and pain at the application site.

Acupuncture is a well-studied, nonpharmacological therapy used by some individuals in the management of migraine. Acupuncture is more effective than oral placebo in reducing migraine frequency, but there is only a small effect of true acupuncture over sham acupuncture.[59,75] Adverse effects of acupuncture are relatively rare but include bleeding, contact dermatitis, infection, nerve damage, and organ puncture.

Various vitamins, supplements, and herbal medications are commonly trialled for migraine prevention. Placebo-controlled studies show mixed results for the efficacy of Vitamin B2 and magnesium as migraine prophylaxis, though consumption rarely leads to side effects.[72,84,99] In randomized controlled trials, coenzyme Q10 reduces the duration and frequency of migraine attacks; however, available studies are of short duration with small sample sizes.[96,97] Butterbur is a plant extract used by some individuals for migraine prophylaxis. Though butterbur decreased migraine frequency compared to placebo in two randomized controlled trials, it has potentially mutagenic and carcinogenic effects in humans.[24,64]

Relaxation therapy, biofeedback, cognitive behavioral therapy, and self-monitoring skills are used as behavioral and psychological techniques for migraine prevention. Meta-analyses show a 35–55% reduction in migraine parameters with various behavioral and psychological therapies.[36,48]

Pharmacological Therapy

Abortive therapy. Up to 90% of Canadians with migraine in the general population use acute pharmacological therapy to abort their headaches.[20] Triptans are one of the most common drug classes used to treat migraines acutely. All oral triptans provide significant relief of pain at their marketed doses by 1 h and the differences between them are relatively small.[83] However, triptan monotherapy does not consistently provide headache relief in about one-third of individuals.[30] Among all triptans and formulation types, the highest efficacy for absence of pain at 2 h is observed in subcutaneous sumatriptan [number needed to treat (NNT) = 2.7]; however, it also has the lowest number needed to harm (3.3).[32] Adverse effects of triptans depend on formulation type, but include vertigo, neck pain, dysphoria, fatigue, and nausea.

Most jurisdictions currently do not allow the use of triptans during flight. Within the USAF, oral triptans are approved for Ground-Based Operator, Air Traffic Control, and Special Warfare Airmen duties; however, a waiver is required. Flight class 2 waivers for abortive migraine therapy are generally restricted to non-high-performance aircraft and duties that involve another qualified pilot. Flight class 1 applicants who require prescription abortive medication are not eligible for waiver consideration.

Various nonsteroidal anti-inflammatory drugs and simple analgesics are commonly used to treat migraines acutely. Oral ASA at doses of 900 mg to 1000 mg is superior to placebo at eliminating pain at 2 h (NNT = 8.1) and providing 24-h headache relief (NNT = 6.6).[50] A dose of 1000 mg of oral acetaminophen is slightly less effective than ASA in the short-term, with an NNT of 12.0 for eliminating pain at 2 h.[22] Ibuprofen 400 mg is more effective than both ASA and acetaminophen, with numbers needed to treat of 7.2 and 4.0 for 2-h elimination of pain and 24-h sustained headache relief, respectively.[90]

Intramuscular and intravenous dopamine receptor antagonists, corticosteroids, and antiepileptics can be used in acute medical settings to abort migraines; however, these formulations are not easily accessible to the outpatient population.

Prophylactic therapy. Patients with a high frequency of migraine attacks or whose headaches carry a significant burden despite abortive medical therapy may benefit from prophylactic therapy. Anticonvulsants are one of the most common drug classes used for migraine prophylaxis, with the greatest evidence existing for topiramate and valproate. Specifically, daily oral topiramate reduces headache frequency by approximately 1.2 migraine attacks per month.[61] Similarly, valproate decreases the number of headache attacks by 1.4 at 4 wk of therapy.[43] Results for gabapentin are controversial; it was not superior to placebo in several randomized controlled trials and meta-analyses, though it significantly decreased monthly migraine frequency in other double-blind, placebo-controlled studies.[43,60,74] Common (>10% reported frequency) side effects of topiramate include paresthesias, fatigue, and memory impairment, while common side effects of valproate include nausea, dizziness, drowsiness, insomnia, and tremor.

Tricyclic antidepressants also play a role in migraine prophylaxis. In a systematic review and meta-analysis, tricyclic antidepressants reduced headache frequency by an average of 1.4 attacks per month.[44] Among tricyclic antidepressants, the highest quality of evidence exists for amitriptyline, which has been shown to be noninferior to topiramate in terms of rate reduction of monthly migraine attacks.[25,88] Side effects of tricyclic antidepressants include fatigue, drowsiness, and dizziness.

Beta blockers and angiotensin-receptor blockers have also been shown to be effective for migraine prophylaxis. Specifically, atenolol, metoprolol, and propranolol are each superior to placebo in the prevention of episodic migraine.[43] Propranolol, the most frequently studied, has a pooled relative risk of 4.3 for >50% improvement in episodic migraine headaches at 8 wk when compared to placebo.[43] Candesartan reduces migraine days per month by 0.58 to 3.5 d in cross-over placebo-controlled studies.[112,115] Side effects of beta blockers include fatigue, bradycardia, and hypotension, while side effects of angiotensin-receptor blockers include hypotension, dizziness, and hyperkalemia.

Monoclonal antibodies that target the calcitonin gene-related peptide (CGRP) receptor have shown promising results for migraine prevention in clinical trials. Erenumab, fremanezumab, galcanezumab, and eptinezumab each significantly reduce migraine frequency compared to placebo, with eptinezumab and galcanezumab decreasing migraine frequency as early as 1 d and 1 mo after the first dose, respectively.[5,106] A case report by Garber et al. described the effectiveness of fremanezumab for a 45-yr-old commercial pilot.[31] While on prophylactic propranolol, the pilot experienced migraines at a frequency of 13 to 15 headache days per month. After stopping propranolol and receiving two monthly injections of fremanezumab with no local or systemic side effects, the pilot's migraines resolved and he returned to commercial flying. Though not all individuals would be expected to experience as dramatic a response, CGRP monoclonal antibodies hold great potential for the future of migraine prophylaxis.

In addition, CGRP antagonists, also known as gepants, have been shown to prevent migraine headaches. In a phase three, double-blind trial, oral atogepant reduced the number of migraine days by 1.7 over 12 wk among patients with episodic migraine when compared to placebo.[1] Common adverse effects included nausea and constipation, while serious adverse effects included asthma and optic neuritis.

As a general principle, headaches of such frequency or severity that prophylaxis is required would be considered higher risk than those that do not and, as a result, would require detailed review. Canadian civil aviation authorities have given waivers on a case-by-case basis for beta blockers, calcium channel blockers, and monoclonal antibody therapies if there has been clinical stability over a least 6 mo with no side effects. Among aircrew in the USAF, no prophylactic pharmacological therapies are formally approved for headache prevention for any flying class, Air Traffic Control, or Special Warfare Airmen duties. Ground-Based Operator personnel may use calcium channel blockers, beta-blockers, or topiramate for migraine prophylaxis.

DISCUSSION

Because randomized controlled trials are not an appropriate method to evaluate safety for medical conditions that may cause subtle or sudden incapacitation, the evaluation of fitness-to-fly must be based on an aeromedical risk assessment, which is often informed by extrapolated evidence and flight safety data. In this review, we provide a cumulative summary of epidemiological data related to a variety of factors that may be present in specific individual cases of migraine to enable evidence-informed aeromedical risk assessment.

A risk matrix is a commonly used approach to guide and standardize the evaluation of the aeromedical risk of medical conditions in Canada.[122] This risk matrix incorporates an evidence-based assessment of both the probability and consequence of a medical event occurring for an individual, taking into account their specific role or trade. The likelihood of the medical event occurring is based on evidence extrapolated from literature and expert opinion from clinical specialists. For each potential medical event, the probability is categorized as: 1) likely (the estimated risk of an event is >2% per year); 2) possible (1–2% per year); 3) unlikely (0.5–1% per year); or 4) highly unlikely (<0.5% per year). Then, the consequences of a medical event are evaluated, considering each the following components: 1) the impact on mission completion and flight safety; 2) the effect on the operational performance of the individual with the medical event; and 3) the requirement for medical evaluation of the affected individual. Based on these factors, the predicted consequence of a medical event is classified into one of four categories, with class 1 indicating a minimal effect and class 4 indicating a critical effect (**Table III**). The final

Table III. Classes of Consequences of a Medical Event as Defined by the Risk Matrix Approach Used Widely in Canada.

MEDICAL EVENT	IMPACT ON MISSION COMPLETION AND FLIGHT SAFETY	IMPACT ON OPERATIONAL PERFORMANCE OF THE INDIVIDUAL	REQUIREMENT FOR MEDICAL ATTENTION
Class 1 event	Minimal or no mission impact.	Low or minimal effect on performance.	Requires only routine medical follow-up.
Class 2 event	May result in mission abort or compromised mission effectiveness with no risk to flight safety.	Moderate effect on performance.	Requires postmission medical follow-up.
Class 3 event	May result in flight safety hazard with a high probability of mission compromise.	Major effect on performance.	Requires immediate medical attention.
Class 4 event	Likely to result in a flight safety critical event and mission termination.	Total incapacitation.	Requires immediate advanced medical care.

Table IV. Categories of Aircrew as Defined by the Risk Matrix Approach Used Widely in Canada.

CATEGORY NO.	AIRCREW
1	Pilots: Fighter, Tactical Helicopter, Maritime Rotary Wing, Search and Rescue Rotary Wing, Instructors of Pre-Wing Students, Search and Rescue Technicians
2	Pilots: Transport, Maritime Fixed Wing, Search and Rescue Fixed Wing, Instructors of Post-Wing Students
3	Air Combat Systems Operators, Flight Engineers, Airborne Electronic Sensor Operators, Mission Specialists, Flight Test Engineers, Loadmasters, Airborne Environmental Control Officers, Airborne Control Operators in designated control positions, Aeromedical Training Officers assigned to chamber duties, Aeromedical Technician, Unmanned Aerial Vehicle Tier 1/2 Operators
4	Flight Surgeon, Flight Nurse, Flight Medical Technician, Flight Steward, Flight Attendant, Airborne Warning and Control System and Automatic Terminal Information Services, Unmanned Aerial Vehicle Payload Ops

component of the risk matrix approach acknowledges the differing impact of a medical event within the spectrum of designated aircrew positions by classifying aircrew into four categories (**Table IV**). Evaluation of these three components—likelihood of a medical event, the consequences of a medical event, and the specific role of the individual—facilitates a comprehensive, three-dimensional approach to the risk assessment of a medical condition (**Fig. 1**).

We will discuss a case to demonstrate application of the risk matrix approach to the assessment of migraine in aircrew. A 31-yr-old Flight Engineer presents for his initial medical examination. He has a history of episodic migraines without aura. His migraines used to occur twice per year while he was in postsecondary school. He has not had a migraine since he finished graduate school at age 25. His typical migraines are accompanied by nausea and photophobia. Approximately 75% of his migraines are aborted within 4 to 5 h using high dose ibuprofen. Self-identified migraine triggers include poor sleep; since completing graduate school, he typically maintains a regular sleep schedule with an average of 7 h of sleep per night. He is otherwise healthy, with no medical history of anxiety, depression, or sleep disorders, and he takes no prescribed or over-the-counter medications. Complete neurological, cardiac, and respiratory exams are unremarkable.

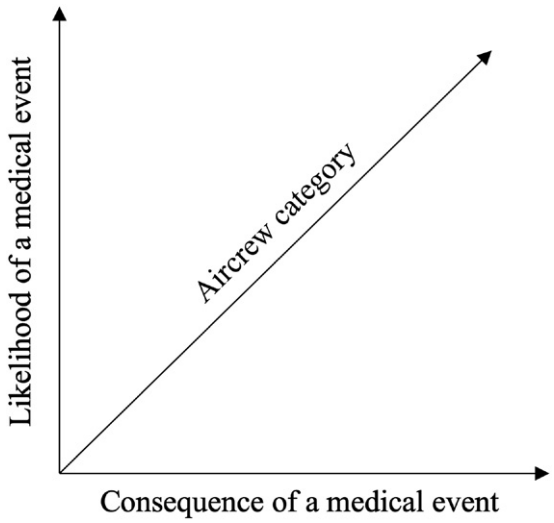

Fig. 1. Visual representation of the three-dimensional risk matrix approach commonly used in Canada to evaluate the aeromedical risk of a medical event.

Given the absence of migraine for 6 yr and a modifiable migraine trigger, his annual risk of migraine occurrence might be estimated at "unlikely" to "possible". If a migraine similar to known prior episodes were to recur, it would be rated as a Class 3 Medical Event, given that it would result in a major effect on performance. Based on the three-dimensional risk matrix, this would place his migraine disorder at an overall low to moderate risk (**Fig. 2**). However, using the risk matrix analysis, if this individual's migraines were predicted to be more frequent and/or triggered by an unavoidable factor, it could be considered high risk. Similarly, if the individual was in a different trade (e.g., Tactical Helicopter Pilot), the same migraine disorder might be considered moderate to high risk. Evidently, the aeromedical risk assessment of a medical event must be highly individualized and based on a detailed understanding of the condition's epidemiology and natural course.

Migraine is a complex disorder with a wide range of clinical phenotypes, some of which carry significant risk to aeromedical duties. Because of its prevalence in the general population and growing availability of advanced imaging, knowledge and pharmacotherapy options are evolving quickly. As more objective information becomes available for integration into the risk

Fig. 2. Application of the three-dimensional risk matrix approach to a case example of episodic migraine. Red = high risk; yellow = moderate risk; green = low risk. Based on the case example, the individual's migraine disorder could be considered low to moderate risk (A). If the individual had more frequent migraines, their risk could be considered high (B). If the individual was a Category 1 Aircrew, their migraine disorder could be considered moderate to high risk (C).

assessment process, in turn, increasingly evidence-based aeromedical disposition for migraines will be possible. Regulatory agencies will need to consider new diagnostic modalities and therapies to enable this. Awareness of the most current epidemiological data related to a variety of migraine parameters facilitates an evidence-based risk assessment of migraine in aircrew and requires iterative updates as new information becomes available.

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