Sex and Gender Issues in Pain Management

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- Differences exist between men and women in response to noxious stimuli.
- Sex-based differences in the perception of noxious stimuli and gender-based differences in the expression of, or behavioral response to, pain have been identified, but much of the current research is difficult to extrapolate to clinical settings.
- The response to opioids and the risks of misuse or addiction vary between men and women, although many studies of addiction do not assess data on the basis of sex or gender.

Over time, the definition of "women's health" has expanded far beyond just reproductive health, now including critical issues such as musculoskeletal conditions, pain, opioid use, and addiction. As noted by the Institute of Medicine (National Academy of Medicine) in 2001[1], "every cell has a sex," defining the word "sex" as reflecting the gonadal (chromosomal) complement. Sex-based differences reflect a varying sex-hormonal milieu and other aspects of physiology, as well as differences in anatomy, and impact all organ systems, including the musculoskeletal system. The word "gender" refers to psychosocial interactions, including responses to societal expectations. Both sex and gender impact all health conditions, resulting in differences between men and women in disease risk factors, prevalence, presentation, and response to treatment. Unfortunately, women historically have not been included in clinical studies in substantial numbers; only recently has there been an emphasis on including sufficient numbers of women to identify differences in health conditions and responses to treatment[2].

Important areas that demonstrate both sex-based and gender-based differences are the causes and perception of nociceptive stimuli and related opioid use and addiction risks. Women are more likely than men to experience a variety of chronic pain syndromes and tend to report more severe pain at more locations than do men[3]. Related opioid use has important consequences: a review of the National Vital Statistics System data from 1999 to 2017 demonstrated that the crude rate of deaths involving prescription opioids increased from 1999 to 2017 for every age group of women, with the largest increase (>1,000%) among women aged 55 to 64 years[4]. In addition, although the death rate from prescription opioid-related overdose is higher among men, between 1999 and 2010, the percentage increase in these deaths was significantly higher among women[5]. Women of childbearing age who use opioids for any purpose present a unique challenge because of the risk of a fetus developing neonatal opioid withdrawal (previously neonatal abstinence) syndrome. The incidence of neonatal opioid withdrawal syndrome has risen dramatically over the past decade as a result of the increased frequency of prescribing opioids for pain control, as well as increased illicit opioid use and the medication-assisted treatment of addiction[6].

To address the public-health issues related to opioid use among women, we need to better understand (1) whether women (females) are more likely to have conditions that can lead to pain; (2) whether the sexes perceive pain differently; (3) whether women experience more pain, or if it is more acceptable for them to express that pain and seek care; and (4) whether there are sex and gender-related differences in the way people respond to opioids, the degree of analgesia obtained from opioids, and the risks of misuse and addiction.

Women and Pain

Although women have been thought to be more "pain sensitive" than men, the issue is much more complex than

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that, including biological, psychological, and cultural factors[7]. Women are more likely than men to develop conditions, especially of the musculoskeletal system, that can lead to nociceptive stimuli or pain, such as osteoarthritis, most inflammatory arthropathies, fibromyalgia, and low back pain. The differences in the prevalence of these conditions can be attributed to differences in sex-hormone production, anatomy, neuromuscular control, and inflammatory responses. In addition, the treatment of some musculoskeletal conditions may have worse outcomes among women compared with men. For example, women are less likely to have the same improvement in pain after joint arthroplasty, although the cause of this is unclear and likely multifactorial. Women with widespread pain, in particular, are less likely to have improvement following total knee arthroplasty[8]. In addition, women are more likely to have unexplained pain after total joint arthroplasty and have greater levels of pain than men with idiopathic postoperative pain. One explanation that has been explored is metal sensitivity: women with painful arthroplasties have been found to have a greater rate and severity of metal sensitivity compared with men[9]. This may reflect the greater innate and adaptive immune responses among women.

A component of how pain is perceived is dependent on patient sex, and differences in processing of painful stimuli have been identified between the sexes. Changes in autonomic indicators, to isolate the impact of sex, in response to pain have been measured and indicate that females have greater response to painful stimuli[10]. Sex-based differences that impact pain perception include the influence of sex hormones on pain-signaling pathways and anatomic differences in the organization of these pathways[11].

Paulson et al.[12] investigated sex-based differences in expression of the response to thermal stimuli, while also evaluating differences in regional cerebral blood flow through the use of positron emission tomography imaging, in healthy subjects. Although both male and female participants rated the 50°C stimuli, which were applied to the volar forearm, as painful, the female participants rated these stimuli as significantly more intense. In addition, differences in cerebral blood flow were noted: although both male and female participants demonstrated bilateral activation of the premotor cortex and a number of contralateral structures, female participants had significantly greater activation of the contralateral prefrontal cortex, insula, and thalamus.

There may also be differences in pain modulation or inhibition of painful stimuli. In a systematic review of studies of healthy individuals, Popescu et al.[13] noted that inhibition of noxious stimuli may be more efficient in males, although this was dependent on the study type and the modality of noxious stimulus. Sex-based differences in brain processing of pain signals have been identified even among neonates, indicating that at a least a component of the difference between the sexes is hardwired at birth. In a study of both pre-term and full-term infants, Verriotis et al.[14] noted that a widespread nociceptive cortical response was more likely to occur in females than males, after application of a clinically indicated heel lance; however, no differences were noted in responses to touch, indicating that signaling pathways for these stimuli are different and that differences in response to pain exist between the sexes at birth. The implications of that study for adults, however, is unclear, as these signaling pathways may change over the course of a lifespan as a result of the impact of sex hormones, chronic pain, and the development of other health conditions.

The impact of sex hormones on the perception of pain is somewhat unclear, especially the role of estrogen. Estrogen receptors are found in almost all cells and tissues, including the spinal cord and areas of the brain that perceive and interpret pain. Studies have variably found that estrogen increases the response to pain (visceral pain), decreases the response to pain (somatic pain), or has no effect. In a review, Paredes et al.[15] noted that animal models have demonstrated an impact of estrogen on serotonin synthesis and reuptake, although there are limited data in humans. Human studies are challenging, as results would be impacted by the reproductive or estrogen status of the participants. Studies among premenopausal women are difficult to interpret because of the impact of the menstrual cycle, but the data are even more mixed among postmenopausal women. In addition, inclusion of participants on chronic opioid therapy adds an additional variable, as these medications, especially those primarily impacting the mu receptor, can lead to the development of hypogonadism because of the altered pulsatile release of gonadotropins. Current questions include whether estrogen impacts the transmission of pain signals, promotes signals to block this transmission, or either or both effects. The role of androgens in pain perception seems to be somewhat clearer: testosterone seems to decrease pain in males and females in human and animal studies, primarily through an impact on inflammation[16], although the clinical impact of aromatase activity and secondary production of estrogen can make results about the isolated role of testosterone challenging to interpret.

Women are more likely than men to have comorbidities that may impact the risk of developing chronic pain, either through modulation of pain perception or an impact on behavioral response, resulting in an increased use of opioids; however, it is unknown if these comorbidities contribute to or are a result of heightened sensitivity or an increased exposure to painful stimuli. Psychologic conditions, such as depression in particular, have been cited as risk factors for the development of an opioid-use disorder[17]. Thompson et al.[18], in a meta-analysis of studies investigating pain response in depressed participants versus healthy controls, noted that for high-intensity pain stimulation, overall pain tolerance was similar across depressed and control groups, whereas for low-intensity stimulation, small but significantly higher mean sensory and pain thresholds were observed in depressed participants. Heterogeneity in results was observed, dependent on the modality evaluated. For example, pain tolerance was increased among

depressed individuals in studies assessing cutaneous stimulation but was decreased among individuals involved in studies of ischemic stimulation. Although there is some evidence to support the idea that the presence of depression impacts the experience of pain, heterogeneity of results suggests that additional factors are present[18], and this is an area that requires additional study.

Behavioral responses to, or expression of, perceived pain is impacted by gender, reflecting societal norms. It is more acceptable for women to be more emotionally vulnerable and more likely to express that they are in pain or that they are more "sensitive" to pain, whereas men are expected to be more stoic and to underreport pain[19]. Catastrophizing, which includes feelings of helplessness and rumination, is associated with pain and pain-related disability in both women and men; however, women are more likely to respond to stress and pain through catastrophizing, and this coping strategy may mediate some of the gender-based differences in the prevalence of pain. When controlling for the presence of catastrophizing, the differences in pain between women and men are less notable. In addition, a low degree of self-efficacy has been found to correlate with higher levels of pain and physical symptomatology, and on the whole, women report lower self-efficacy compared with men. When controlling for levels of perceived physical and task-specific self-efficacy, differences in pain perception between genders are diminished[20].

The numerous variables that can impact the perception of and/or expression of or behavioral response to pain can make studies utilizing human models difficult to interpret or extrapolate to clinical conditions. Most of these studies use models such as pressure, temperature, or ischemia. No consistent results based on sex have been identified, and results seem to depend on the type of stimulus applied and the study design. In a systematic review of 122 articles, Racine et al.[3] found that females and males have comparable thresholds for cold and ischemic pain, that pressure pain thresholds are lower in females than in males, that there is strong evidence to support that females tolerate less thermal (heat, cold) and pressure pain than males, and that ischemic pain response is comparable in both sexes; however, the majority of the included studies reported that measured pain intensity and unpleasantness showed no sex difference for many pain modalities[3]. To our knowledge, no consistent sex-based patterns in human response to applied noxious stimuli have been reported; however, the question remains if the modalities utilized in these studies sufficiently mimic clinical scenarios and typical pain-generating conditions to make the results useful in practice. In addition, these studies use healthy volunteers, whose physiologic and psychologic response to acute pain may differ from those of patients with chronic pain, especially when chronic pain is accompanied by other mental or physical health conditions.

Women and Opioids

Females not only experience pain differently, they may also respond differently to opioids. With use of a thermal hind-paw withdrawal model, Wang et al.[21] demonstrated significantly greater and longer pain relief from morphine administered to male compared with female rats. Although no sex-based differences have been identified in humans in the area of opioid pharmacokinetics, differences in pharmacodynamics, such as mu-opioid receptor density and binding affinity[7], have been noted. For example, mu-opioid receptor binding potential has been found to be higher in female than male healthy individuals[22], with decreased binding after menopause. Animal studies support this finding of an impact from sex hormones and indicate that mu opioid receptor availability fluctuates on the basis of estrous phase[23]. In addition, opioids that act through the kappa receptor have been found to have greater analgesic effect in women than in men[24] and may be important targets for future development of novel opioids. Although there are significant data from animal models, sex-based differences in response to opioids in humans are not clear, and additional study is needed to determine any sex-based differences in analgesic response or respiratory depression from opioids and relative impacts of medications that act through the mu versus kappa receptors.

Women and Opioid Misuse or Addiction

Rates of addiction to opioids do not vary between the sexes; however, women are more likely to report greater misuse of prescription opioids, either using their own prescriptions or those from friends and family[25], even among girls as young as seventh through eleventh grade[26], whereas men who misuse opioids are more likely to obtain them illicitly[27]. Women with opioid dependence typically have more physical and mental-health conditions than men, and it has been hypothesized that these women are using opioids to self-medicate[28]. Specific mental-health conditions that can lead to opioid misuse are depression and posttraumatic stress disorder (PTSD); these conditions can occur as a result of experiencing intimate partner violence, a situation much more common among women[29].

Conclusions

Although sex-based differences in perception of nociceptive stimuli and gender-based differences in behavioral response have been identified, more research is needed in these areas. Much of the work to this point has been conducted in animal models or healthy human volunteers. It is unknown if the results from animal studies will translate into similar results in humans. In addition, painful stimuli applied to humans in a research setting may not reflect the clinical picture of acute or chronic pain, and healthy volunteers may not have the same physiologic or psychologic response to a painful stimulus as a patient with chronic pain, especially one who is older and/or has other comorbidities. Many studies regarding pain or the response to opioids do not assess for or report sex-based differences, or they report results only for 1 sex, making it difficult to extrapolate results[30]. Future studies should strive to include both men

and women and assess and report results on the basis of sex and/or gender. Ideally, these studies would account for comorbidities such as depression or PTSD that are usually more frequent among women and can alter either the sex-based perception of or gender-based response to pain. Additional study is also needed to determine sex-based responses to opioids, both in terms of degree of analgesia and risk of dependence and overdose, and options for development of other modalities for pain relief for both men and women. The use of opioids is of concern for women of all ages, but it especially impacts the independence of older women, as opioids can increase the risk of falls and related fractures, and the lives of women of childbearing age, because of the risk of a newborn developing neonatal opioid withdrawal (abstinence) syndrome. ■

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