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Pain Tolerance Differences in Clinical and Experimental Findings

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Abstract

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 men. Gerdle and colleagues 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.

Keywords: Severity of pain; Treatment seeking patients; Chemical stimuli; Pain modulation; Experimental pain; Clinical studies; Gene alleles

Introduction

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, Temporo-mandibular disorders, and interstitial cystitis. 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 [1]. This issue is surprisingly more difficult to address. For example, several investigators have examined sex differences in pain severity among samples of patients seeking care for their chronic pain. While some studies have reported greater pain severity among women than men, other studies have found no sex differences in pain severity among treatment-seeking patients [2]. 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 [3]. 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, others reporting more severe pain among men, and others reporting no sex differences. On balance, the trend is towards greater acute post-procedural pain in women [4]. Interpretation of these studies is complicated by potential sex differences in responses to pain treatments because pharmacological interventions are always provided in these settings.

Methodology

A recent study exploited a large electronic medical record database to study sex differences in pain severity in patients. 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 [5]. 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. Sex differences in responses to experimental pain have been investigated using a wide variety of stimulus modalities including mechanical, electrical, thermal, ischaemic, and chemical stimuli [6]. Increasingly in recent years, more sophisticated experimental pain models have been used to characterize dynamic pain modulatory processes, such as temporal summation of pain and conditioned pain modulation. Pain responses have been assessed by a number of different outcome measures including behavioural indices of threshold and tolerance, and self-report measures of pain intensity and unpleasantness [7]. Previous qualitative and quantitative reviews have generally concluded that women display greater sensitivity to multiple pain modalities compared with men, and that women show greater temporal summation of pain while men display greater conditioned pain modulation. In contrast, a recent systematic review concluded that few years of laboratory research have not been successful in producing a clear and consistent pattern of sex differences in human pain sensitivity [8].

Discussion

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 [9]. The typical pattern of findings across studies of sex differences in experimental pain responses, which helps explain the varying interpretations by some authors. 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 as shown in (Figure 1). Sex differences in response to pain treatment have also been described in the literature. In a review of few studies, Miaskowski and colleagues observed lower opioid consumption postoperatively among women. This has not been a consistent finding and may depend on the type of surgical procedure or result from increased prevalence of side-effects in women [10]. A recent meta-analysis 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

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Figure 1: Pain sensitivity with women.

Figure 2: Sensory components of pain for women.

restricting analyses to patient-controlled analgesia 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 [11]. 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 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. 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 [12]. 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. 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 [13]. 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, men reported less pain when asked to focus on the sensory components of pain, while focusing on affective pain was not beneficial for women as shown in (Figure 2). There is also evidence that acceptance-based interventions for pain may be helpful towards reducing affective-related pain for women relative to men. 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. 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. 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. 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 [14]. 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, testosterone 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 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 [15]. 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. 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 gene, associated with red hair and fair skin, has been found to moderate analgesia in a sex-dependent manner. Specifically, women with two variant alleles of the gene demonstrate greater analgesic responses to pentazocine 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 was found to be associated with pressure pain sensitivity in men but not women.

Conclusion

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.

Acknowledgement

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Conflict of Interest

None.

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