

## Sex and Gender Differences in Migraine—Evaluating Knowledge Gaps

Rachel A. Schroeder, BS<sup>1</sup>, Jan Brandes, MD<sup>2,3</sup>, Dawn C. Buse, PhD<sup>4</sup>, Anne Calhoun, MD<sup>5</sup>,  
Katharina Eikermann-Haerter, MD<sup>6</sup>, Katie Golden, BS<sup>7</sup>, Rashmi Halker, MD<sup>8</sup>, Joanna Kempner, PhD<sup>9</sup>,  
Nasim Maleki, PhD<sup>10,11</sup>, Maureen Moriarty, DNP<sup>12</sup>, Jelena Pavlovic, MD, PhD<sup>4</sup>, Robert E. Shapiro, MD, PhD<sup>13</sup>,  
Amaal Starling, MD<sup>8</sup>, William B. Young, MD<sup>14</sup>, and Rebecca A. Nebel, PhD<sup>1</sup>

### Abstract

Migraine is a common chronic neurological disease that disproportionately affects women. Migraine has significant negative effects on physical, emotional, and social aspects of health, and can be costly for patients, employers, and society as a whole. Growing evidence supports the roles of sex and gender in migraine risk, pathophysiology, presentation, diagnosis, treatment, and management. However, sex and gender differences in migraine have received limited attention, which can impede advancements in migraine detection, treatment, care, and education. The Society for Women's Health Research convened an interdisciplinary expert panel of researchers, clinicians, and advocates for a roundtable meeting to review the current research on sex and gender differences in migraine. This review summarizes discussions from the roundtable and prioritizes areas of need that warrant further attention in migraine research, care, and education. Examining sex and gender differences in migraine and addressing knowledge gaps will decrease the health and economic burden of migraine for both women and men.

**Keywords:** sex, gender, migraine, headache, pain

### Introduction

**M**IGRAINE IS A NEUROLOGICAL disease characterized by severe head pain and often accompanied by nausea, vomiting, phonophobia, and photophobia. It is three times more common in women than in men, with a lifetime prevalence of 43% and 18%, respectively.<sup>1</sup> Globally, >14% of the adult population has migraine, resulting in migraine ranking as the second leading cause of global burden of disability.<sup>1-4</sup>

During childhood, migraine is slightly more prevalent in boys than in girls, with boys on average presenting at a slightly earlier age (Fig. 1). However, after the onset of puberty, migraine becomes more prevalent in women than in men and remains as such for the majority of the lifespan.<sup>5,6</sup> Migraine reaches peak prevalence at 30–39 years of age, during which time a quarter to a third of people with migraine will have at least four attacks per month.<sup>3</sup> The peaks of migraine prevalence in women are bimodal, reaching the highest rates at ages 25 ( $\pm 8.6$ ) and 50 ( $\pm 15.8$ ) years. By this

<sup>1</sup>Society for Women's Health Research, Washington, District of Columbia.

<sup>2</sup>Nashville Neuroscience Group, Nashville, Tennessee.

<sup>3</sup>Department of Neurology, Vanderbilt University, Nashville, Tennessee.

<sup>4</sup>Department of Neurology, Albert Einstein College of Medicine, Bronx, New York.

<sup>5</sup>Carolina Headache Institute, Durham, North Carolina.

<sup>6</sup>Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.

<sup>7</sup>Golden Graine, Los Angeles, California.

<sup>8</sup>Department of Neurology, Mayo Clinic, Phoenix, Arizona.

<sup>9</sup>Department of Sociology, Rutgers University, New Brunswick, New Jersey.

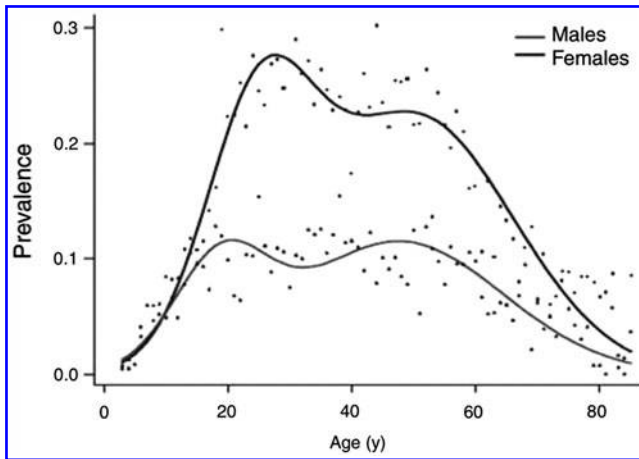
<sup>10</sup>Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.

<sup>11</sup>Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, Massachusetts.

<sup>12</sup>Department of Nursing, Marymount University, Arlington, Virginia.

<sup>13</sup>Department of Neurological Sciences, University of Vermont, Burlington, Vermont.

<sup>14</sup>Department of Neurology, Thomas Jefferson University, Philadelphia, Pennsylvania.



**FIG. 1.** Lifetime prevalence of migraine by sex. Migraine is more prevalent in boys than in girls during early childhood. After the onset of puberty and for the remainder of the lifespan, migraine is more prevalent in women than in men, with bimodal peaks of prevalence at 25 ( $\pm 8.6$ ) and 50 ( $\pm 15.8$ ) years of age. Figure reproduced from Victor T, et al.<sup>5</sup> Migraine prevalence by age and sex in the United States: A life-span study. *Cephalalgia* 2010. Reprinted by permission from SAGE Publications, Ltd.

measure, at the average age of 30.2 years, women experience migraine at a rate of 2.9 times higher than men.<sup>2,5</sup>

Migraine has wide-ranging adverse effects on physical, emotional, and social aspects of daily living,<sup>7,8</sup> and can be disabling and costly for patients, employers, and society as a whole.<sup>9</sup> The total costs of migraine are estimated to be \$78 billion per year in the United States.<sup>9</sup> Most of these costs are indirect, with lost productivity (presenteeism and absenteeism) playing a large role.<sup>10</sup>

Migraine is broken down into two categories based on the frequency of attacks: episodic migraine and chronic migraine. Episodic migraine involves <15 headache days per month, and chronic migraine is 15 or more headache days per month, 8 days of which are migraine attacks, for at least 3 months in succession.<sup>11</sup> Those with chronic migraine constitute 6% of the migraine population, and two-thirds of individuals with migraine experience three or fewer headache days per month on average.<sup>12</sup> Per person, the economic burden of migraine in the United States is estimated to be \$2649 for individuals with episodic migraine and \$8243 for individuals with chronic migraine.<sup>10</sup> Compared with men, women with migraine shoulder a great deal of the economic burden, accounting for ~80% of direct medical costs and 80% of total lost labor costs.<sup>13</sup> With such high prevalence rates and economic costs, migraine is an immense burden on families, healthcare professionals, and society.<sup>14</sup>

Sex and gender play critical roles in the risk, pathophysiology, presentation, diagnosis, treatment, and management of migraine. Throughout this review, *sex* refers to the classification of living things according to reproductive organs and functions assigned by chromosomal complement, and *gender* refers to the social, cultural, and environmental influences on the biology of women or men.<sup>15</sup> Despite clear differences in migraine between women and men, more attention in this area is needed. By examining sex and gender differences in migraine and addressing knowledge gaps, the large health and economic burden of this disease can be lessened for both sexes.

TABLE 1. SOCIETY FOR WOMEN'S HEALTH RESEARCH MIGRAINE ROUNDTABLE PARTICIPANTS

<b>Jan Brandes, MD, MS</b> , Founder, Nashville Neuroscience Group and Assistant Clinical Professor, Department of Neurology, Vanderbilt University
<b>Dawn C. Buse, PhD</b> , Professor, Department of Neurology, Albert Einstein College of Medicine
<b>Anne Calhoun, MD</b> , Co-founder, Carolina Headache Institute
<b>Katharina Eikermann-Haerter, MD</b> , Clinical Fellow, Department of Radiology, Massachusetts General Hospital, Harvard Medical School
<b>Katie Golden</b> , Patient Advocate, Golden Graine
<b>Rashmi Halker, MD</b> , Assistant Professor, Department of Neurology, Mayo Clinic
<b>Joanna Kempner, PhD</b> , Associate Professor, Department of Sociology, Rutgers University
<b>Nasim Maleki, PhD</b> , Assistant Professor, Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School
<b>Maureen Moriarty, DNP</b> , Associate Professor, Department of Nursing, Marymont University
<b>Jelena Pavlovic, MD, PhD</b> , Assistant Professor, Department of Neurology, Albert Einstein College of Medicine
<b>Robert E. Shapiro, MD, PhD</b> , Professor, Department of Neurological Sciences, University of Vermont
<b>Amaal Starling, MD</b> , Assistant Professor, Department of Neurology, Mayo Clinic
<b>William B. Young, MD</b> , Professor, Department of Neurology, Thomas Jefferson University

To this end, the Society for Women's Health Research (SWHR<sup>®</sup>) convened an interdisciplinary expert panel of researchers, clinicians, and advocates for a roundtable meeting (Table 1). Meeting objectives were to (1) review the current state of the science in sex and gender differences in migraine, (2) identify knowledge gaps in the field, and (3) highlight areas of need that warrant further attention. This review summarizes discussions from the roundtable and prioritizes areas for further exploration.

## Biological Mechanisms

### Hormones

It is believed that female sex hormones play a large role in the development of migraine and are likely contributors to observed sex and gender differences in this disease. This can be seen as the rate of migraine prevalence correlates with periods of large hormonal changes throughout the lifespan.<sup>5</sup> Changes in migraine prevalence resulting from fluctuations in hormones disproportionately affect women due to the cyclical nature of their hormonal cycles. For example, variations in age of first menarche show a relationship with migraine prevalence. A longitudinal study following young women revealed that earlier age of menarche predicted increased odds of developing migraine, with those who underwent menarche by age 11 years having a 7% increased likelihood of developing migraine than those who reached menarche at age 12 years and later.<sup>16</sup>

Researchers now understand that small shifts during specific hormonal phases may be the key to identifying differences among those who experience migraine. Interestingly, recent work that measured hormonal changes throughout the menstrual cycle suggested that women with migraine have a faster drop in estrogen levels during the late luteal phase, irrespective of when during the menstrual cycle migraine attacks occurred.<sup>17</sup> Based on these findings, a current hypothesis relates estrogen withdrawal as a hormonal trigger in women with migraine. However, this concept needs additional work to fully elucidate the role of estrogen in migraine. There is also a lack of large longitudinal studies capturing both hormonal and migraine data. More studies are needed to increase understanding of hormonal influences on migraine not only during the monthly menstrual cycle but also throughout a woman's lifespan.

### Mouse models

Mouse models can be useful tools in understanding mechanisms underlying pain and pathways believed to be involved in migraine attacks. Owing to the confounding effect of the female hormonal cycle on many study outcomes, the field has traditionally used male mice as models, greatly limiting our understanding about potential sex differences in pain processing.

Characterization of migraine in animal models has resulted in multiple phenotypes reflective of disturbances in brain and vascular function. Mouse models of cortical spreading depolarization, the electrophysiological event underlying migraine, are used to explore the role of hormones in migraine because of the model's sensitivity to hormonal fluctuations. In a study that compared female and male FHM1 mutant mice, which carry a human mutation causing migraine, female mice were more likely to experience cortical spreading depolarization than male mice.<sup>18</sup> Furthermore, neurological deficits secondary to cortical spreading depolarization that clinically resemble migraine aura symptoms persisted for a longer period of time in female mice than in male mice. This increased susceptibility in female mice could be normalized by ovariectomy. In contrast, orchietomy increased susceptibility to cortical spreading depolarization in male FHM1 mutant mice, which could be prevented by testosterone replacement.<sup>19</sup> Reflecting the clinical improvement of migraine in postmenopausal women, increased susceptibility to cortical spreading depolarization normalized with advanced age in female FHM1 mutant mice.<sup>18</sup> Together, these results strongly suggest that female gonadal hormones increase the susceptibility to migraine *via* an estrogen-dependent electrophysiological effect, whereas testosterone suppresses it.

Further exploration of sex differences and different stages of the female hormonal cycle across various migraine mouse models will broaden our understanding of the role of sex hormones. For many women, fluctuations in estrogen, either throughout menses or over their lifetime, can worsen migraine and may play a role in other migraine symptoms typically experienced by women.

### Neuroimaging

Neuroimaging provides insights into structural, chemical, and functional characteristics of migraine. It allows assessment of areas in evoked or resting brain activation during and

between migraine attacks and can be used to understand the mechanisms of the disease. Although neuroimaging studies have revealed multiple abnormalities in brain regions in association with migraine,<sup>20–27</sup> there is a limited, yet growing, number of studies on sex differences in neuroimaging and migraine, which represents an area needing more research.

Recent studies suggest that the brains of women and men may be affected differently in association with migraine. Structural brain differences between women and men with migraine have been seen in the insula and precuneus.<sup>28</sup> Of note, the left posterior insula was thicker in women with migraine than in men with migraine and controls. The insula is involved in pain processing, interoception,<sup>29</sup> autonomic function,<sup>30,31</sup> and sensation.<sup>32,33</sup> Women with migraine also showed greater activation than men with migraine in brain regions involved in emotional processing.<sup>28</sup> Taken together, these sex-specific differences suggest a possible mechanism for higher subjective ratings of headache unpleasantness experienced by women with migraine.<sup>28</sup>

Furthermore, functional networks are derived from correlations between time courses of brain activity in different regions and may reveal differences between organized and disorganized brain processes. Functional brain networks in women with migraine showed decreased network robustness and nodal centrality and more dysfunctional connections than men with migraine, which may reflect impaired communication within and between brain regions in women.<sup>34</sup>

In contrast to basic science studies, the majority of neuroimaging studies in migraine include mostly female subjects. To gain a strong understanding of sex differences in disease, there is a need to study more men with migraine in neuroimaging. Further exploring the role of sex differences in the brain in those with migraine and continuing to broaden the understanding of migraine etiology may lead to new avenues for therapeutic intervention.

### Risk factors

Environmental, genetic, and epigenetic factors can also increase risk for migraine. Sex differences may also play a role in cases wherein episodic migraine transforms to chronic migraine. Individuals with transformed migraine have reported higher rates of depression, anxiety, and headache-related nausea,<sup>35–37</sup> which are all more common in women than in men. This suggests that women may have an increased likelihood in transitioning from episodic to chronic migraine, although more research in this area needs to be done.<sup>38–40</sup>

Social and environmental factors also play an important role in the disease. Victims of intimate partner violence and adverse childhood experiences are associated with increased risk for migraine.<sup>41–43</sup> Sexual harassment and assault are predominantly a women's issue and underscore the importance of gender in disease etiology.

## Clinical Perspectives

### Presentation

Research to understand women's increased prevalence in migraine revealed differences in the types of migraine women and men experience and variations in comorbidities. Women are more likely than men to have moderate to severe pain, rather than mild or extreme pain; experience longer and

more intense migraine attacks; and report more migraine-associated symptoms, including nausea, visual aura, blurred vision, photophobia, and phonophobia.<sup>44,45</sup> Strengthening the understanding of the differences between women and men in migraine presentation will allow for improvements in diagnosis and treatment options.

A female-only migraine subtype is menstrual migraine. Conceptualized differences in migraine are defined by the International Classification of Headache Disorders, 3rd Edition (ICHD-3) and list criteria for menstrually related, pure menstrual, and nonmenstrual migraine.<sup>11</sup> Menstrual migraine is defined as migraine attacks occurring in at least two of three menstrual cycles, extending from 2 days before onset of menses through 3 days after onset. Compared with nonmenstrual migraine, menstrual migraine is associated with more disability and the attacks are more severe, more resistant to treatment, and longer lasting.<sup>46,47</sup> This includes worsened prodromal features such as irritability, fatigue, and nausea.<sup>40</sup> Lost work productivity is also greater in those who experience menstrually related migraine than those who do not.<sup>48</sup>

### Comorbidities

Comorbid conditions are very common in individuals with migraine, particularly those with chronic migraine. Comorbidities can reveal what system is affected and help better understand which treatment may be most fitting. Women with migraine have a greater number of comorbid conditions than men, with an average of 11 and 5 comorbid conditions, respectively.<sup>49</sup> Some research shows women are more likely to have comorbid psychiatric conditions such as depression and anxiety, whereas men are more likely to have comorbid somatic symptoms such as obesity and blurred vision.<sup>44,50</sup> Restless legs syndrome, which can cause sleep disturbances, is also comorbid with migraine and is approximately twice as prevalent in women.<sup>51-54</sup> Relationships between comorbidities are not well understood, which is particularly problematic as comorbid conditions such as depression, anxiety, and obesity are associated with increased frequency of migraine attacks and are risk factors in the transition from episodic to chronic migraine.<sup>35,36,55-57</sup> More research is needed to better understand these differences and the role they play in migraine etiology and treatment.

### Treatment

Until earlier this year, the FDA had not approved a new drug specifically designed for the prevention of migraine since methysergide in 1962, despite efforts from researchers and clinicians to get new interventions to market. Furthermore, identifying sex differences in migraine treatment is largely overlooked. Often, during study design and data analysis, sex differences in efficacy of treatments are not considered. One study comparing the efficacy of three different triptans showed no statistical differences between women and men.<sup>58</sup> However, it is known that some pharmacological interventions react differently in women and men,<sup>59-61</sup> and thus it is critical to consider sex in trial design and analysis. Unlike in basic science research, wherein male animals are heavily favored, clinical trial populations are representative of the migraine population in terms of gender, with women represented—two to three times more than men. More work is needed, however, in diversifying studies re-

garding race/ethnicity. Although recent headache studies meet NIH requirements for minority inclusion, minorities remain underrepresented in trials compared with the population of those with migraine, creating difficulties in researchers' ability to investigate race-based differences in migraine etiology and treatment.<sup>62</sup>

All current headache therapies are Class B or C, meaning that there is a lack of human research regarding whether migraine treatments are safe during pregnancy and lactation.<sup>63-66</sup> Triptans, the most common abortive pharmacological treatment option for migraine, are currently not recommended during pregnancy, although preliminary research has indicated they are safe.<sup>67,68</sup>

Owing to widespread use of opioids for pain treatment, a greater amount of data exists regarding opioid use during pregnancy.<sup>69,70</sup> This can influence healthcare providers in recommending opioids over triptans for migraine treatment for women who are pregnant or lactating. In addition, behavioral treatments and healthy lifestyle recommendations have strong efficacy and are extremely important during pregnancy and lactation.<sup>71-73</sup> Transitioning from prescribing opioids to triptans, as well as incorporation of other available treatment options for women who are pregnant or lactating, may be safer and more effective for women with migraine, although more research is needed to ensure safety.

Hormonal fluctuations are a common trigger for the majority of women with migraine.<sup>74</sup> Given the role of estrogen in migraine pathophysiology, administering women estradiol during the last luteal phase of the menstrual cycle can delay the onset of migraine.<sup>75</sup> Of note, women with migraine have an increased risk of cardiovascular disease including stroke,<sup>47,76,77</sup> which is important to consider when prescribing birth control for women with migraine because of the association between birth control and increased stroke risk.<sup>78</sup> However, these conclusions may have been based on older data rather than current low-dose estrogen contraceptives, and a recent review concluded that there has been a lack of studies assessing stroke risk in women with migraine who use low-dose estrogen contraceptives.<sup>79</sup> Together these findings indicate that women may benefit from further exploration of the role of hormones in migraine attacks and treatment.

### Barriers to Care

Migraine accounts for more than half of all neurological disability and is the second leading cause of global burden of disability.<sup>2</sup> Yet, women's disproportionate role in migraine disease burden is not appropriately appreciated. Although this disease mainly affects women, gaps remain in sex-specific research at the preclinical and clinical level. Currently, translation of research findings into treatment options and access to care for women has been inadequate.

### Disability

The highest peak of prevalence rates for migraine occurs in women during 20-39 years of age,<sup>5</sup> when many women are forced into balancing disease with careers, families, and social lives. Migraine-related disability increases as the number of migraine attacks per month increases.<sup>12</sup> Compared with men, women are more likely to require bed rest with attacks and experience disabling attacks that last from 1 to 6 days.<sup>44</sup>

TABLE 2. PERCENTAGES OF INDIVIDUALS WITH EPISODIC MIGRAINE AND CHRONIC MIGRAINE WHO HAVE SOUGHT CONSULTATION FROM A HEALTHCARE PROFESSIONAL, RECEIVED A DIAGNOSIS, AND WERE APPROPRIATELY TREATED

	Consulting (%)	Diagnosed (%)	Appropriately treated (%)
Episodic migraine	45.5	39.5	26.3
Chronic migraine	40.8	10.0	4.5

Adapted from Dodick et al.<sup>80</sup>

### Care received

Seeking and receiving proper care for migraine remain enormous public health problems. A minority of individuals who have episodic or chronic migraine seek consultation (45.5% episodic and 40.8% chronic) (Table 2). Only a small fraction of those with episodic or chronic migraine are properly diagnosed (39.5% episodic, 10.0% chronic) and receive evidence-based treatment (26.3% episodic, 4.5% chronic).<sup>80,81</sup>

Women with migraine are more likely than men with the disease to have talked to a provider and received a diagnosis, whereas more men are likely to have significant disability by the time they seek care.<sup>44</sup> Women are more likely to be taking prescription medications, whereas men are more likely to be taking no medications at all or only over-the-counter medications. Women are also more likely than men to have sought care in an emergency setting.<sup>44</sup>

Women face increased barriers to receiving proper diagnosis for menstrual migraine as a prevalent migraine subtype. There is a general lack of education and awareness about menstrual migraine, leading to difficulties in obtaining proper diagnosis and an absence of effective treatments. These barriers may be exacerbated by the placement of menstrual migraine in the appendix, rather than the main text of ICHD-3, thereby implying to healthcare providers that it is not of high importance. The ICHD-3 requires that to research women with menstrual migraine, diary documentation of at least three cycles is necessary to confirm the diagnosis, creating yet another barrier to diagnosis and to investigating new treatments for women with menstrual migraine. Studies of large randomized controlled trials would be highly valuable in the legitimization of a disease that many providers and patients know exist but are unable to diagnose and treat.

Of those providing care, 85% of doctors certified in headache medicine by the United Council for Neurologic Subspecialties (UCNS) are neurologists, 63% of whom are

men.<sup>82</sup> More research is needed to clarify whether a health-care provider's gender affects health outcomes for individuals seeking care for migraine; however, studies have shown differences in patient outcomes that were associated with their healthcare provider's gender.<sup>83-87</sup> For example, compared with men, women healthcare professionals across all specialties are more likely to adhere to clinical guidelines, more often provide preventative care, and more often provide psychosocial counseling.<sup>83-86,88</sup> Interestingly, migraine has a higher prevalence among neurologists and headache specialists for both sexes (Table 3).<sup>82</sup> The effect of this on a provider's ability to empathize with people with migraine or develop knowledge of treatment regimens remains unknown.

### Stigma

A major root cause for many of the challenges in delivering and receiving optimal migraine care is stigma toward those with the disease. Because migraine is three times more prevalent in women, some perceive it as a feminized and less legitimate disease.<sup>89</sup> Men with migraine may delay care due to this feminization,<sup>44</sup> and individuals with migraine may be less motivated than those with other diseases to seek care due to fear of not being taken seriously or not being able to receive appropriate care.<sup>90</sup>

The accumulation of stigma has a negative impact on the lives of all individuals with migraine, but particularly women, who are often responsible for a larger amount of traditionally noncompensated labor (*e.g.*, housework and caregiving) compared with men. The Migraine Disability Assessment Test and the Headache Impact Test 6 are the most widely implemented scales used to evaluate the impact of migraine on health-related quality-of-life issues.<sup>91-93</sup> However, with these current instruments, the disproportionate impact migraine has on women may not be well captured. For example, these questionnaires only evaluate the impact of headaches on the individual with migraine and only during attacks. Meaning, the family burden of migraine is not adequately captured as well as the burden of disease in between attacks. Individuals with migraine may have lost productivity and/or miss family or social obligations in between migraine attacks because of prodromal symptoms or anxiety about the uncertainty of their next attack. New scales have been developed to measure the impact of migraine on spouses and children, but they have yet to be widely adopted.<sup>14,94</sup>

Despite its high prevalence, stigma also exists toward migraine research among academics.<sup>89</sup> Funding of NIH migraine research is the lowest relative to disease burden among the most impactful diseases.<sup>95</sup> This fact may discourage academic neurologists from pursuing this specialty, as it could be perceived to be difficult to secure research funding or academic positions. In addition, healthcare providers may be

TABLE 3. BREAKDOWN OF MALE AND FEMALE INDIVIDUALS WITH MIGRAINE VERSUS PRACTITIONERS

	Male			Female		
	General population (%)	Neurologists (%)	Headache specialists (%)	General population (%)	Neurologists (%)	Headache specialists (%)
Migraine 1-year prevalence	~12	35	59	~23	58	74

Adapted from Evans et al.<sup>82</sup>

reluctant to specialize in headache medicine because migraine is not taken as seriously as other neurological diseases and headache medicine might not reimburse as favorably as other neurospecialties that may rely more heavily on procedural treatments. Lack of investment in migraine research also harms treatment development. By increasing funding for migraine research, migraine may be able to move forward as a field and greatly improve patient care, including the much needed advancements in understanding sex differences.

## Conclusions

To address gaps in knowledge, more research is needed to broaden our understanding of the etiology, presentation, treatment, and care for those with migraine. Sex hormones play a key role in the pathophysiology of migraine, yet little is known about the role of hormones in the brain.

TABLE 4. PRIORITY AREAS IN SEX AND GENDER DIFFERENCES IN MIGRAINE RESEARCH, CARE, AND EDUCATION

Expanding current animal models	<ul style="list-style-type: none"> <li>• Increase inclusion of female animals</li> <li>• Expand pain and migraine model phenotypes</li> <li>• Explore role of female hormones throughout animal lifespan</li> </ul>
Broadening clinical studies	<ul style="list-style-type: none"> <li>• Diversify ages and race/ethnicities of individuals enrolled in studies</li> <li>• Include sex and gender differences in study design and analysis</li> <li>• Improve understanding of the roles of social, epigenetics, and environmental factors in migraine</li> <li>• Conduct longitudinal studies of hormones, migraine, and women</li> <li>• Increase research on safety and efficacy of treatment options during pregnancy and lactation</li> <li>• Improve understanding of the roles of sex and gender differences in comorbidities in migraine etiology and treatment</li> </ul>
Increasing awareness to better identify and treat migraine	<ul style="list-style-type: none"> <li>• Engage in more effective outreach and dissemination of current data regarding women and migraine for:               <ul style="list-style-type: none"> <li>○ Hormonal therapies</li> <li>○ Options during pregnancy and lactation</li> </ul> </li> </ul>
Improving quality-of-life measures	<ul style="list-style-type: none"> <li>• Improve assessment of disability with inclusion of work, school, social life, and family</li> <li>• Enhance understanding of migraine's impact on workplace productivity</li> </ul>
Destigmatizing migraine	<ul style="list-style-type: none"> <li>• Improve employer understanding of migraine as a valid reason to miss work</li> <li>• Increase rates of those seeking and continuing care</li> <li>• Include menstrual and menstrually related migraine in the main text of ICHD</li> <li>• Increase funding for migraine research and treatment development in areas that are important for women (e.g., safe treatments during pregnancy and lactation, issues related to perimenopause and menopause, and cardiac health)</li> <li>• Increase funding and support of biobehavioral treatments and lifestyle factors</li> <li>• Increase number of headache specialists</li> </ul>

Including both female and male animals into future study design will better reflect migraine phenotypes. Because of varying prevalence of migraine throughout the lifespan, animal models that incorporate different age groups are also necessary. Furthermore, hormonal effects vary among age groups, so sex and gender differences will need consideration throughout the lifespan. By analyzing age groups and sex in migraine research, we can gain a more robust understanding of migraine etiology, allowing basic science research to better bridge the gap between animal and human studies.

In addition, few studies have investigated sex differences in response to current approved interventions for migraine, as well as their use in women who may be pregnant or lactating. Deficiencies in sex and gender differences in reported treatment efficacy and side effect data must be addressed. Treatment options for specific age groups and those with a combination of comorbidities should also be explored. Gender differences in migraine need to be better understood, as measured through the gendered dimensions of violence, trauma, precarity, obesity, and education, and their role on migraine. Understanding the diverse contributors to migraine will lead to more robust treatment options.

In evaluating stigma, there is a need for more data describing employer and general population views on migraine, as well as research that develops social frames to improve support for people with migraine. This includes improvements in patient-reported outcomes and an increase in the number of studies investigating societal views of migraine. With this information, evidence-based initiatives addressing knowledge gaps in overcoming stigma may be designed.

Through evaluation of the current landscape on sex and gender differences in migraine, the expert panel at the SWHR roundtable meeting identified clear gaps in our understanding that require more research (Table 4). Better understanding how sex and gender impact the etiology, diagnosis, treatment, and management of migraine can lead to improved access to care and health outcomes for both women and men.

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received honoraria from Teva. Dr. Halker has served on the advisory board for Amgen. Dr. Moriarty had served on the advisory boards of Allergan and Amgen. Dr. Kempner has received honoraria from Amgen. Dr. Pavlovic has served on the advisory board for Alder and received consulting honoraria from Allergan and Promeus Pharma. Dr. Shapiro has received consulting fees from Eli Lilly & Company. Dr. Starling has received consulting fees from Amgen and Eli Lilly & Company; served on the advisory boards of Alder, Amgen, Eli Lilly & Company, and eNeura; and received speaking honoraria from eNeura and Medscape. In the past 24 months, Dr. Young has served on the advisory boards of Alder, Allergan, Avanir, and Supernus; received consulting fees from Alder, Allergan, and Supernus; and served on the speaker's bureau for Amgen. He has received research support from Alder, Allergan, Amgen, Autonomic Technologies, Colucid, Cumberland, Dr. Reddy Laboratories, Eli Lilly & Company, Merz, Novartis, PCORI, Scion, Teva, and Zosano.

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Address correspondence to:

*Rebecca A. Nebel, PhD*  
*Society for Women's Health Research*  
*1025 Connecticut Avenue, NW, Suite 1104*  
*Washington, DC 20036*

*E-mail: rebecca@swhr.org*

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