Sex differences in pain: a brief review of clinical and experimental findings

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Editor’s key points

- There is increasing evidence for sex differences in pain sensitivity and analgesic response.
- Clinical pain, both acute and chronic, and experimental pain models all show sex differences.
- While chronic pain is commoner in women the evidence on pain severity is less clear.
- Further study is needed of underlying mechanisms, including the contribution of hormonal and genetic factors.

Summary. Recent years have witnessed substantially increased research regarding sex differences in pain. The expansive body of literature in this area clearly suggests that men and women differ in their responses to pain, with increased pain sensitivity and risk for clinical pain commonly being observed among women. Also, differences in responsivity to pharmacological and non-pharmacological pain interventions have been observed; however, these effects are not always consistent and appear dependent on treatment type and characteristics of both the pain and the provider. Although the specific aetiological basis underlying these sex differences is unknown, it seems inevitable that multiple biological and psychosocial processes are contributing factors. For instance, emerging evidence suggests that genotype and endogenous opioid functioning play a causal role in these disparities, and considerable literature implicates sex hormones as factors influencing pain sensitivity. However, the specific modulatory effect of sex hormones on pain among men and women requires further exploration. Psychosocial processes such as pain coping and early-life exposure to stress may also explain sex differences in pain, in addition to stereotypical gender roles that may contribute to differences in pain expression. Therefore, this review will provide a brief overview of the extant literature examining sex-related differences in clinical and experimental pain, and highlights several biopsychosocial mechanisms implicated in these male–female differences. The future directions of this field of research are discussed with an emphasis aimed towards further elucidation of mechanisms which may inform future efforts to develop sex-specific treatments.

Keywords: gender differences; opioid analgesics; pain; pain perception; sex differences

Sex differences in clinical pain

Population-based research consistently demonstrates greater pain prevalence among women relative to men. For example, large-scale epidemiological studies across multiple geographic regions find that pain is reported more frequently by women than by men1 (Fig. 1). Gerdle and colleagues9 found that for each of 10 different anatomical regions, a greater proportion of women than men reported pain in the past week, and women were significantly more likely to report chronic widespread pain. Moreover, the population prevalence of several common chronic pain conditions is greater for women than men, including fibromyalgia, migraine and chronic tension-type headache, irritable bowel syndrome, temporomandibular disorders, and interstitial cystitis.1 4

In addition to these findings demonstrating that pain is reported more frequently by women compared with men, another relevant research question is whether the severity of pain differs by sex. This issue is surprisingly more difficult to address. For example, several investigators have examined sex differences in pain severity among samples of patients

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seeking care for their chronic pain. While some studies have reported greater pain severity among women than men,10–13 other studies have found no sex differences in pain severity among treatment-seeking patients.14–16 There is a potential for bias in these results as patients with less severe pain are under-represented in these studies. Sex differences in the delivery, effectiveness or both of pain treatments in these clinical samples could also influence the presence, magnitude and direction of sex differences in pain severity. Another approach to studying sex differences in pain severity has been to compare levels of post-procedural or post-surgical pain in women and men. Results from these studies have been inconsistent, with some reporting more severe pain among women,17–19 others reporting more severe pain among men,20 and others reporting no sex differences.21 On balance, the trend is towards greater acute post-procedural pain in women.1 Interpretation of these studies is complicated by potential sex differences in responses to pain treatments because pharmacological interventions are always provided in these settings. A recent study exploited a large electronic medical record database to study sex differences in pain severity in >11 000 patients.22 Importantly, pain ratings were collected as part of standard care, but these patients were not necessarily seeking treatment for pain and procedural pain was excluded. The investigators reported consistently higher pain ratings for women compared with men across the vast majority of diagnostic groups.

Taken together, the findings from epidemiological and clinical studies demonstrate convincingly that women are at substantially higher risk for many common pain conditions. Regarding pain severity, the findings are less consistent and are likely influenced by multiple methodological factors, including selection biases in clinical studies and the potential for sex differences in the effects of pain treatments. In order to exert greater control over such sources of variability, investigators have exploited quantitative sensory testing in order to explore sex differences in pain in response to controlled noxious stimuli, and these findings are discussed next.

**Sex differences in response to experimentally induced pain**

Sex differences in responses to experimental pain have been investigated using a wide variety of stimulus modalities including mechanical (blunt pressure and punctate mechanical stimuli), electrical, thermal (heat and cold), ischaemic, and chemical stimuli (e.g. capsaicin, hypertonic saline). Increasingly in recent years, more sophisticated experimental pain models have been used to characterize dynamic pain modulatory processes, such as temporal summation of pain (pain facilitatory measure) and conditioned pain modulation (measure of pain inhibition). Pain responses have been assessed by a number of different outcome measures including behavioural indices of threshold (defined by time or intensity to the first sensation of pain) and tolerance, and self-report measures of pain intensity and unpleasantness. Previous qualitative and quantitative reviews have generally concluded that women display greater sensitivity to multiple pain modalities compared with men, and that women show

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**Fig 1.** $Z$-scores for multiple pain measures in a sample of healthy young adults (166 female, 167 male). $Z$-scores were computed such that the mean for the entire sample is 0. Higher $Z$-scores reflect lower pain sensitivity and lower $Z$-scores reflect higher pain sensitivity. Sex differences were statistically significant for all pain measures ($P < 0.05$); however, the effect sizes ranged from small to large (Cohen’s $d$ in parentheses below), with a mean effect size in the moderate range ($d = 0.62$). HPTH = heat pain threshold ($d = 0.48$), HPTO = heat pain tolerance ($d = 0.98$), IPTH = ischaemic pain threshold ($d = 0.24$), IPTO = ischaemic pain tolerance ($d = 0.52$), CPTH = cold pain threshold ($d = 0.41$), CPTO = cold pain tolerance ($d = 0.55$), PPTTrap = pressure pain threshold at the trapezius muscle ($d = 0.90$), PPTMass = pressure pain threshold at the masseter muscle ($d = 0.89$). Details regarding pain testing methods have been reported previously.25 26
greater temporal summation of pain while men display greater conditioned pain modulation.\textsuperscript{1, 4, 8 23 24} In contrast, a recent systematic review concluded that ‘10 years of laboratory research have not been successful in producing a clear and consistent pattern of sex differences in human pain sensitivity’.\textsuperscript{5} A quantitative analysis of the studies that served as the foundation of their conclusion did however reveal a very consistent pattern of results in the direction of greater pain sensitivity in females.\textsuperscript{5} Figure 1 provides a graphical presentation of a dataset that reflects the typical pattern of findings across studies of sex differences in experimental pain responses, which helps explain the varying interpretations by some authors (for details regarding methodology see refs\textsuperscript{25 26}). The direction of sex differences in pain responses across multiple stimulus modalities and pain measures is highly consistent, with women showing greater sensitivity than men. However, the magnitude (and statistical significance) of the sex difference varies across measures, as it does across published studies. The potential mechanisms underlying these differences and the clinical implications of sex differences in pain sensitivity will be discussed further below.

**Sex differences in response to pain intervention**

Sex differences in response to pain treatment have also been described in the literature. In a review of 18 studies, Miaskowski and colleagues\textsuperscript{27} observed lower opioid consumption postoperatively among women. This has not been a consistent finding and may depend on the type of surgical procedure\textsuperscript{28} or result from increased prevalence of side-effects in women.\textsuperscript{29} A recent meta-analysis\textsuperscript{7} reported mixed results for sex differences in opioid analgesia. While the authors found no sex-specific effects for mu-opioid analgesia across clinical studies of mu-opioids, greater ‘analgesic’ effects were observed for women when restricting analyses to patient-controlled analgesia (PCA) and were even more robust when considering only PCA morphine studies. It is important to note that these studies actually assessed opioid consumption rather than pain relief, which may be influenced by factors other than analgesia (e.g. side-effects). Despite this, results were similar for experimental studies that directly assessed analgesic responses, suggesting greater morphine analgesia for women. Interestingly, while no sex-dependent effects were found for mixed action opioids (e.g. buprenorphine, nalbuphine, and pentazocine) across experimental studies, it was concluded that women exhibit greater analgesia than men in response to mixed action opioids in clinical studies.

Several investigators have also examined gender biases in pain treatment. In an often-cited study with multiple methodological shortcomings, women were given sedatives more often for pain after surgery, whereas men were more likely to receive analgesics.\textsuperscript{30} This has led many to conclude that women are at risk for under-treatment of their pain. However, a recent review of this literature concluded that while women and men are often treated differently, this disparity sometimes favours women and sometimes favours men.\textsuperscript{31} Moreover, such gender biases are influenced by both patient and provider characteristics, which sometimes interact. For example, in a medical vignette study, physicians were more likely to prescribe opioid analgesics to patients of the same sex.\textsuperscript{32} More recent studies using virtual human technology have demonstrated that females are considered to have greater intensity and unpleasantness of pain than males and are more likely to be recommended for opioid treatment as evaluated by healthcare professionals and students.\textsuperscript{33- 35} These studies suggest that biases exist in healthcare, an effect which may lead to disparities in pain management.

Other research has investigated the impact of sex differences on non-pharmacological pain interventions. In a study by Keogh and Herdenfeldt,\textsuperscript{36} men reported less pain when asked to focus on the sensory components of pain, while focusing on affective pain was not beneficial for women. There is also evidence that acceptance-based interventions for pain may be helpful towards reducing affective-related pain for women relative to men.\textsuperscript{37} In another study, pain sensitivity was decreased after treadmill exercise in female athletes while these effects were only seen in male athletes after engaging in a video game competition.\textsuperscript{38} In an interdisciplinary pain management programme, improvements in pain were found in both male and female patients after treatment; however, these effects disappeared 3 months later for women as they reported significantly more pain and catastrophizing than men.\textsuperscript{39} More recently, results from a 5-week multimodal pain management programme found that women exhibited an improvement in pain-related disability as compared with men.\textsuperscript{40} Hence, the literature seems to suggest that responses to non-pharmacologic treatments may differ for men and women, but the pattern of results is somewhat variable across studies.

**Mechanisms underlying sex differences in pain**

As the above summary indicates, it is well established that sex differences in pain exist; however, the specific underlying mechanisms contributing to this disparity are far from clear. It has been suggested that an interaction of biological, psychological, and sociocultural factors likely contribute to these differences. The following section will present a brief overview of the possible mechanisms implicated in sex-related differences in pain (see refs\textsuperscript{1 6 41} for a more extensive review).

**Biological mechanisms**

The influence of sex hormones represents a significant source of pain-related variability that likely impacts men and women differently. This is not surprising given the distribution of sex hormones and their receptors in areas of the peripheral and central nervous systems associated with nociceptive...
transmission. Although oestradiol and progesterone’s effects on pain sensitivity are relatively complex (both exert pro-nociceptive and anti-nociceptive effects on pain), testostosterone appears to be more anti-nociceptive and protective in nature, especially given the association between decreased androgen concentrations and chronic pain. Research on progesterone and testosterone’s effects on pain is still very limited, thus reflecting the need for further research assessing their specific modulatory effects. Most of the research to support sex hormone effects on pain stems from studies demonstrating exacerbation of clinical pain across the menstrual cycle. Furthermore, exogenous hormone use increases risk for some types of clinical pain and also reduces menstrual cycle effects on experimental pain sensitivity. It is also suggested that experimental pain sensitivity changes across the menstrual cycle, with increased sensitivity to most pain modalities (with the exception of electrocutaneous stimuli) during the luteal phase relative to the follicular phase. Unfortunately, much of the research in this area suffers from methodological limitations and more recent research suggests that these effects are absent or small at best. There is also evidence suggesting sex-related cortical differences during the processing of pain-related stimuli thus potentially implicating the influence of sex hormones on differential brain activation. A recent brain imaging study revealed that women using oral contraceptives who had low levels of testosterone showed reduced pain-related activation in pain inhibitory brain regions (e.g. the rostral ventromedial medulla). However, given the limited degree of studies in this area, further research is needed before firm conclusions can be drawn regarding hormonal influences on cerebral responses to pain.

Sex-related differences in pain may also reflect differences in the endogenous opioid system. For instance, there are distinct differences between men and women in pain-related activation of brain mu-opioid receptors. Smith and colleagues found that women in high oestradiol/low progesterone states exhibit decreased pain sensitivity and increased brain mu-opioid receptor binding than women in low oestradiol states, while decreased endogenous opioid neurotransmission was associated with low oestradiol. Therefore, these findings suggest that the interactive effects of the opioidergic system with gonadal hormones may be an important determinant of sex-based differences in pain sensitivity.

It is established that genotype may be a contributing factor to sex differences in pain. Preclinical research consistently shows that genotype and sex interact to influence nociceptive sensitivity, and these findings have been extended to humans in recent years. For example, the melanocortin-1 receptor (MC1R) gene, associated with red hair and fair skin, has been found to moderate algesia in a sex-dependent manner. Specifically, women with two variant alleles of the gene demonstrate greater analgesic responses to pentazocine (kappa opioid) relative to men and women who do not have the variant alleles. In another study suggesting a sex-dependent genetic association, the A118G single nucleotide polymorphism of the mu-opioid receptor gene (OPRM1) was found to be associated with pressure pain sensitivity in men but not women. Furthermore, differential effects on thermal pain sensitivity were observed between the sexes in that women with a rare allele exhibited increased pain sensitivity while the opposite was observed for men with the rare allele. These findings were recently extended to a clinical population, in that women with the rare allele showed poorer recovery from lumbar disc herniation, while the rare allele predicted enhanced recovery among men.

### Psychosocial mechanisms

Various psychosocial mechanisms may play a fundamental role in sex-related differences in pain. For instance, pain coping strategies have been found to differ between men and women. While men tend to use behavioural distraction and problem-focused tactics to manage pain, women tend to use a range of coping techniques including social support, positive self-statements, emotion-focused techniques, cognitive reinterpretation, and attentional focus. Two constructs proven to be integral to pain responsivity are catastrophizing and self-efficacy. Catastrophizing is a method of pain coping referring to the magnification and rumination of pain-related information, while self-efficacy refers to the belief that one can successfully perform a behaviour to achieve a desirable goal. Research has shown that catastrophizing is associated with pain and pain-related disability and women engage in catastrophizing more often than men. Furthermore, catastrophizing appears to mediate sex differences in pain responsivity; however, it has been suggested that the effect of catastrophizing on sex differences in pain may be modulated by other factors such as personality disposition. A lower degree of self-efficacy has been found to be associated with higher levels of pain and physical symptomatology. Other evidence has indicated that men demonstrate greater self-efficacy which was subsequently related to lower cold pressor pain sensitivity. Sociocultural beliefs about femininity and masculinity also appear to be an important determinant of pain responses among the sexes as pain expression is generally more socially acceptable among women, an effect which may lead to biased reporting of pain. In a study by Robinson and colleagues, both men and women believed that men are less willing to report pain than the typical woman and such gender role expectations may contribute to sex differences in experimental pain. Supporting the role of gender expectancies on pain are studies finding that sex differences in pain sensitivity may be influenced by sex-related expectations regarding performance on the pain task, suggesting that gender-related motivation may influence pain expression. A study by Fowler and colleagues found that social priming may impact sex differences in pain. When primed with a feminine gender role, men reported increased cold pressor pain. The authors highlighted that feminine role...
cues may alter pain report more than masculine role cues. Culture-related variability in stereotypical beliefs about pain may also play a role in noted differences between men and women. For instance, a recent study assessing pain sensitivity and gender roles among Israelis and Americans found that both Israeli and women reported a more masculine role in regards to views of pain sensitivity when compared with Americans,84 thus implying the importance of cultural differences in pain-related beliefs.

Early exposure to environmental stress, such as prior pain and history of abuse, may also contribute to variability in pain report between men and women. Childhood abuse has been linked to adult chronic pain with individuals having pain complaints later in life reporting a history of early-life abuse.85 With respect to sex differences, Fillingim and colleagues86 observed that a history of childhood abuse was associated with decreased pain sensitivity; however, this effect was only observed in women. It has also been reported that a family history of pain is associated with greater pain symptoms87 88 and increased pain sensitivity among females relative to men;86 although this has not been a consistent finding.89

Conclusions

Sex differences in pain have been a topic of increased interest in recent years. Epidemiologic and clinical findings clearly demonstrate that women are at increased risk for chronic pain and some evidence suggests that women may experience more severe clinical pain. Studies of experimentally induced pain have produced a very consistent pattern of results, with women exhibiting greater pain sensitivity, enhanced pain facilitation and reduced pain inhibition compared with men, though the magnitude of these sex differences varies across studies. In addition, some evidence suggests sex differences in responses to pharmacological and non-pharmacological pain treatments, though the findings differ depending on the specific treatment and perhaps on characteristics of the pain. Also, gender biases in pain treatment appear to exist, which are influenced by characteristics of both the patient and the provider.

Multiple biopsychosocial mechanisms contribute to these sex differences in pain, including sex hormones, endogenous opioid function, genetic factors, pain coping and catastrophizing, and gender roles. At present, the available evidence does not support sex-specific tailoring of treatments; however, this is a conceivable outcome in the foreseeable future. Additional research to elucidate the mechanisms driving sex differences in pain responses is needed in order to foster future interventions to reduce these disparities in pain.

Authors’ contributions

Both authors contributed to this work. E.J.B. generated the chief discussion points of the review article, wrote the abstract, and drafted the article. R.B.F. assisted in drafting the article and provided the statistical data. Both authors conducted the literature review, edited the manuscript, and approved the final version for publication.

Declaration of interest

E.J.B. declares no financial interests. R.B.F. is a consultant and equity stock holder in Algynomics, Inc., a company providing research services in personalized pain medication. Also, R.B.F. has received an honorarium from MedScape.

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