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PAIN MEDICINE (GJ MEREDITH, SECTION EDITOR)

Gender and Pain

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Abstract
Purpose of Review Sex differences in pain have become a topic of significant interest over the past two decades. This brief review addresses the epidemiological literature on sex-related influences on pain, with an emphasis on the mechanisms that may account for the greater incidence of chronic pain in women.
Recent Findings Although the magnitude of effects varies, overwhelming evidence suggests that women are at greater risk for clinical pain and have heightened sensitivity to experimental pain stimuli. There are also notable differences between men and women in their response to pharmacologic and non-pharmacologic pain treatments; however, findings across studies have been mixed.
Summary Given the evidence of pain disparities, a number of biological and psychosocial mechanisms accounting for the variation in pain among men and women have been proposed. Continued investigation of the factors driving sex differences in pain may facilitate advances in pain management for both sexes.

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Introduction

Interest in sex differences in pain has proliferated over recent years, as observed from the 110 % increase in the number of publications in the past 10 years when compared to growth in the previous decade (based on a PubMed search using the terms “sex or gender” and “pain”). This has largely been spurred by studies finding extant differences between men and women in their experience of pain, mandates requiring that research be conducted in both sexes, as well as the recognized imbalance between males and females in preclinical experimental testing [1, 2]. Although the magnitude of effects varies, research has consistently shown that women are at a greater disadvantage for chronic pain that is more frequent than men, experience higher rates of widespread pain, and exhibit greater sensitivity to experimentally induced pain [3, 4]. There is also evidence of sex-specific mechanisms driving the divergence in pain among men and women. While sexual dimorphisms in the brain due to the organizational effects of hormones or genes likely impact sex differences in pain, these effects are also shaped by numerous biological, sociocultural, environmental, and psychological factors. Although much is known about the differences in pain in men and women, further research is needed to explicate the underlying mechanisms facilitating this differential impact. Thus, the focus of this review will be to summarize the existing literature on sex differences in clinical and experimental pain, as well as discuss potential biological and psychosocial mechanisms fostering sex-based disparities.

Sex Differences in Clinical Pain

Over the past few decades, a number of epidemiologically based studies have documented a higher prevalence of pain among women (Fig. 1). In fact, data from the National Health and Nutrition Examination Survey (NHANES) from 2003 to 2004 observed higher estimates of chronic pain in women (18.3 % in women compared to 12.9 % in men) [5•], while an internet-based survey in 2008–2009 found that 34.3 % of women reported chronic pain, as compared to only 26.7 % of men [6]. Similarly, women tend to have pain in a greater number of anatomical body regions (and significantly more so for headache and abdominal pain), have a higher prevalence of widespread pain [7], report pain more frequently and of greater duration than men [3, 4, 8, 9], and are at greater risk for persistent pain [10] such as fibromyalgia, headaches (migraines and chronic-tension type), irritable bowel syndrome, interstitial cystitis, and chronic fatigue syndrome [11].

While women appear to dominate the picture in terms of pain prevalence, the impact of sex differences on pain severity and disability is not as clearly delineated. Research examining the potential for such differences has mostly assessed pain severity in treatment-seeking individuals with chronic pain. These studies show some inconsistencies, such that some note greater pain severity and disability in women across pain conditions (e.g., knee osteoarthritis) [12–14], whereas others report no sex differences [15–17]. Methodological limitations and variability across studies may potentially account for these inconsistencies, and factors such as provider sex, effectiveness of treatment, and sample characteristics of patients with chronic pain (e.g., willingness to seek treatment) may compromise the generalizability of these findings

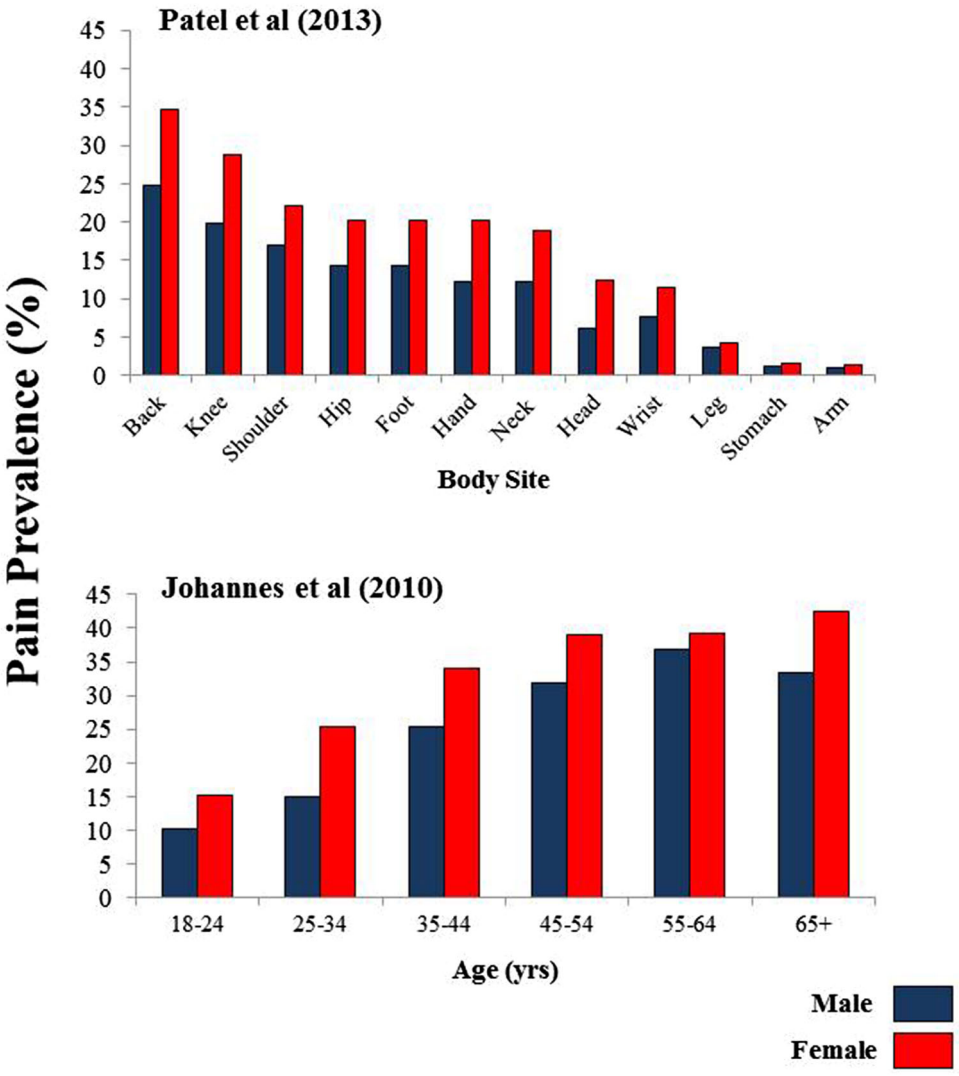

Fig. 1 Sex differences in pain prevalence. *Top panel*: Prevalence of pain across anatomic sites among adults 65 years and older. As reflected, women have higher rates of pain across multiple body regions (data are from Patel et al. [26••]). *Bottom panel*: Sex differences in chronic pain (pain lasting at least 6 months) across the lifespan. Compared to men, women report a greater prevalence of chronic pain at each age group. Data represent weighted estimates (based on findings from Johannes et al. [6])

[3, 12, 18]. Moreover, lower severity pain is not as well represented in clinical settings, with patients reporting a higher degree of moderate-to-severe pain; thus, pain report in clinical samples may be biased in the direction of attenuated sex differences [16]. An additional approach to examining sex differences in pain has been in post-operative pain assessment. A recent study observed greater mean pain scores and a higher incidence of pain in women after nonambulatory surgery, with a 16 % greater likelihood of a severe pain event occurring in women post-surgically, relative to men [19]. Although similar effects have been observed in other studies [20–22], this has not always been a reliable finding [23]. Collectively, while we know that women are at greater risk for many chronic pain conditions, the existence or direction of sex differences in pain severity in clinical settings is mixed [3].

Sex differences in clinical pain are also age dependent as a recent systematic review in children and adolescents found higher prevalence rates of pain in girls than boys, effects which only increased with age [24]. Relatedly, data from the U.S. Health and Retirement Study demonstrated a higher frequency of pain among women 60 years and older [25], while the National Health and Aging Trends Study reported a greater number of pain sites in women over the age of 64, compared to men of the same cohort [26••]. Pain prevalence for males and females across age can even vary by the type of pain [27]. Taken together, these findings highlight the importance of incorporating a lifespan perspective to fully understand pain in men and women.

Sex Differences in Experimental Pain

To further examine sex differences in pain, quantitative sensory testing (QST) has been used as a means to understand the pain system and capture potential mechanisms that may subserve sex differences. Several experimental modalities have been used including electrocutaneous, mechanical pressure, thermal (heat and cold), ischemic, and chemical stimuli (e.g., capsaicin). Pain sensitivity is often measured via behavioral responses, such as pain threshold (time or intensity of stimulus until pain is elicited) and tolerance, as well as subjective report of pain intensity and unpleasantness. Additionally, pain modulation can be investigated using dynamic procedures such as conditioned pain modulation (measure of descending pain inhibitory processes) and temporal summation (measure of central nervous system sensitization and pain facilitation). Generally, women tend to show greater sensitivity to pain (lower thresholds/tolerances, higher pain intensity/unpleasantness ratings) and enhanced temporal summation compared to men, whereas greater pain modulation is observed in men [3, 4, 11, 28–30]. Supporting this, a recent study found that healthy women evidenced greater sensitivity to ischemic pain and reduced pain inhibition compared to healthy men, even after controlling for differences in psychosocial variables such as depression and sleep quality [31]. Further, women with symptomatic knee osteoarthritis were more sensitive to painful stimuli (i.e., thermal, pressure) and had greater temporal summation compared to men with similar pain severity, and these differences did not vary significantly across age [32]. Findings such as these have been observed in children and adolescents as a recent meta-analysis found greater cold pain intensity in girls, but higher heat pain thresholds and tolerances in boys [33]. Still, it is important to note that sex differences are sometimes found in studies utilizing certain pain induction stimuli and procedures, but not among other modalities, which again may lead to variable conclusions to be drawn from these data. Given this, a recent review suggests that in addition to static and dynamic measures of pain sensitivity as are traditionally measured in such studies, sex differences in adaptation and habituation to pain should be further explored. Indeed, women exhibit greater adaptation to sustained stimuli and habituation to repeated long stimuli, suggesting that they may have a better capacity than men to modulate pain over longer periods of time [34].

Sex differences in spinal nociception [e.g., withdrawal reflexes such as the nociceptive flexion reflex (NFR)] and cerebral responses to pain have also been investigated. In an early study, women were found to have lower NFR thresholds (stimulation intensity needed to evoke the reflex) compared to men [35]. More recently, no such difference was found in NFR threshold; thus, the role of spinal-level pain processing on sex differences in pain is indeterminate [36]. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies examining supraspinal mechanisms have also provided mixed results, although there is inconsistency across studies in which areas of the brain are examined. Generally, these investigations suggest differential activation of cortical and brainstem regions associated with pain perception and modulation (e.g., anterior cingulate cortex, insula, medial prefrontal cortex, and periaqueductal gray) between women and men [37–41], effects which may vary according to hormone status [42, 43•]. Further, recent research suggests that the default mode network and regions specific to pain affect may be more salient in women, while sensory/discriminative networks play a greater role in pain among men [44].

Taken together, the majority of evidence supports the notion that women have greater pain sensitivity and that pain modulatory mechanisms differ between the sexes, although these findings vary across published studies. Psychosocial (e.g., emotion and gender roles) and

Table 1 Proposed biopsychosocial mechanisms underlying sex differences in pain

	Proposed mechanisms
Biological	Sex hormones (e.g., estrogens, progestins, androgens); endogenous opioid receptor function (e.g., μ-opioid receptor); neurotransmitters (e.g., dopamine, serotonin); neurochemical (e.g., NMDA receptor function); neuroimmune (e.g., microglia, T cells); genetic (e.g., AVPR1A, MC1R, COMT, OPRM1)
Psychological	Cognitive/behavioral coping; catastrophizing; emotion (e.g., anxiety, depression, anger, anxiety sensitivity, negative affect); empathy; perceived control; self-efficacy; somatic awareness; fear avoidance
Sociological/contextual	Gender roles (e.g., femininity, masculinity); gender role expectations; demographic (e.g., age, race, ethnicity, SES); culture; experimenter sex; early-life stressors (e.g., abuse, neglect, trauma); family pain history (i.e., modeling of pain behaviors); history of painful experiences (e.g., previous pain)

Note: *NMDA N*-methyl-D-aspartate, *AVPR1A* arginine vasopressin receptor 1A, *MC1R* melanocortin 1 receptor, *COMT* catechol-*O*-methyltransferase, *OPRM1* opioid receptor mu 1, *SES* socioeconomic status

biological (e.g., endocrine) factors may contribute more specifically to sex-related differences in pain and pain processing, making these important to consider and are explored later in this review.

Sex Differences in Pain Treatment Response

Sex differences in response to pharmacological and non-pharmacological interventions for pain have also been documented. With respect to opioid analgesia, a meta-analysis revealed that in experimental studies, opioids appear to be more effective in women, especially morphine, but sex differences were not noted for clinical studies [45]. Studies examining patient-controlled analgesia (PCA) found opioids to be more efficacious for women, as men consumed more analgesics [45]. However, the results of these studies should be interpreted with caution because "efficacy" of opioids was based on retrospective reporting of opioid consumption (which can vary due to factors such as adverse effects), rather than direct measures of pain relief [3, 4]. A more recent review suggests that morphine may actually not be as effective for women as once thought. In fact, important sex differences in the neurobiology involved in pain modulation may impact the way analgesics function and could contribute to opioids being less efficacious for women, implicating a potential need to tailor different treatments to this population [46•]. Moreover, after veterans underwent an interdisciplinary treatment for chronic pain, men had longer lasting benefits post-treatment compared to women, even after opioid cessation (i.e., women did not maintain pain reduction) [47].

Additionally, sex-associated biases can lead to disparities in pain management. Recent evidence suggests that men and women experience negative consequences from such biases, and characteristics particular to the provider, patient, or both may impact pain assessment and intervention [48, 49]. The use of virtual technology has been helpful to study the extent and nature of these outcomes. For example, one study noted that both undergraduates and healthcare trainees viewed women as experiencing greater pain intensity, and also recommended more treatment for women than for men [50]. Also, female providers may be more prone to recommend psychosocial pain interventions to women, rather than men [51]. Interestingly, patients have also been found to alter pain report depending on the sex of the provider. In an emergency room setting, men experiencing lower pain intensity were more likely to report higher pain ratings to male rather than female examiners, while both sexes were willing to report high levels of pain consistent with their experienced pain intensity to female providers [18].

Furthermore, sex can influence response to non-pharmacological pain treatment, but these effects also vary. Some studies report women have greater benefits (e.g., reduction of pain-related disability) from multimodal treatment than men [52], while others suggest that women may not maintain treatment gains [47, 53]. Although non-pharmacological remedies appear helpful to men and women, the mode of treatment and other factors (e.g., sociocultural) likely influence response to and overall effectiveness of these interventions between the sexes.

Biopsychosocial Mechanisms Associated with Sex Differences in Pain

The evidence overwhelmingly supports disparities among men and women in their experience of pain, yet the potential mechanisms (i.e., qualitative factors) fundamentally triggering these differences are more complex to tease apart. A number of biological and psychosocial factors likely play a role in pain and promote variation between the sexes, and it is very likely that these factors are dynamic and interact with one another at the individual level. The resulting section will briefly summarize some of the key contributors to sex differences in pain (Table 1).

Biological Factors

Sex Hormones

Perhaps one of the most frequently studied mechanisms is gonadal hormones (for excellent reviews see [54•, 55–57]), namely due to the profound differences that exist between men and women in basal levels as well as sex hormone fluctuations. It is well established that sex hormones have numerous influences that extend beyond the reproductive system. Indeed, hormone receptors are located at multiple points along the central and peripheral nervous system [54•]; thus, it is no surprise that they are highly implicated in the experience of pain. Additionally, gonadal hormones may enhance nociception through the modulation of various neurotransmitters (i.e., serotonin, dopamine, β-endorphin, and γ-aminobutyric acid), interaction with other sex hormones, effect on limbic systems, and mediation by endogenous opioids [42, 54•, 58, 59]. This is certainly not an exhaustive list which adds to the complexity of sex hormone modulation of pain. Estrogen, progesterone, and testosterone are the three most commonly studied sex hormones, and it is suggested that sexual differentiation in pain is partially due to the organizational and activational effects of hormones across the lifespan. While the specific actions of these hormones are beyond the scope of this review, it is alluded that estrogens and progestins have both pro- and anti-nociceptive properties [56], while testosterone acts more as an inhibitor of pain [56, 60], effects which have been observed both in preclinical and human research. Patterns of gene expression on hormone receptors are also implicated in pain processing as certain estrogen receptor polymorphisms (ERα) increase risk for pain, while others take on more of a protective effect [61, 62].

The most notable differences in pain between men and women occur after the onset of puberty where dramatic shifts in sex hormones take place. Sex hormones are generally stable in men throughout the lifespan (although testosterone decreases with age); however, gonadal hormones in women are subject to significant fluctuations. It is suggested that sex hormones may account for increased pain among women, especially given that pain (e.g., temporomandibular disorder, fibromyalgia) increases during periods of increased hormone fluctuation (e.g., perimenstrual period of the menstrual cycle, postpartum, and perimenopause). Moreover, exogenous hormone use through oral contraceptives reduces clinical pain across the menstrual cycle [63], yet hormone replacement after menopausal transition is linked to increased pain report in women [64]. Highlighting the role of the sex–hormone relationship, Aloisi et al. conducted a fascinating study whereby transsexuals underwent hormone administration during sex reassignment. These authors found that 30 % of male-to-female patients developed chronic pain after estrogen and progestogen (anti-androgen) treatment, while female-to-male patients exhibited an improvement in pain following testosterone therapy [65]. In contrast to clinical findings, menstrual cycle effects on experimentally based pain are less than robust. While women tend to be more sensitive to laboratory pain during the luteal phase (the exception to this is electrocutaneous pain which shows increased sensitivity during the follicular phase), these effects are small to moderate at best [66]. Interestingly, sex differences in pain markedly decrease after menopause when hormones stabilize in women. While less work has been done in older adults, a recent study found that lower sex hormone levels were associated with chronic musculoskeletal pain in women, but not in men [67].

Genetics

One of the most studied genes in the context of pain is catechol-*O*-methyltransferase (COMT), an enzyme that has strong functionality in regulating, and namely, inactivating neurotransmitters and their metabolites. Studies have noted attenuated opioid responsivity to pain for individuals homozygous for the Met variant, while opposing effects are observed for the Val allele [68]. These effects appear to diverge across men and women, with females displaying greater pain sensitivity to capsaicin for those with low COMT activity [69].

Due to its dramatic opioid effects, the single nucleotide polymorphism (SNP) A118G of the μ-opioid receptor gene, OPRM1, has also been widely investigated [70]. This gene has been associated with mechanical pressure pain sensitivity more strongly in males than females, while higher heat pain sensitivity in women but lower heat pain ratings in men have been observed in individuals with the minor (G) allele [71]. Interestingly, the G allele predicted better recovery 1 year after lumbar disc herniation in males, yet women with the same genetic variant exhibited higher pain and disability [72]. However, a null pattern was observed in another study examining the analgesic effects of fentanyl to cold pain sensitivity. While analgesia was greater in males than females, and individuals with the G allele were less sensitive to fentanyl (and exhibited greater cold pain sensitivity), there was no interaction between sex, pain, and genotype [73].

Stress may also interact with sex and genotype to influence pain response. In a set of elegant studies by Mogil et al., a SNP of arginine vasopressin receptor 1A (AVPR1A) influenced capsaicin pain but only in men who reported high levels of acute stress prior to the procedure. The authors also corroborated these findings in mice [74]. Additionally, a sex-specific genetic association between the melanocortin-1 receptor (MCR1), a gene involved in the

regulation of skin and hair color, has also been observed with pain. In another study by Mogil et al., men and women of different hair colors were recruited and sensitivity to pain was measured before and after the administration of pentazocine, a κ-opioid analgesic. Redheaded women with multiple alleles exhibited greater pentazocine analgesia, relative to men [75]. Moreover, it has been speculated that females use a different pathway (i.e., MCR1) than men (i.e., *N*-methyl-D-aspartate receptor [NMDAR]) for opioid analgesia/hyperalgesia [11]. Taken together, these observations suggest that genotype can differentially impact pain in men and women, but multiple factors may influence outcomes.

Neuroimmunity

More recently, immune system cells have been considered as potential contributors to neuronal excitability in the central and peripheral nervous system. In a series of preclinical experiments, Sorge et al. demonstrated that male and female rats modulate pain through differential activation of immune cells. After administration of microglial inhibitors following nerve injury, males evidenced mechanical analgesia, but no significant effects were observed in female rodents. Rather, males seem to rely on the activation of spinal toll-like receptor 4 (TLR4)—an immune system receptor expressed in microglia, while pain in females may be more dependent upon a microglia-independent pathway such as T lymphocytes [76••, 77, 78]. While these findings are still in their infancy and need to be translated to humans, they represent a promising discovery that could shed light on the potential mechanisms underlying variance in pain processing in men and women.

Psychological and Sociological Factors

Although biological factors certainly play a strong role in sex differences in pain, psychosocial factors have also long been appreciated in explaining variation between men and women. These factors range from differences in mood and coping to the impact of gender roles and early-life trauma, among others.

Negative Mood

Women have a higher prevalence of depression and anxiety than men, and it is widely recognized that these two emotions are comorbid with pain and show sex-dependent effects [4]. While depression is suggested to have a stronger role in women, anxiety tends to show an opposite effect. For example, Edwards et al. observed poorer pain-related outcomes in men with higher levels of anxiety (these effects were not observed in women) [79]. Interestingly, in a later study by the same authors, higher pre-treatment anxiety predicted greater pain reductions to pharmacological treatment in men while the reverse pattern was observed in women [15]. Contrary to these findings, anxiety sensitivity (fear of anxiety-focused pain sensations) is notably higher in women, with differential responsivity to pain demonstrated among men and women [80].

Coping

Catastrophizing is the tendency to magnify, ruminate, and feel helpless in the presence of pain [81], and numerous studies have reported significant relationships between pain catastrophizing and adverse pain-related functioning. Despite some research reporting no sex differences in catastrophizing [36, 82], the general trend is higher rates of engagement among women. Such findings were also observed in a recent systematic review examining coping strategies among adults with chronic pain [83]. Coping mechanisms also impact pain, and it is suggested that women manage their pain by using more emotionally based and adaptive coping strategies (i.e., cognitive restructuring, problem solving, perceived self-competence, mental diversion, counterbalancing activities, positive self-statements, attentional focus, reinterpretation of pain), and have a greater propensity to seek emotional support. Conversely, males engage in behavioral distraction, passive coping, and avoidance behaviors (e.g., substance use) to cope with pain [4, 84–86, 87•].

Social and Contextual Influences

Social roles must also be considered in the context of sex-related differences in pain. For example, females are taught at an early age to express emotions; however, this is traditionally deemed as socially unacceptable for males and instead stoicism is encouraged. Commonly accepted views by both sexes are that men are less willing to report pain while women are considered to be more pain sensitive [88], and taking on more of a masculine role is associated with lower sensitivity to pain [89]. Robinson et al. found that manipulating gender-associated beliefs about pain tolerance abolished sex differences in cold pain sensitivity [90], while Fowler et al. observed lower pain (from the cold pressor task) in men primed with a feminine role cue [91]. Other contextual factors differentially influencing pain for males and females include the sex of the experimenter [92] and maternal pain-promoting behavior [93]. Thus, differences in pain reporting and prevalence may be due to sociocultural factors including gender expectancies and social learning.

It is also established that early-life experiences of pain (e.g., neonatal pain, childhood abuse/neglect) can produce

neuroplastic changes that modify the functioning of pain pathways [94]. Childhood adversity is associated with increased clinical pain [95] and greater sensitivity to experimental stimuli [96], and it is suggested that women may be more vulnerable to specific insults (e.g., sexual abuse) [97] which could explain negative pain outcomes in this cohort. These effects may also be dependent upon genotype as a recent study found that a history of early adverse events was associated with thinning of the left subgenual cingulate cortex (sgACC) in women with a minor IL-1β allele [98].

Conclusions

Sex-related factors undeniably impact the experience of pain, and a relatively clear picture has emerged depicting greater prevalence of chronic pain among women. Although the magnitude of differences varies across studies, evidence also indicates that women may be more "sensitive" to experimental stimuli and vary in their response to pain treatment, relative to men. While these quantitative differences provide valuable insight into the variation that occurs between men and women in their pain experience, what may be more critical is gaining a better understanding of the specific processes that drive extant differences. Considerable groundwork has been made in illuminating these mechanisms; however, many unanswered questions remain regarding how and why sex differences in pain exist. This picture is complicated by the nature of pain as it is truly a biopsychosocial problem and a multitude of highly dynamic processes likely impact differential pain response across men and women. Historically, ovarian hormones were believed to be one of the chief regulators of the sex/pain relationship, but several lines of evidence over the years support the role of other biological processes including genetic factors and neuroimmune functioning, among others. However, one must not dismiss the importance of psychosocial factors as gender roles and biases, negative emotion, coping style, and early-life experiences also contribute to sex differences in pain. Ultimately, qualifying the effects of these differences constitutes an important directive in understanding the factors that promote both adverse and adaptive (i.e., resilience) pain-related functioning among men and women. While much work has yet to be done, it is anticipated that greater clarity in the underlying mechanisms may facilitate improved treatment outcomes across both sexes.

Compliance with Ethics Guidelines

Conflict of Interest Emily J. Bartley and Shreela Palit declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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