

Commentary

Women and the Experience of Pain and Opioid Use Disorder: A Literature-based Commentary



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ABSTRACT

It is generally understood that pain experience and opioid abuse have relied on male-dominated models. However, sex and gender play a role in both pain experience and opioid use disorder.

Using the previously validated Texas Tech University Health Sciences Center Sex and Gender Specific Health PubMed Advanced Search Tool, the authors used pertinent literature to develop this literature-based commentary on sex and gender differences in pain experience and opioid use disorder. Women report their experience of pain more frequently, have increased rates of diagnoses related to pain, have increased pain sensitivity, and have a variable response to pain and analgesia. This variable response is due to anatomic, physiologic, hormonal, psychological, and social factors that differ by sex and gender. Women have been found to be at greater risk for opioid abuse in all age groups. This may be due to the differences in pain experience, as well as sex and gender differences in prescribing patterns, cultural norms, and the increased likelihood to experience dependency and withdrawal. Approaches to the treatment of opioid use disorder are also subject to sex and gender differences—an area in need of further investigation. (*Clin Ther.* 2018;40:190–196) © 2018 Elsevier HS Journals, Inc. All rights reserved.

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care utilization has been discussed previously in the literature.¹ Of specific concern is that sex and gender are key variables in the current opioid epidemic for several reasons. In the context of the opioid epidemic and its effects on many populations, it is important to recognize those groups that are at higher risk for substance use disorder. It is also essential to understand the physiologic and psychological processes underlying these differences in risk, as well as the effectiveness of treatment modalities.

There are many differences between the sexes in diagnoses related to pain, pain perception, opioid disbursement, response to opioids, opioid use disorder, and psychosocial factors.² These differences occur in several areas. First, the experience of pain differs between the men and women. Women experience more pain-related diseases and have an increased sensitivity to the perception of pain.² Further, it is possible that expression of pain may be interpreted differently, depending on the gender of the provider.

Women are at greater risk than men for the misuse of prescription opioid medication and thus for the development of opioid use disorder, with a recent shift in the prevalence of opioid misuse and abuse toward the female population.³ Data from the National Health and Nutrition Examination Survey 1999–2012 indicate that women are more likely to be prescribed opioid analgesics (7.2% vs 6.3%).⁴ Although overall opioid overdose deaths are more prevalent among men, the percentage increase in

INTRODUCTION

The influence of sex and gender on the development and management of disease and on subsequent health

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overdose deaths among women has been more dramatic compared with men (5-fold increase for women vs 3.6-fold increase for males) between 1999 and 2010.⁵

Opioid use disorder treatments have focused largely on a “one size fits all” mentality that does not appropriately address these differences.

In this literature-based commentary, we explore what is known about women and both pain experience and opioid use disorder. Furthermore, we will discuss the importance of continued and increased awareness on the topic.

METHODS

Using the previously validated Texas Tech University Health Sciences Center Sex and Gender Specific Health PubMed Advanced Search Tool,⁶ we searched PubMed database from 2000 through 2016.

Search terms utilized were as follows:

((("opioid abuse") OR "opioid addiction") OR "opioid dependence")) AND ((sex based OR sex factors OR sex distribution OR sex characteristics OR sex dimorphism OR gender difference* OR gender based) AND (gender[ti] OR sex[ti] OR women[ti] OR female[ti]) AND (Humans[Mesh] AND English[lang])) and ("pain management") AND ((sex based OR sex factors OR sex distribution OR sex characteristics OR sex dimorphism OR gender difference* OR gender based) AND (gender [ti] OR sex[ti] OR women[ti] OR female[ti]) AND (Humans[Mesh] AND English[lang])).

Articles were also gathered by searching the article bibliographies and “related articles” sections using the search tool. The authors screened 200 titles and abstracts of the articles found using these processes for inclusion into this narrative literature-based commentary. Articles were included if the authors thought the content informed the commentary by specifically describing sex or gender differences in pain experience or opioid use disorder. Forty-eight articles were reviewed in depth and are included in this commentary. Given a broad topic affected by multiple factors, this commentary addresses the most relevant and recent articles as chosen by the authors.

COMMENTARY AND DISCUSSION

Response to Pain and the Pain Experience

The difference in pain experience between the genders is well-documented in the literature.^{2,7–10}

Women report more severe levels of pain, more frequent episodes of pain, more areas of pain on the body, and pain of longer duration than men.² Women have a higher prevalence of painful conditions, such as fibromyalgia, irritable bowel syndrome, and interstitial cystitis.¹¹ Other contributors to the increased prevalence of pain in women include a longer lifespan and increased risk of osteoporosis and joint inflammation.² Unfortunately, the side effects of the treatments for these conditions also differ between the genders. Women experience medication overuse headache much more often than men.¹² One potential psychosocial confounding factor to these pain reports is that men are less likely to report pain than women.^{9,13} The expression of pain can be perceived differently between the sexes by the prescriber.¹⁴ Male patients undergoing coronary artery bypass grafting receive opioids more often than female patients, and female patients receive sedatives more often, suggesting that female patients are more often perceived as anxious rather than in pain.¹⁴ It is important to reduce these disparities and be aware that there are gender differences in the assessment and treatment of pain.

Pain experience and perception are intrinsically different in men versus women. Estrogens and androgens play a role in the experience of pain, including both perception and modulation.^{2,7,8,15,16} Gonadal hormones and male and female biology differentially predispose individuals to pain and analgesic effects of drugs and stress.⁷ Variations in estrogen plasma levels in women during their menstrual cycle and those undergoing estrogen replacement correlate with recurrent pain.² The concentration of estrogen in the blood correlates with a fluctuation of number of opioid receptors in the tissue.² Estradiol increases the hyperalgesic response.² Male gonadal hormones have a nociceptive adaptive effect to pain. An inverse relationship exists between plasma testosterone and female patients with neck and shoulder pain.² Because females intrinsically have more estrogen, it can be inferred that fluctuations in opioid receptors are more drastic and pronounced in the female population. Further, given that males have intrinsically more testosterone, men may have increased endogenous nociceptive effect than women.

Bodnar and Kest¹⁶ found that testosterone replacement increases μ -opioid analgesia and estradiol replacement decreases μ -opioid analgesia.

The concentration of specific subtypes of opioid receptors differs between male and female animals. Male rodents have a significantly greater analgesic responses to μ -agonists than female rodents. It is hypothesized that the μ -receptor alone more effectively mediates analgesia in males, while females need a combination of the μ - and κ -subtypes. Though it has been documented that morphine, which acts mainly at the μ -receptor, has more potent effects in women than in men, women require more morphine to achieve a similar degree of analgesia. The specific drugs morphine, oxycodone, and butorphanol are more effective in producing pain relief in male than in female rats.¹⁶

Genetic differences in the manifestation of opioid dependence exist in male versus female animal models.¹⁷ Female rats are more sensitive and have a higher concentration than males of corticotropin-releasing factor.¹⁷ This factor has been hypothesized to mediate the motivational effects of drug dependence.¹⁸

Men and women respond differently to acute pain in imaging studies of the brain. Pain-related cerebral activation detected in functional brain imaging differs between the sexes.¹⁹ Signal-intensity changes during muscle and cutaneous pain induced by intramuscular and subcutaneous injections of hypertonic saline also differs significantly between the sexes.¹⁹ The presence of sex-specific signal intensity changes in areas of the brain involved in both detection of painful stimuli and emotional response to pain, indicate that sex differences in both pain sensitivity and emotional response to pain may underlie gender differences in pain processing.¹⁹

Given that the literature clearly found that the pain experience between men and women differs in reports of pain, prevalence of experiencing painful conditions, how this pain is interpreted by providers, hormonal influence on pain response, and pain medication side effects, it is imperative that sex and gender differences be considered in pain research.^{2,7-9,10,13-15} Consensus reports agree that both sexes should be included in medication trials in greater numbers to detect gender effects.²⁰ Eighty percent of animal studies published between 2000 and 2010 in the journal *Pain* use male subjects exclusively and only 4% of studies are designed to test for sex differences.¹⁶ Differences in analgesic sensitivity between men and women is observed after administration of diverse classes of non-opioid compounds, including nicotine, cocaine,

and cholinergic and noradrenergic agonists, which suggests the importance of the consideration of co-administered medications in pain management.¹⁰

Opioid Use Disorder

In a large study from 2013, women, along with white and middle-aged individuals, were among the top 3 populations with the largest increase in prescription opioid and heroin overdoses.²¹ Emergency department visits by women who misused certain opioids tripled from 2005 to 2011.³ National data in both the United States and Canada indicate that women are at greater risk for opioid abuse compared with men.²² A Canadian survey quoted that women who abused opioids who were age >14 years outnumbered men of the same age (18.3% vs 15.5%).²³ In the United States, women reported significantly higher rates of abuse according to a survey done of treatment centers (15.4% vs 11.1%), were more likely to be prescribed opioids, and were 48% more likely than men to use any prescription drugs.²⁴ Concurrent use of sedative-hypnotic drugs is also more common among the female population.²⁵

Increasing rates of prescription opioid abuse and prescribing patterns involving women are based on several factors. First, women seek out health professionals more often than men and are more frequently targeted in pharmaceutical marketing.²⁶ This, along with the fact that female patients are more likely to be prescribed opioids by physicians, places women at higher risk for medication misuse and therefore subsequent opioid use disorder. Second, women have a higher prevalence of gender-based violence and sexual abuse, as well as the subsequent psychological effects, such as post-traumatic stress disorder, anxiety, and depression.²⁷ Psychological effects of trauma may increase vulnerability to opioid abuse.²³

In a study within substance-use treatment centers, women were more likely to have a psychiatric comorbidity, including depression, self-injury, and suicide attempts.²⁸ Furthermore, women who have been the victims of mental or physical violence are more likely to report conditions such as fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, and premenstrual syndrome. These afflictions are difficult to treat and are treated with opioids more often than other disease processes.²³

Sex- and gender-specific risk factors play an important role in opioid use disorder. Risk factors for

opioid use disorder among women include a history of problem drinking, age <54 years old, history of inhalant use, and history of drug overdose.²⁹ Men, on the other hand, have different risk factors, which include age <34 years old, currently living with their children, hallucinogen use, and recent depression.²⁹ Women with opioid use disorder have more physical and psychological health problems, family history of psychiatric illness, childcare responsibilities, and initially begin using opioids through a prescription more often than men.¹⁵ A history of tobacco abuse among women has also been correlated with non-medical use of prescription opioids.³⁰ Prescribing patterns resulting in increased availability of controlled medications such as opioids are associated with a greater risk of misuse and abuse.²³ While men are more likely to obtain opioids from dealers, women are often able to acquire the medications through friends, family, or legitimate prescriptions.²³

Age is an important covariable when assessing women for the risk of opioid use disorder. In Canada, young women relatively outnumbered the men in the use of psychoactive medications (26.7% vs 21.3%).²³ A study done in Detroit found that girls aged 10–18 years outnumbered boys in the same age group in medication misuse (22% vs 7%) and opioid misuse specifically (15% vs 7%).³¹ Young and middle-aged women report higher global pain scores (when compared with men and younger women) while being treated for chronic pain, which, under current therapy guidelines, increases their risk for dose escalation.³² This dose escalation could theoretically lead to a longer course of treatment and increased risk for dependence and withdrawal. Older women are at increased risk of opioid misuse, with multiple reports noting the greater risk for opioid misuse among women ≥65 years old when compared with men of the same age group.^{25,32} Older women have the highest prevalence of long-term opioid use at almost 10%.²⁵ Other risk factors, including low income, mental health issues, and physical health issues, increase the risk of opioid abuse and misuse among women of this age group.²³ Women begin their drug use at lower doses, escalate their use more rapidly than men, and are at greater risk for relapse after a period of abstinence than men.³³

There is little information about sex-based dosing of opioids in the outpatient or inpatient clinical

settings. While greater doses of opioids are needed to achieve similar effects in women as in men, given a smaller relative body mass and differences in metabolism of medications, the therapeutic window for women is likely smaller than that of men.²³ Therefore, women are more likely to experience adverse effects of opioids, and have an increased vulnerability to becoming dependent on these medications.³⁴ Given the higher likelihood of women having a chronic painful condition that is treated with opioids, the health risks of such long-term treatment have sex- and gender-specific consequences as well. These include, but are not limited to a woman's increased risk of endocrinopathy, infertility, neonatal health risks, anxiety and depression, polypharmacy, cardiac sequelae, and potential for overdose.³⁵

Sex-specific opioid treatment regimens are sparse. In fact, the study of methadone treatment for opioid addiction has largely been limited to the male population.¹⁵ Women with opioid use disorder are typically younger, married, unemployed, and have an earlier onset age of heroin use.^{15,28} Despite these differences, knowledge gaps remain about differences in methadone treatment outcomes between the sexes.¹⁵ One study found a difference in satisfaction in methadone treatment based on dosage in men versus women.³⁶ Another study noted that gender was a factor in reducing mortality risk based on treatment plan.³⁷ Men had reduced mortality when the focus was placed on employment and medical problems with interventions to reduce overdose risk; women had more success with attending to the concurrent use of sympathomimetics and other opioids.³⁷ Women have a higher rate of adverse effects to naltrexone therapy than men.³⁸ Buprenorphine has been found to be more effective in treating women than men.³⁹

Despite an equal need for opioid addiction treatment interventions between the sexes, and existing literature reporting sex and gender differences in response to such treatment, there remains a dearth in studies addressing these differences.²² It is known that out-of-treatment females use opioids more often, spend more money on drugs, and earn more illegal income than those not in treatment programs.⁴⁰

While this commentary touches on US and Canadian literature primarily, the United Nations released an article in August 2017 addressing the opioid epidemic from an international perspective. It surmises

that women continue to be disproportionately affected by drug use and have decreased access to treatment worldwide.⁴¹ This problem has been chronically understudied and under-represented in literature and policy.⁴¹ As an example, one US survey found that women are in significantly fewer treatment programs than men.⁴²

Rates of opioid abuse among women of several age groups outnumber those of men in the same age group.^{22–25,31,32} Women have an increased prevalence of comorbid psychiatric conditions.²⁷ Increased visits to providers who are more likely to prescribe opioid medications to women also factor into their increased risk.^{24,26} Given these sex and gender differences in risk of developing opioid abuse, as well as response to treatment of opioid abuse, more studies are needed that evaluate treatment retention, response, remission, adverse events, and mortality with a specific focus on such differences.¹⁵ Awareness of these differences can help guide providers in opioid stewardship.

Special Populations

Pregnant women must be considered when discussing the pain experience and opioid use disorder, not only because of pregnancy-related pain, but because there are direct consequences of opioid exposure to the fetus. In the United States, neonatal abstinence syndrome rose by nearly 300% between 2000 and 2009.⁴³

Women of child-bearing age are also at risk of adverse effects from opioids. Medication sharing is greater in the child-bearing population than in any other group.⁴⁴ The reproductive side effects of opioid abuse include amenorrhea, fertility issues, and depression.²³

Risks versus benefits of opioid use for pain management must be weighed, and screening and referral for opioid use disorder carefully considered in female patients of child-bearing age, as well as pregnant or breast-feeding women.⁴⁵

It is important to be aware of sex- and gender-based consequences of the opioid epidemic on the lesbian, gay, bisexual, transgender, and queer (LGBTQ) populations. LGBTQ individuals are at increased risk for opioid use and abuse for multiple reasons. Lesbians are at an increased risk for mental and physical trauma due to sexual abuse and physical abuse.⁴⁶ This leads to increased rates of

post-traumatic stress disorder, psychological distress, anxiety, depression, and the increased reported use of controlled substances.⁴⁷ LGBTQ individuals are subject to barriers in accessing employment, housing, and medical and social services, and thus are at increased risk of psychosocial stressors that can lead to substance abuse.²³

CONCLUSIONS

Sex and gender differences in the experience of pain, rate and risk factors for opioid use disorder, and response to treatment indicate a need for research on how to account for and manage these differences in the context of the opioid epidemic. Specifically, research is needed that informs how screening, brief intervention, referral to treatment, and medication-assisted treatment approaches should be tailored to a patient's sex and gender.

Special populations, such as women who are victims of violence, of child-bearing age, or part of the LGBTQ community, are at especially increased risk for the negative effects of opioid abuse. Increasing awareness and specific education and resources for these groups are important in the response to the opioid epidemic.

Further studies, along with the development of clinical and educational resources, are needed surrounding sex and gender variables that influence the spectrum of conditions affected by the opioid epidemic, including the experience of pain and opioid use disorder. Data are needed that inform how clinicians may safely and effectively use sex- and gender-based approaches to screening for risk factors associated with opioid pain management, and appropriately incorporating opioid therapy into medical treatment.

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