2020

The Influence of Migraine on Driving: Current Understanding, Future Directions, and Potential Implications of Findings

S. J. Tepper

S. D. Silberstein

N. L. Rosen
Zucker School of Medicine at Hofstra/Northwell

R. B. Lipton

E. B. Dennehy

See next page for additional authors

Headache
© 2019 Eli Lilly and Company. Headache: The Journal of Head and Face Pain
published by Wiley Periodicals, Inc. on behalf of American Headache Society

ISSN 0017-8748
doi: 10.1111/head.13716
Published by Wiley Periodicals, Inc.

Views and Perspectives

The Influence of Migraine on Driving: Current Understanding, Future Directions, and Potential Implications of Findings

Stewart J. Tepper, MD; Stephen D. Silberstein, MD; Noah L. Rosen, MD; Richard B. Lipton, MD; Ellen B. Dennehy, PhD; Sherie A. Dowsett, PhD; Erin Doty, MD

Objective.—To review the published findings relevant to migraine and driving performance, with an intent to encourage discussion on research which may broaden understanding in this area and help educate healthcare providers and their patients.

Background.—Motor vehicle crashes result in more than 35,000 deaths and more than 2 million injuries annually in the United States. Migraine is one of the most prevalent diseases in the world, and many symptoms associated with migraine attacks have the potential to negatively influence driving ability.

Methods.—We reviewed the published findings related to migraine and driving performance. Study findings relevant to symptoms of migraine and their potential effect on driving were also reviewed. This required a more expansive exploration of the literature beyond migraine, for example, review of the literature relating to the effect of pain, sleepiness, visual disturbances, or vertigo on driving. Finally, the potential effects of treatment for migraine on driving were reviewed.

Results.—Literature on the effect of migraine on driving performance is sparse and, in general published studies on the topic have a number of limitations. Based on review of the literature pertaining to other disorders, it seems feasible that some symptoms occurring as part of the migraine attack could impact driving performance, although formal study in this area is lacking. Many of the approved treatments for migraine have the potential to impact driving, yet this has not been specifically studied, and the extent to which these risks are communicated to patients is not clear.

Conclusion.—The impact of migraine on driving performance has been largely neglected, with few studies specifically designed to address the topic, and relevant studies were generally small with limited control of confounders. This area requires more focus, given a potential for impact on road safety.

Key words: migraine, driving performance, motor vehicle accident, treatment

Abbreviations: CGRP calcitonin gene-related peptide, CNS central nervous system, FDA Food and Drug Administration, MVC motor vehicle crash, NSAID nonsteroidal anti-inflammatory drug, TCA tricyclic antidepressant, USPI United States Prescribing Information

(*Headache* 2020;60:178-189)

From the Geisel School of Medicine at Dartmouth, Hanover, NH, USA (S.J. Tepper); Jefferson Headache Center, Thomas Jefferson University, Philadelphia, PA, USA (S.D. Silberstein); Northwell Health Physician Partners Neuroscience Institute, Great Neck, NY, USA (N.L. Rosen); Montefiore Headache Center, Albert Einstein School of Medicine, The Bronx, NY, USA (R.B. Lipton); Eli Lilly and Company, Indianapolis, IN, USA (E.B. Dennehy, S.A. Dowsett, and E. Doty); Department of Psychological Sciences, Purdue University, West Lafayette, IN, USA (E.B. Dennehy).

Address all correspondence to E. Doty, Eli Lilly and Company, Indianapolis, IN, USA, email: doty_erin_gautier@lilly.com.

Accepted for publication November 6, 2019.

INTRODUCTION

Motor vehicle crashes (MVCs) are responsible for more than 35,000 deaths and more than 2 million injuries annually in the United States, resulting in an economic loss of hundreds of billions of dollars.[1-3] Given the central role of driving in maintaining independence and empowering personal autonomy, better understanding of factors contributing to MVCs and the severity of associated injuries is paramount. Increased awareness, improvements in vehicular design, and legislative focus on speeding, seat belt use, and driving while intoxicated have reduced the number and severity of accidents in many parts of the developed world. Since operating a motor vehicle involves a wide range of cognitive, perceptual, and motor activities, focus has now shifted to initiatives that reduce individual driving impairment associated with distracted driving, as well as that associated with certain medical conditions, most notably epilepsy,[4,5] diabetes,[6] sleep disorders,[7] pain,[8,9] dementia,[10,11] and use of drugs (both illicit and prescribed).[12-14]

Migraine is one of the most prevalent diseases in the world, affecting over 30 million adults in the United States.[15] Based on the most recent analysis from the World Health Organization Global Burden of Disease, it was the second largest cause of years lost to disability.[16] It is a neurologic disorder characterized by episodic attacks of moderate to severe head pain and other symptoms.[17-19] A migraine attack can begin with premonitory (prodromal) symptoms occurring hours or days before the onset of pain, with symptoms including yawning, tiredness, fatigue, changes in mood, impaired concentration, photophobia/phonophobia, and neck stiffness. The headache phase characteristically lasts 4-72 hours with head and neck pain, as well as other associated symptoms, including photophobia, phonophobia, nausea, and dizziness or vertigo. A postdromal phase follows and usually lasts less than 12 hours. The most common postdromal symptoms include asthenia, fatigue, somnolence, difficulty with concentration, photophobia, and irritability. In about a third of people with migraine, reversible neurological symptoms (migraine aura) can occur before the onset, during, or in the absence of pain. Migraine with aura is characterized by visual, sensory, or speech/language disturbances in addition to the pain and other

Financial Support: This review paper was a collaboration between Eli Lilly and Company and migraine experts external to Lilly. Three authors on this paper are full time employees at Eli Lilly and Company. Authors external to Lilly were not reimbursed for their involvement in writing this paper. All other conflicts are disclosed in the conflicts of interest statement.
Conflict of Interest: ST – Grants for research (no personal compensation): Alder, Allergan, Amgen, Dr. Reddy's, ElectroCore, Eli Lilly, eNeura, Neurolief, Novartis, Scion Neurostim, Teva, Zosano; Consultant and/or Advisory Boards: Acorda, Alder, Alexsa, Allergan, Alphasights, Amgen, Aperture Venture Partners, Aralez Pharmaceuticals Canada, Axsome Therapeutics, BioDelivery Sciences International, Biohaven, Charleston Labs, Decision Resources, DeepBench, Dr. Reddy's, ElectroCore, Eli Lilly, eNeura, Equinox, ExpertConnect, GLG, GSK, Guidepoint Global, Impel, M3 Global Research, Magellan Rx Management, Marcia Berenson Connected Research and Consulting, Medicxi, Navigant Consulting, Neurolief, Nordic BioTech, Novartis, Pfizer, Reckner Healthcare, Relevale, Satsuma, Scion Neurostim, Slingshot Insights, Sorrento, Spherix Global Insights, Sudler and Hennessey, Teva, Theranica, Thought Leader Select, Trinity Partners, XOC, Zosano. Royalties: Springer. Salary: Dartmouth-Hitchcock Medical Center, American *Headache* Society. SDS – As a consultant and/or advisory panel member, Dr. Stephen Silberstein receives, or has received, honoraria from Abide Therapeutics; Alder Biopharmaceuticals; Allergan, Inc.; Amgen; Avanir Pharmaceuticals, Inc.; Biohaven Pharmaceuticals; Cefaly; Curelator, Inc.; Dr. Reddy's Laboratories; Egalet Corporation; GlaxoSmithKline Consumer Health Holdings, LLC.; eNeura Inc.; electroCore Medical, LLC; Impel NeuroPharma, Inc.; Eli Lilly USA, LLC; Medscape, LLC; Novartis, Inc.; Satsuma Pharmaceuticals; Supernus Pharmaceuticals, Inc.; Teva Pharmaceuticals; Theranica; and Trigemina, Inc. NLR – Allergan: honoraria for speaking, advisory board and research support. Alder: honoraria for advisory board. Amgen/ Novartis: honoraria for advisory board. Biohaven: honoraria for advisory board. Eli Lilly and Company: honoraria for advisory board, research support. Promius: honoraria for advisory board. Supernus: honoraria for advisory board. Teva: honoraria for advisory board. RBL – Edwin S. Lowe Professor of Neurology at the Albert Einstein College of Medicine in New York. Receives research support from the NIH: 2PO1 AG003949 (mPI), 5U10 NS077308 (PI), R21 AG056920 (Investigator), 1RF1 AG057531 (Site PI), RF1 AG054548 (Investigator), 1RO1 AG048642 (Investigator), R56 AG057548 (Investigator), U01062370 (Investigator), RO1 AG060933 (Investigator), K23 NS09610 (Mentor), K23AG049466 (Mentor), K23 NS107643 (Mentor). Receives support from the Migraine Research Foundation and the National *Headache* Foundation. Serves on the editorial board of Neurology, senior advisor to Headache, and associate editor to Cephalalgia. Reviewed for the NIA and NINDS, holds stock options in eNeura Therapeutics and Biohaven Holdings; serves as consultant, advisory board member, or has received honoraria from: American Academy of Neurology, Alder, Allergan, American *Headache* Society, Amgen, Autonomic Technologies, Avanir, Biohaven, Biovision, Boston Scientific, Dr. Reddy's, Electrocore, Eli Lilly and Company, eNeura Therapeutics, GlaxoSmithKline, Merck, Pernix, Pfizer, Supernus, Teva, Trigemina, Vector, Vedanta. Receives royalties from Wolff's *Headache* 7th and 8th Edition, Oxford Press University, 2009, Wiley and Informa. ED, EBD and SAD are full time employees and minor stock holders at Eli Lilly and Company, IN, USA

associated symptoms of migraine. Vestibular migraine, occurring in a small subset of those with migraine, is associated with moderate or severe vestibular symptoms including spontaneous, positional, and head motion- or visually-induced vertigo.[20,21] Many of the symptoms associated with a migraine attack have the potential to negatively influence driving ability.

For a more complete understanding of any influence of migraine on driving ability, the effects of migraine treatments must be considered. A Food and Drug Administration (FDA) guidance document, available in draft form in 2015 and issued in 2017, outlines the circumstances under which drug developers need to assess drug effects on driving ability during development of a new treatment.[22] Acute treatments for migraine in current use were approved prior to the issuance of this guidance document. As a result, they have not been subject to a thorough assessment of their impact on driving; any driving warnings in the United States Prescribing Information (USPI) appear to be the result of adverse event findings (eg, fatigue, dizziness) that could *potentially* affect driving and other activities.

Individuals with migraine have reported concerns about driving during an attack. A Canadian population survey reported that 45% of patients with migraine or tension headache worry about driving because of headache.[23] In a cross-sectional study of 1200 Spanish drivers questioned about their health, psychosocial characteristics, and driving, 63% considered headaches or migraine to impair driving performance "a lot" (vs "little" or "not at all").[24]

We reviewed the published findings related to migraine and driving performance, as well as literature relevant to symptoms of migraine and their potential effect on driving. In the latter case, more expansive exploration of the literature beyond migraine was required. Finally, we reviewed published findings on the potential effects of treatment for migraine on driving. Throughout this review, we use the terminology *motor vehicle crash* (*MVC*) to cover the individual vehicular collision terms used in the various publications cited; these terms included motor vehicle accident, motor vehicle crash, motor vehicle collision, vehicular crash, vehicular accident, road traffic accident, and motor vehicle injury. The intent of this review is to encourage discussions and research that could broaden understanding in this area and, ultimately, help patients manage their disease, treatment, and activities accordingly.

EFFECT OF MIGRAINE ON DRIVING PERFORMANCE – A REVIEW OF THE LITERATURE

Effect of Migraine Disorder on Driving Performance.—Published epidemiological data that address the effect of a diagnosis of migraine (regardless of whether the individual is experiencing a migraine attack) on driving performance are limited. Findings from population studies in New Zealand and Canada both suggest that having a diagnosis of migraine is associated with greater risk for injury from MVCs. In New Zealand, among 10,289 individuals enrolled in a prospective observational study of risk factors for serious injury and chronic disease and for whom relevant information was available, among those who reported a history of treated migraine, 18% reported a MVC compared with 10% of those who reported no history of treated migraine ($P < .0001$).[25] A longitudinal, prospective dataset from the Canadian National Population Health Survey was used to examine the effects of medical conditions and medication use on subsequent MVCs.[26] A significantly higher proportion of respondents with migraine reported subsequent a MVC compared with those without migraine (n = 60 [12%] vs n = 861 [7%], $P < .0001$); significant differences in the proportion reporting a MVC were also seen in the case of the presence/absence of asthma, back problems, or distress but not in the case of presence/absence of arthritis/rheumatism, high blood pressure, or diabetes. Neither of these studies included information on the timing of the MVC in relation to the migraine attack or treatment.

In a study to evaluate the burden of migraine, 102 consecutively enrolled patients with migraine (with or without aura) and with ≤15 headache days/month were enrolled at a headache center in Italy. Patients reported function and disability over the past month, using a model endorsed by the International Classification of Functioning Disability and Health.[27] About 20% of patients reported being severely limited in driving due to migraine, and about 15% communicated that they had severe issues with driving performance. No further

details on driving performance were reported, nor was information available on healthy controls (ie, no individuals without migraine).

In a cross-sectional hospital-based study in the United Arab Emirates, investigators assessed the association between migraine and MVCs. Of 1985 consecutive vehicle drivers seen for accidents and trauma in an Accident and Emergency Department, 1715 consented to participate, of which 80 were diagnosed with migraine based on clinical interview.[28] There was a significantly higher risk of careless driving and property damage in those with migraine vs controls, while risks of excessive speed violations, traffic violations, alcohol and drug use, or road traffic accident were not increased.

In a study of Israel Defense Forces professional male drivers (1300 involved in prior MVCs; 4305 not involved), findings from a multivariate analysis to identify health parameters associated with MVCs suggested that migraine increased this risk, as did valvular heart disease and perianal disease.[29]

While these studies provide a valuable contribution to the literature, there are study limitations. Sample sizes were often small; migraine was defined based on self-reporting in some cases; and migraine cases were defined as individuals with migraine and not individuals who experienced a migraine attack while driving. The possibility of confounding factors was not thoroughly addressed and any identified association between migraine and driving impairment or accident risk does not equate to causality. For example, sleepiness or alcohol may be a trigger for a migraine attack but may also independently contribute to impaired driving. The potential effects of migraine treatment were not addressed. As will be discussed in more detail below, this is an important consideration given the recognized side effects of acute and preventive treatments for migraine.

In conclusion, migraine has been associated with impaired driving performance and MVCs but the few studies published have a number of limitations. To explore the effect of migraine on driving performance further, we reviewed the available data pertaining to commonly experienced symptoms of a migraine attack and their potential influence on driving performance.

Impact of Migraine Symptoms on Driving Performance.—In this section, we focus on the symptoms of a migraine attack with potential to affect driving performance. These include pain, cognitive impairment, sleepiness, dizziness and vertigo, as well as visual disturbances (not necessarily independent of each other).

In migraine specifically, both head and neck pain are common symptoms in both the premonitory and pain phases of a migraine attack,[17,30] and there is potential for neck pain to limit neck movement while driving. Pain can affect physical function and has been associated with impaired cognitive performance in relation to attention, reaction time, and executive function.[8] In a small study (N = 28), highway driving performance, assessed using a standardized on-the-road driving test, was impaired in patients with chronic pain (mostly related to lower back) vs controls, although patients with chronic pain rated their own driving quality to be normal.[31] In a mail questionnaire study of 223 patients seen at a chronic pain rehabilitation center, 70% indicated that pain limited their driving in some manner.[9]

Cognitive dysfunction, whether a result of pain or arising as an independent symptom, is a common complaint of individuals with migraine, and deficits in attention, executive function, memory, processing speed, cognitive efficiency, and reaction time have all been reported.[32-36] Individuals with vestibular migraine may have more pronounced cognitive impairment than those with a non-vestibular migraine.[37] Cognitive symptoms can occur during any phase of a migraine attack, and some individuals with migraine also complain of cognitive symptoms outside migraine attacks.[36] Interictal cognitive dysfunction may reflect a prolonged postdrome, effects of preventive migraine medications, or cogniphobia (the specific fear and avoidance of cognitive exertion because the individual believes that it will precipitate or exacerbate a headache).[38]

Migraine can be associated with symptoms of tiredness, fatigue, and somnolence during premonitory and postdromal phases, and sleep disturbance is one of the most common triggers for migraine.[39,40] Sleepiness or drowsiness can result in cognitive impairment, including reduced vigilance and focus, delayed reaction

time, memory impairment, poor coordination, and slowed information processing and decision making. The association between sleepiness and road traffic accidents has been well documented.[41-44] In 2017 alone, there were 91,000 MVCs and 795 deaths attributed to drowsy driving.[45] The U.S. National Highway Traffic and Safety Administration is working with a number of Federal agencies, including the Centers for Disease Control and Prevention and the National Institutes, to raise public awareness about the risks of drowsy driving.

Dizziness, a nonspecific term, includes a sensation of imbalance, unsteadiness, lightheadedness, and vertigo (the illusion of movement). A migraine attack can be accompanied by one or more of these symptoms. Cohen et al[46] compared self-reported driving experience in individuals with various vestibular disorders (individuals with vestibular migraine were not included) to that in subjects without vestibular disorders (169 individuals in total). In general, individuals with vestibular disorders were aware that their driving performance was not optimal; they drove less and remained in their immediate neighborhood more so than healthy controls. Although some were advised by their physicians not to drive, they continued to drive, usually because they did not have alternative means of transportation. Individuals with a vestibular disorder had difficulty driving under conditions where useful visual cues were reduced, precise spatial navigation skills were needed, and rapid head movements were elicited, and they reported having to pull off the road due to vertigo in some cases. In an analysis of data from the 2001-2004 National Health and Nutrition Examination Survey study, Wei et al[47] evaluated the influence of vestibular dysfunction on driving difficulty in Americans aged ≥50 years (N = 3071). They found that vestibular dysfunction was associated with self-reported driving difficulty; those with clinically symptomatic (vs self-reported) vestibular dysfunction had a 4-fold increase in odds of reporting difficulty with driving. Individuals with migraine may experience dizziness and/or vertigo, and these symptoms are most prominent in those with vestibular migraine.[48] While vestibular dysfunction is not equivalent to vestibular symptoms occurring during migraine, the association of vestibular dysfunction with driving difficulty raises concern that individuals with migraine attacks accompanied by vestibular symptoms may experience similar difficulty.

Visual disturbances are common in migraine, both preceding an attack (visual aura) and during an attack (photophobia), and there is the potential for interference with the ability to operate a motor vehicle safely. Photophobia may be particularly problematic while driving at night, when facing bright headlights from oncoming vehicles. The overall burden associated with visual disturbances in migraine is not well understood. In a small study, investigators reported that vision-specific quality of life scores was lower in individuals with migraine vs healthy controls, particularly for those with chronic migraine (vs episodic).[49] More data are needed to elucidate whether there is any relationship between deficits in visual quality of life and driving impairment.

In conclusion, while it seems likely that symptoms occurring as part of the migraine attack (for example, pain, cognitive impairment, sleepiness, dizziness, and vertigo, and visual disturbances) could impact driving performance, formal study in this area is lacking. Generally, and understandably, studies of the effect of pain on driving ability have focused on the effect of treatment (opioids, for example) rather than the pain symptom itself. The impact of treatment on driving ability is further explored in the following paragraphs.

Impact of Treatment on Driving Performance.—The potential for some classes of medications to influence driving ability is well recognized.[50-52] Even over-the-counter medications for minor ailments, such as antihistamines for seasonal allergies, can result in drowsiness and impair driving ability; patients are not always aware of these side effects.[53,54]

Treatments for migraine include acute treatments taken at the time of an attack to reduce pain and associated symptoms,[55] and preventive medications to decrease attack frequency.[56] Currently available medications for acute treatment include triptans, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioids, butalbital (a barbiturate, compounded with one or more other agents eg, aspirin, acetaminophen, caffeine, codeine phosphate), and ergot (taken as monotherapy or in combination), with the most recommended treatments being analgesics and triptans.[55,57] Where necessary, antiemetics may also be employed.[55]

Table 1.—Side Effects of Common Migraine Treatments With Potential to Effect Driving Performance

Treatment	Possible Effects Relevant to Driving • Key scientific literature • US Prescribing Information (USPI)
Acute treatments	
Triptans	CNS side effects (eg, dizziness, somnolence, fatigue) associated with triptan use. Incidence increases with increasing dose and is dependent upon which triptan is used (lower with sumatriptan, higher with eletriptan)[58]
Almotriptan	PI: *May cause dizziness, sleepiness, and problems seeing. Do not drive, operate machinery, or do other dangerous activities until you know how drug affects you*[59]
Frovatriptan	PI: *Can cause dizziness, weakness, or drowsiness. If you have these symptoms do not drive a car, use machinery, or do anything where you need to be alert*[60]
Sumatriptan	PI: *Can cause dizziness, weakness, or drowsiness. If you have these symptoms, do not drive a car, use machinery, or do anything where you need to be alert*[61]
Rizatriptan	PI: *May cause dizziness, weakness, or fainting. If you have these symptoms, do not drive a car, use machinery, or do anything that needs you to be alert*[62]
Eletriptan	PI: *Can cause dizziness, weakness, or drowsiness. If you have these symptoms, do not drive a car, use machinery, or do anything where you need to be alert*[63]
Naratriptan	PI: *Can cause dizziness, weakness, or drowsiness. If you have these symptoms, do not drive a car, use machinery, or do anything where you need to be alert*[64]
Zolmitriptan	PI: No relevant information included[65]
Opioids	Use associated with increased risk of road trauma[50,66] PI for hydrocodone bitartrate and acetaminophen tablets: *May impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly*[67]
Butalbital (barbiturate)	Associated with increased risk of road trauma[68] PI: *… may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while taking this product*[69]
Preventive treatments	
Propranolol (β-blocker)	PI: *Light-headedness, mental depression manifested by insomnia, lassitude, weakness, fatigue; catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics*[70]
Amitriptyline (TCA)	TCAs associated with cognitive impairment[71] PI: *While on therapy with amitriptyline hydrochloride, patients should be advised to the possible impairment of mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a motor vehicle*[72]
Anti-epileptic treatments	Have been associated with increased incidence of MVCs[50]
Topiramate	PI: *Cognitive/neuropsychiatric adverse reactions: use caution when operating machinery including cars; depression and mood problems may occur*[73]
Divalproex (valproic acid derivative)	PI: *Can cause drowsiness and dizziness. Do not drive a car or operate dangerous machinery until you know how drug affects you*[74]
Gabapentin	PI: *Driving Impairment; Somnolence/Sedation and Dizziness: Warn patients not to drive until they have gained sufficient experience to assess whether their ability to drive or operate heavy machinery will be impaired*[75]
OnabotulinumtoxinA	PI: *Patients should be counseled that if loss of strength, muscle weakness, blurred vision, or drooping eyelids occur, they should avoid driving a car or engaging in other potentially hazardous activities*[76]
CGRP antagonists	PI: No relevant information included for erenumab,[77] fremanezumab,[78] or galcanezumab[79]

CGRP = calcitonin gene-related peptide; CNS = central nervous system; TCA = tricyclic antidepressant.

Commonly prescribed preventive treatments include β-blockers, antidepressants, topiramate, divalproex, calcitonin gene-related peptide monoclonal antibodies, and onabotulinumtoxinA. The side effects of acute and preventive migraine treatments that are of relevance to driving are summarized in Table 1. Drowsiness and sleepiness are known side effects with triptans, opioids, butalbital and antiemetics, and can also occur with NSAIDs. Dizziness is a recognized side effect with triptans, opioids, and butalbital.

While side effects associated with treatment can be similar to symptoms experienced in a migraine attack (for example, dizziness or drowsiness), treatment also alleviates the symptoms of an attack. If acute treatment leads to prompt resolution of migraine, driving might actually improve as a result of a reduction in all of the migraine-associated symptoms. For example, in small studies, sumatriptan nasal spray has been shown to reverse migraine-related cognitive deficits observed during an untreated attack.[35,80] Of course, the benefits of treatment on symptoms that impair driving could be outweighed by treatment side effects.

The side effects of treatments may vary from population to population, and studies in healthy controls may not be directly applicable to individuals with migraine. The incidence of adverse events associated with topiramate use appears to be disorder dependent. An analysis comparing data from double-blind, randomized controlled trials of topiramate in migraine and in newly diagnosed epilepsy found that the incidence of paresthesia, cognitive symptoms, as well as discontinuations, associated with topiramate was higher in individuals with migraine vs those with epilepsy.[81]

Lasmiditan, a selective serotonin (5-HT) 1F agonist (a ditan), was approved by the FDA in October 2019 for the acute treatment of migraine in adults. The effect of lasmiditan on simulated driving performance was examined in healthy adults, consistent with guidance recently issued by the FDA.[22] In simulated driving studies, lasmiditan was associated with clinically meaningful impairment of simulated driving performance at 1.5 hours postdose, around the time when lasmiditan is at peak concentration in the blood, and that impairment resolved by 8 hours.[82] Findings from these studies to assess directly the effect of a migraine treatment on driving (under simulated conditions) are the first to be published in this area.

As a result of the development of new migraine treatments and the recent FDA guidance document outlining the circumstances under which drug developers need to assess the effects of a new treatment on driving ability,[22] there will be increasing focus on migraine and driving. In other disease states, treatments are already being tested in driving studies.[83-85] Conducting specific driving studies will result in the inclusion of more specific wording related to driving in the prescribing information. The FDA guidance document[22] instructs that studies of driving impairment should be described in the Clinical Studies section of labeling, including a brief description of the design and pertinent results, and that safety information from driving studies should be included in other sections of labeling as appropriate, including Warning and Precautions, Patient Counseling Information, and FDA-approved patient labeling. Recently, two placebo-controlled studies were conducted to assess the effects of Spravato™ (esketamine), indicated for treatment of treatment-resistant depression, on the ability to drive; the findings resulted in the inclusion of the following warning in the PI – "*Impaired Ability to Drive and Operate Machinery:* Do not drive or operate machinery until the next day after a restful sleep."[86]

In conclusion**,** some of the approved treatments for migraine have the potential to impact driving, yet this topic has not generally been specifically studied, and the extent to which these risks are communicated to patients is not clear. Increased focus on the effects of medications on driving, including regulatory guidance on this topic, will ensure that more information on any potential impact on driving will be available for newly approved drugs. While many of these treatments include precautionary statements in their labeling, patient education on the effects of medication on driving will also require increased attention.

FUTURE DIRECTIONS

Based on this assessment of the current literature, there is insufficient data to support or refute driving impairment or an increased risk of MVCs in individuals with migraine. To generate more robust data on this topic, definitive studies designed to distinguish the effect of disease from that of treatment are required. The authors acknowledge the difficulties that may accompany these evaluations.

A full review of the methodology to assess driving performance is beyond the scope of this manuscript. However, it is worth noting the current regulatory recommendations in the United States. In their recent guidance on evaluating drug effects on the ability to operate a motor vehicle,[22] the FDA recommends a tiered approach. Using this approach, relevant information obtained early in the drug development

(pharmacological, toxicological, epidemiological, phase 1 clinical information) is used to guide continued clinical study and to characterize the clinical relevance of findings. When an early study suggests the potential for CNS impairment, this should be investigated further. The FDA recommended that the broad functional domains of alertness/arousal/wakefulness, attention and processing speed, reaction time/psychomotor functions, sensory-perceptual functioning, and executive functions (all relevant to driving) should be assessed with increasingly focused studies. If accumulating data suggests a potential for driving impairment, then dedicated driving studies may be required to assess more specifically the effect of the drug on driving performance. On-the-road driving assessment and driving simulators are recommended. The FDA guidance document notes that the need to evaluate driving performance depends upon a number of factors, including the indications for use of the drug, the intended patient population, and the severity of the CNS impairing effects.

Cognitive tests that permit an accurate and reliable assessment of a complex real world activity provide valuable contributions to societal health. The King-Devick test, for example, provides a rapid sideline screening for concussion, useful in improving sports safety.[87] The driving simulator and on-the-road driving test are currently considered state of the art for measurements of driving performance, although this methodology is not readily available to all. A neurocognitive assessment that replicates results of driving simulators or on-the-road tests would facilitate broader assessment of driving ability in clinical practice. To date, this research has not been fruitful, with modest associations between individual cognitive tests and driving performance and inconsistent findings across studies. Further research to identify predictors of impaired driving, and to reliably detect and assess this complex behavior, would be beneficial. Importantly, measurements should be objective rather than subjective, since drivers poorly predict their own driving impairment.[88]

DISCUSSION

Migraine has a substantial impact on patient function and quality of life[27,89,90] and is the second largest disease cause of years lost to disability.[91] The impact of migraine on an individual's driving performance has been largely neglected, and studies to date have not distinguished ictal and interictal effects or the confounding effects of medication and comorbidities.

A reliable test, or battery of tests, are needed to evaluate effects of both disease and treatment, with the recognition that treatment can both relieve and contribute to symptoms that may impair driving. Ultimately, studies need to address real world scenarios. For example, migraine attacks commonly occur away from home and, if driving impairment is a concern, may force the decision as to whether to travel home without treatment before symptoms become incapacitating, treat in anticipation, or make alternative plans to avoid driving.

As the effects of certain medical conditions and drug treatments on driving receive more attention, the implications of increased knowledge will need to be considered. Specifically, if well designed studies support an association between migraine and impaired driving, how will this influence the diagnosis and management of the patient with migraine? Potential outcomes include a greater opportunity for patient and healthcare provider recognition and education of the potential impact of migraine on driving.

CONCLUSION

The impact of migraine on an individual's driving performance has been largely neglected, with few studies specifically designed to address this topic. With a potential for impact on road safety, this area requires more focus.

REFERENCES

1. National Highway Traffic Safety Administration. The economic and societal impact of motor vehicle crashes, 2010 (Revised). *Ann Emerg Med*. 2015;66: 194-196.
2. Center for Disease Control and Prevention. *Winnable Battles Final Report*. Atlanta, GA: Center for Disease Control and Prevention; 2016:26.
3. Kochanek KD, Murphy SL, Xu J, Arias E. Deaths: Final data for 2017. *Natl Vital Stat Rep*. 2019;68:51.
4. Classen S, Crizzle AM, Winter SM, Silver W, Eisenschenk S. Evidence-based review on epilepsy and driving. *Epilepsy Behav*. 2012;23:103-112.

5. Sundelin HE, Chang Z, Larsson H, et al. Epilepsy, antiepileptic drugs, and serious transport accidents: A nationwide cohort study. *Neurology*. 2018;90:e1111-e1118.
6. Graveling AJ, Frier BM. Driving and diabetes: Problems, licensing restrictions and recommendations for safe driving. *Clin Diabetes Endocrinol*. 2015;1:8. doi:10.1186/s40842-015-0007-3.
7. Liu S-Y, Perez MA, Lau N. The impact of sleep disorders on driving safety—Findings from the Second Strategic Highway Research Program naturalistic driving study. *Sleep*. 2018;41. doi:10.1093/sleep/zsy023.
8. Moriarty O, McGuire BE, Finn DP. The effect of pain on cognitive function: A review of clinical and preclinical research. *Prog Neurobiol*. 2011;93:385-404.
9. Fan A, Wilson KG, Acharya M, Cranney A, Buenger U, Marshall S. Self-reported issues with driving in patients with chronic pain. *PM&R*. 2012;4:87-95.
10. American Academy of Neurology. *Driving with Dementia: Understanding the Safety Risks*. 2010. Available at https://www.aan.com/Guidelines/home/GetGuidelineContent/398. Accessed August 16, 2019.
11. Alzheimer's Association. *Dementia and Driving*. 2010. Available at http://www.alz.org/care/alzheimers-dementia-and-driving.asp. Accessed August 16, 2019.
12. Kay GG, Logan BK. *Drugged Driving Expert Panel Report: A Consensus Protocol for Assessing the Potential of Drugs to Impair Driving*. Washington, DC: National Highway Traffic Safety Administration; 2011.
13. Rudisill TM, Zhu M, Kelley GA, Pilkerton C, Rudisill BR. Medication use and the risk of motor vehicle collisions among licensed drivers: A systematic review. *Accid Anal Prev*. 2016;96:255-270.
14. National Highway Traffic Safety Administration. *Drug Impaired Driving*. Available at https://www.nhtsa.gov/risky-driving/drug-impaired-driving. Accessed August 16, 2019.
15. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed M, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*. 2007;68:343-349.
16. Vos T, Allen C, Arora M, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: A systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388:1545-1602.
17. Dodick DW. Migraine. *Lancet*. 2018;391:1315-1330.
18. Giffin N, Ruggiero L, Lipton RB, et al. Premonitory symptoms in migraine: An electronic diary study. *Neurology*. 2003;60:935-940.
19. Giffin NJ, Lipton RB, Silberstein SD, Olesen J, Goadsby PJ. The migraine postdrome: An electronic diary study. *Neurology*. 2016;87:309-313.
20. Lempert T, Olesen J, Furman J, et al. Vestibular migraine: Diagnostic criteria. *J Vestib Res*. 2012;22:167-172.
21. Headache Classification Committee of the International Headache Society. *The International Classification of Headache Disorders (beta version)*. 2013. Available at https://www.ichd-3.org/wp-content/uploads/2016/08/International-Headache-Classification-III-ICHD-III-2013-Beta-1.pdf. Accessed June 19, 2019.
22. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). *Evaluating Drug Effects on the Ability to Operate a Motor Vehicle – Guidance for Industry*. 2017. Available at https://www.fda.gov/media/90670/download. Accessed August 16, 2019.
23. Edmeads J, Findlay H, Tugwell P, Pryse-Phillips W, Nelson R, Murray T. Impact of migraine and tension-type headache on life-style, consulting behaviour, and medication use: A Canadian population survey. *Can J Neurol Sci*. 1993;20:131-137.
24. Alonso F, Esteban C, Useche SA, Serge A. Perception of the impact of certain health conditions on driving performance. *Public Health Int*. 2017;2:1-7.
25. Norton R, Vander Hoorn S, Roberts I, Jackson R, MacMahon S. Migraine: A risk factor for motor vehicle driver injury? *Accid Anal Prev*. 1997;29:699-701.
26. Vingilis E, Wilk P. Medical conditions, medication use, and their relationship with subsequent motor vehicle injuries: Examination of the Canadian National Population Health Survey. *Traffic Inj Prev*. 2012;13:327-336.
27. Leonardi M, Raggi A, Ajovalasit D, Bussone G, D'amico D. Functioning and disability in migraine. *Disabil Rehabil*. 2010;32:S23-S32.
28. Bener A, Dunn EV, Achan NV, Moussa NA, Abu Azab I. Migraine associated with road traffic accidents in United Arab Emirates. *Neurosciences*. 2001;6:33-37.
29. Lerman Y, Matar M, Lavie B, Danon YL. Effect of valvular heart diseases, migraine headaches, and perianal diseases on the risk of involvement in motor vehicle crashes. *J Trauma Acute Care Surg*. 1995;39:1058-1062.
30. Lampl C, Rudolph M, Deligianni CI, Mitsikostas DD. Neck pain in episodic migraine: Premonitory symptom or part of the attack? *J Headache Pain*. 2015;16:80. doi:10.1186/s10194-015-0566-9.

31. Veldhuijzen DS, Van Wijck A, Wille F, et al. Effect of chronic nonmalignant pain on highway driving performance. *Pain*. 2006;122:28-35.
32. Gil-Gouveia R, Oliveira AG, Martins IP. Cognitive dysfunction during migraine attacks: A study on migraine without aura. *Cephalalgia*. 2015;35:662-674.
33. Gil-Gouveia R, Martins IP. Clinical description of attack-related cognitive symptoms in migraine: A systematic review. *Cephalalgia*. 2018;38:1335-1350.
34. Foti M, Buono VL, Corallo F, Palmeri R, Bramanti P, Marino S. Neuropsychological assessment in migraine patients: A descriptive review on cognitive implications. *Neurol Sci*. 2017;38:553-562.
35. Farmer K, Cady R, Bleiberg J, et al. Sumatriptan nasal spray and cognitive function during migraine: Results of an open-label study. *Headache*. 2001;41: 377-384.
36. Vuralli D, Ayata C, Bolay H. Cognitive dysfunction and migraine. *J Headache Pain*. 2018;19:109. doi:10.1186/s10194-018-0933-4.
37. Wang N, Huang H, Zhou H, Yu C. Cognitive impairment and quality of life in patients with migraine-associated vertigo. *Eur Rev Med Pharmacol Sci*. 2016; 20:4913-4917.
38. Seng EK, Klepper JE. Development of the Cogniphobia Scale for Headache Disorders (CS-HD): A pilot study. *Psychol Assess*. 2017;29:1296-1301.
39. Walters AB, Hamer JD, Smitherman TA. Sleep disturbance and affective comorbidity among episodic migraineurs. *Headache*. 2014;54:116-124.
40. Kelman L. The triggers or precipitants of the acute migraine attack. *Cephalalgia*. 2007;27:394-402.
41. Horne J, Reyner L. Vehicle accidents related to sleep: A review. *Occup Environ Med*. 1999;56:289-294.
42. Connor J, Norton R, Ameratunga S, et al. Driver sleepiness and risk of serious injury to car occupants: Population based case control study. *BMJ*. 2002; 324:1125.
43. Lyznicki JM, Doege TC, Davis RM, Williams MA. Sleepiness, driving, and motor vehicle crashes. *JAMA*. 1998;279:1908-1913.
44. Czeisler CA, Wickwire EM, Barger LK, et al. Sleep-deprived motor vehicle operators are unfit to drive: A multidisciplinary expert consensus statement on drowsy driving. *Sleep Health*. 2016;2:94-99.
45. National Highway Traffic and Safety Administration. *Drowsy Driving*. 2019. Available at https://www.nhtsa.gov/risky-driving/drowsy-driving. Accessed August 16, 2019.
46. Cohen HS, Wells J, Kimball KT, Owsley C. Driving disability and dizziness. *J Safety Res*. 2003;34: 361-369.
47. Wei EX, Agrawal Y. Vestibular dysfunction and difficulty with driving: Data from the 2001–2004 National Health and Nutrition Examination Surveys. *Front Neurol*. 2017;8:557. doi:10.3389/fneur.2017.00557.
48. Lempert T, Neuhauser H. Epidemiology of vertigo, migraine and vestibular migraine. *J Neurol*. 2009; 256:333-338.
49. Hanson LL, Ahmed Z, Katz BJ, et al. Patients with migraine have substantial reductions in measures of visual quality of life. *Headache*. 2018;58:1007-1013.
50. Hetland A, Carr DB. Medications and impaired driving. *Ann Pharmacother*. 2014;48:494-506.
51. Rudisill TM, Zhu M, Kelley GA, Pilkerton C, Rudisill BR. Medication use and the risk of motor vehicle collisions among licensed drivers: A systematic review. *Accid Anal Prev*. 2016;96:255-270.
52. Brunnauer A, Laux G. The effects of most commonly prescribed second generation antidepressants on driving ability: A systematic review. *J Neural Transm*. 2013; 120:225-232.
53. Verster JC, Volkerts ER. Antihistamines and driving ability: Evidence from on-the-road driving studies during normal traffic. *Ann Allergy Asthma Immunol*. 2004;92:294-304.
54. US Food and Drug Administration. *Allergy Meds Could Affect Your Driving*. 2014. Available at https://www.fda.gov/consumers/consumer-updates/allergy-meds-could-affect-your-driving. Accessed August 28, 2019.
55. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: The American Headache Society evidence assessment of migraine pharmacotherapies. *Headache*. 2015;55:3-20.
56. Silberstein S, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78:1337-1345.
57. Evers S, Afra J, Frese A, et al. EFNS guideline on the drug treatment of migraine–revised report of an EFNS task force. *Eur J Neurol*. 2009;16:968-981.
58. Dodick DW, Martin V. Triptans and CNS side-effects: Pharmacokinetic and metabolic mechanisms. *Cephalalgia*. 2004;24:417-424.

59. AXERT® (almotriptan malate) tablets [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2009. Available at http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/AXERT-pi.pdf. Accessed August 16, 2019.
60. FROVA® (frovatriptan succinate) tablets [package insert]. Malvern, PA: Endo Pharmaceuticals Inc.; 2013. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021006s019lbl.pdf. Accessed August 16, 2019.
61. Imitrex (sumatriptan succinate) tablets [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2017. Available at https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Imitrex_Tablets/pdf/IMITREX-TABLETS-PI-PIL.PDF. Accessed August 16, 2019.
62. MAXALT (rizatriptan benzoate) tablets [package insert]. Whitehouse Station, NJ: Merck & Company Inc; 2011. Available at https://www.merck.com/product/usa/pi_circulars/m/maxalt/maxalt_ppi.pdf. Accessed August 16, 2019.
63. RELPAX® (eletriptan hydrobromide) tablets [package insert]. New York, NY: Pfizer; 2013. Available at http://labeling.pfizer.com/ShowLabeling.aspx?format=PDF&xml:id=621. Accessed August 16, 2019.
64. AMERGE® (naratriptan hydrochloride) tablets [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2016. Available at https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Amerge/pdf/AMERGE-PI-PIL.PDF. Accessed August 16, 2019.
65. ZOMIG (zolmitriptan) tablets [package insert]. Bridgewater, NH: Astra Zeneca, distributed by Amneal Specialty, a division of Amneal Pharmaceuticals LLC; 2019. Available at https://www.azpicentral.com/zomig/zomig.pdf#page=1. Accessed August 16, 2019.
66. Gomes T, Redelmeier DA, Juurlink DN, Dhalla IA, Camacho X, Mamdani MM. Opioid dose and risk of road trauma in Canada: A population-based study. *JAMA Intern Med*. 2013;173:196-201.
67. VICODIN (hydrocodone bitartrate and acetaminophen) tablet [package insert]. North Chicago, IL: AbbVie Inc.; 2012. Available at https://www.rxabbvie.com/pdf/vicodin_apap_300mg_hydrocodone_5mg-7_5mg-10mg_PI.pdf. Accessed August 16, 2019.
68. Yeakel JK, Logan BK. Butalbital and driving impairment. *J Forensic Sci*. 2013;58:941-945.
69. Fiorinal® (Butalbital, Aspirin, and Caffeine Capsules, USP) [package insert]. Madison, NJ: Allergan; 2018. Available at https://www.allergan.com/assets/pdf/fiorinal-pi. Accessed August 16, 2019.
70. Inderal® (propranolol hydrochloride) tablets [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc; 2017. Available at http://labeling.pfizer.com/ShowLabeling.aspx?xml:id=9895. Accessed August 16, 2019.
71. Stein RA, Strickland TL. A review of the neuropsychological effects of commonly used prescription medications. *Arch Clin Neuropsychol*. 1998;13:259-284.
72. Amitriptyline hydrochloride tablet [package insert]. Morgantown, WV: Mylan Pharmaceuticals Inc; 2016. Available at https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setxml:id=61d2da8d-b435-4ada-a013-401786f7cace&type=display. Accessed August 16, 2019.
73. TOPAMAX® (topiramate) tablets [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2009. Available at http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/TOPAMAX-pi.pdf. Accessed August 16, 2019.
74. Depakote (divalproex sodium) delayed-release tablets [package insert]. North Chicago, IL: AbbVie Inc.; 2019. Available at https://www.rxabbvie.com/pdf/depakote.pdf. Accessed August 16, 2019.
75. NEURONTIN (gabapentin) capsules [package insert]. New York, NY: Pfizer; 2017. Available at http://labeling.pfizer.com/ShowLabeling.aspx?xml:id=630. Accessed August 16, 2019.
76. BOTOX (onabotulinumtoxinA) for injection [package insert]. Irvine, CA: Allergan, Inc; 2011. Available at https://www.allergan.com/assets/pdf/botox_pi.pdf. Accessed August 16, 2019.
77. AIMOVIG® (erenumab) injection [package insert]. Thousand Oaks, CA: Amgen Inc; 2019. Available at https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/aimovig/aimovig_pi_hcp_english.ashx. Accessed August 19, 2019.
78. AJOVY® (fremanezumab) injection [package insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc; 2019. Available at https://www.ajovyhcp.com/globalassets/ajovy/ajovy-pi.pdf. Accessed August 19, 2019.
79. EMGALITY (galcanezumab) injection [package insert]. Indianapolis, IN: Eli Lilly and Company; 2019. Available at https://pi.lilly.com/us/emgality-uspi.pdf. Accessed August 19, 2019.

80. Farmer K, Cady R, Bleiberg J, Reeves D. A pilot study to measure cognitive efficiency during migraine. *Headache*. 2000;40:657-661.
81. Silberstein SD. Topiramate in migraine prevention: A 2016 perspective. *Headache*. 2017;57:165-178.
82. Pearlman E, Doty E, Dennehy E, et al. Effects of lasmiditan on driving performance: Results of 2 randomized, blinded, crossover simulated driving studies with placebo and active controls. *Headache*. 2019;59(Suppl. 1):22-23.
83. Vermeeren A, Sun H, Vuurman EF, et al. On-the-road driving performance the morning after bedtime use of suvorexant 20 and 40 mg: A study in non-elderly healthy volunteers. *Sleep*. 2015;38:1803-1813.
84. Kay GG, Schwartz HI, Wingertzahn MA, Jayawardena S, Rosenberg RP. Next-day residual effects of gabapentin, diphenhydramine, and triazolam on simulated driving performance in healthy volunteers: A phase 3, randomized, double-blind, placebo-controlled, crossover trial. *Hum Psychopharmacol*. 2016;31:217-226.
85. van de Loo AJ, Bervoets AC, Mooren L, et al. The effects of intranasal esketamine (84 mg) and oral mirtazapine (30 mg) on on-road driving performance: A double-blind, placebo-controlled study. *Psychopharmacology*. 2017;234:3175-3183.
86. SPRAVATO™ (esketamine) nasal spray, CIII [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2019. Available at https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SPRAVATO-pi.pdf. Accessed August 16, 2019.
87. Galetta KM, Brandes LE, Maki K, et al. The King-Devick test and sports-related concussion: Study of a rapid visual screening tool in a collegiate cohort. *J Neurol Sci*. 2011;309:34-39.
88. Verster JC, Roth T. Drivers can poorly predict their own driving impairment: A comparison between measurements of subjective and objective driving quality. *Psychopharmacology*. 2012;219:775-781.
89. Abu Bakar N, Tanprawate S, Lambru G, Torkamani M, Jahanshahi M, Matharu M. Quality of life in primary headache disorders: A review. *Cephalalgia*. 2016;36:67-91.
90. Chaushev N, Milanov I. Impact of migraine and migraine treatment on patient's capacity to work and quality of life. *J Clin Med*. 2009;2:26-31.
91. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390:1211-1259.