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Sex, Gender, and Pain: A Review of Recent Clinical and Experimental Findings

Roger B. Fillingim^{*,†,‡}, Christopher D. King^{*}, Margarete C. Ribeiro-Dasilva^{*}, Bridgett Rahim-Williams^{*,†}, and Joseph L. Riley III^{*}

^{*} *University of Florida, College of Dentistry, Gainesville, Florida*

[†] *College of Public Health and Health Professions, Gainesville, Florida*

[‡] *North Florida/South Georgia Veterans Health System, Gainesville, Florida*

Abstract

Sex-related influences on pain and analgesia have become a topic of tremendous scientific and clinical interest, especially in the last 10 to 15 years. Members of our research group published reviews of this literature more than a decade ago, and the intervening time period has witnessed robust growth in research regarding sex, gender, and pain. Therefore, it seems timely to revisit this literature. Abundant evidence from recent epidemiologic studies clearly demonstrates that women are at substantially greater risk for many clinical pain conditions, and there is some suggestion that postoperative and procedural pain may be more severe among women than men. Consistent with our previous reviews, current human findings regarding sex differences in experimental pain indicate greater pain sensitivity among females compared with males for most pain modalities, including more recently implemented clinically relevant pain models such as temporal summation of pain and intramuscular injection of algesic substances. The evidence regarding sex differences in laboratory measures of endogenous pain modulation is mixed, as are findings from studies using functional brain imaging to ascertain sex differences in pain-related cerebral activation. Also inconsistent are findings regarding sex differences in responses to pharmacologic and non-pharmacologic pain treatments. The article concludes with a discussion of potential biopsychosocial mechanisms that may underlie sex differences in pain, and considerations for future research are discussed.

Perspective—This article reviews the recent literature regarding sex, gender, and pain. The growing body of evidence that has accumulated in the past 10 to 15 years continues to indicate substantial sex differences in clinical and experimental pain responses, and some evidence suggests that pain treatment responses may differ for women versus men.

Research regarding sex and gender, differences in pain has increased substantially in recent years. As Fig 1 depicts, publications regarding sex, gender, and pain have increased at a much greater rate over the past 25 to 30 years relative to the pain field in general. In particular, a dramatic increase in publications began in the mid-1990s, which may be attributable to several influential review articles along with other events occurring in the 1990s that drew considerable attention to the topic. In 1992, an important publication by Karen Berkley³² highlighted the importance of sex-related issues in neuroscience research. This brief paper included a survey of 100 articles in reputable neuroscience journals, which found that 45% of the articles failed to report the sex of their subjects, and the author stated "... the differences between females and males, which we all know to be important, can and should be exploited in scientific research." Shortly thereafter, an editorial appeared in *The Journal of Pain*, which encouraged

studying the differences between women and men, a topic that had been out of favor given the 1980s' emphasis on equality of the sexes.³⁴⁸ These two publications both reflected and created increased interest in studying sex differences in pain. Subsequently, a review article appeared in *Pain Forum*, the predecessor of this journal, which discussed the literature regarding sex differences in responses to experimentally induced pain and offered a heuristic model outlining multiple mechanisms underlying these sex differences.¹³⁷ Subsequently, Karen Berkley's³³ review article appeared in *Behavioral and Brain Sciences*, accompanied by extensive commentary from several prominent pain scientists, and Unruh⁴¹⁸ published a comprehensive review of sex differences in clinical pain in the journal *Pain*. Thus, the early to mid-1990s was a period of increased scholarly activity regarding sex differences in pain.

The burgeoning interest in sex, gender, and pain embodied in this series of prominent publications culminated in two NIH initiatives, which ensured the continued growth of research on the topic. In 1997, NIH issued a request for applications entitled "Sex and Gender-Related Differences in Pain and Analgesic Responses," which was sponsored by multiple institutes as well as the Office for Research on Women's Health. This generated substantial interest from the scientific community and launched multiple new research programs related to sex differences in pain. Then, in April 1998, the NIH Pain Research Consortium hosted a scientific conference entitled "Gender and Pain: A Focus on How Pain Impacts Women Differently than Men," which featured presentations by many prominent basic and clinical pain scientists and garnered considerable attention in the popular media. An additional development began in August 1996 at the World Congress on Pain in Vancouver, where an initial meeting of researchers interested in sex, gender and pain led to the establishment of an IASP Special Interest Group (SIG) on Sex, Gender, and Pain, which held its first formal meeting in Vienna in 1999. Thus, a combination of events has prompted the recent and dramatic increase in research on issues regarding sex, gender, and pain.

In addition to those alluded to above, several subsequent reviews of this rapidly expanding literature have been provided, often focusing on particular segments of research regarding sex, gender, and pain. More than 10 years ago, a quantitative review of the literature regarding sex differences in experimental pain responses concluded that females show greater sensitivity than males to several modalities of experimental pain.³²⁷ Other reviews have been published since this time,^{35,81,117,441} including reviews of sex differences in responses to analgesic interventions,^{74,122,221,277} and a recent consensus statement providing recommendations for conducting research on sex, gender, and pain.¹⁶⁸ In an attempt to increase the value of this review article, we will focus predominantly (though not exclusively) on findings from human studies that have emerged since the first two reviews by members of our research group.^{127, 327} In addition, rather than emphasizing a specific segment of the literature, we will provide a representative summary of multiple areas of investigation, including sex differences in the prevalence and severity of clinical pain, sex differences in responses to experimental pain, sex differences in treatment responses, as well as discussion of viable biological and psychosocial mechanisms that contribute to sex differences in pain. We will conclude with a synopsis of the current state of the literature followed by a discussion of important issues to be addressed in future research.

Sex Differences in Clinical Pain

Reviews of the pain epidemiology literature have addressed the question "whether there is consistent support for sex differences in the prevalence of pain, or whether sex differences exist only for selected pain conditions."^{243,418} These reviews have concluded that the relationship between sex and pain is not simple; nevertheless, most population-based studies have found higher prevalence in women than in men, but there are studies that have found no

differences. The goal of this section is to examine whether more recent studies corroborate these findings.

Methodological Considerations

The organization of studies for this review has been challenging as publications have focused on differing dimensions or characteristics of clinical pain. Pain studies can be organized by chronicity (chronic, acute), site (low-back, abdominal), number of sites (regional, widespread), tissue type (musculoskeletal, neuropathic), or etiology (iatrogenic, trauma, insidious). A complete review of sex differences in pain prevalence across all possible pain conditions, sites or etiologies is not feasible given the constraints of this broad review of sex differences in pain. Consequently, we will consider recent findings regarding the following pain conditions: cancer pain, neuropathic pain, musculoskeletal pain, oral pain, headache, abdominal pain, headache, pain in children and adolescents, and postprocedural pain.

Sampling—The general goal of all sampling methods is to obtain a sample that is representative of the target population. The most accurate inferences about sex differences in pain would derive from studies based on a randomly selected representative national or regional sample. However, sex differences in pain have been investigated in samples collected in a variety of ways. Studies that report on clinical samples, often from pain treatment centers, can suffer from the bias associated with health care seeking. Caution must be exercised when interpreting these data because women utilize health care services to a greater extent than men,^{48,428} consequently a clinical sample does not reflect the general population. Where possible, we will rely on studies drawn from general population-based samples.

As epidemiological studies of pain typically rely on self-report via surveys or telephone interviews, one potential problem can be nonparticipation bias^{114,224}; that is, differences in the outcome of interest between persons willing to participate and those that decline to do so.⁴³² The higher the participation rate, the less bias will be introduced. Some studies report participation rates, and fewer test for differences between participants and nonparticipants as often little information is available from nonparticipants. In complex sampling designs, weighting adjustments can account for some bias, but whether this has occurred is seldom described in the papers we have reviewed.

Another issue concerns geographic or cultural characteristics of the reference population. It cannot be assumed that sex differences are consistent across the world. Because of strong interests in public health, most epidemiological data on pain conditions come from Europe and particularly the Scandinavian countries. However, we have attempted to select studies from a range of geographic regions and cultures.

Measures—Epidemiologic studies of pain typically report point prevalence (currently in pain), period prevalence (ie, experiencing pain during the past month or year), or lifetime prevalence. Some of the studies reviewed have measured pain intensity or severity ratings and depression, a common impact of chronic pain, and when sex differences were tested, we will report the findings. One issue worth mentioning is over interpretation of positive findings for sex differences in pain due to publication biases. It seems plausible that in some cases sex differences were tested, found to be nonsignificant, and then not reported in a manuscript.⁹³ This may be particularly true for population-based studies of prevalence in which pain intensity or severity is of secondary interest.

Pain in Multiple Anatomic Regions—Several studies drawn from multiple geographic locations report prevalence of pain by sex across a number of anatomic sites. Gerdle et al¹⁵⁷ found the 7-day prevalence for females was higher than males for all 10 anatomic regions

assessed, but no sex difference was found for pain intensity ratings. Several papers from a Dutch population-based study of musculoskeletal complaints have reported higher pain prevalence among females at nearly all body sites.^{315,442,443} Also, women reported greater functional limitation than men but no differences were found for pain intensity ratings. A study in the Spanish population noted higher prevalence of pain at one or more locations for women (86%) compared with men (72%) and as well as for all individual musculoskeletal sites.²⁴ Another Spanish study reported greater prevalence of pain at any site during the previous day for women (37%) versus men (21%), whereas sex differences in pain prevalence across specific body sites were mixed.⁶⁰ Significant sex differences in the 1-year prevalence of pain at any body site (F = 40%, M = 35%) were reported in working adults living in Taiwan.¹⁷⁰ This sex difference was relatively consistent across the age categories with the largest difference in the 45 to 54 and 55 to 64 age ranges. An estimate of pain prevalence is also available for rural India. Chopra and colleagues⁶⁹ found higher 7-day point prevalence across all 24 body sites for females compared with males. Small sex differences in pain prevalence emerged for most sites in a representative sample of the US noninstitutionalized population.¹⁷⁹

Cancer Pain

Chronic cancer pain is experienced by approximately 30% to 85% of patients with cancer, depending on type of cancer and the stage.⁴²³ Because studies of cancer pain prevalence in representative population samples are rare, we have used data from clinical samples to examine sex differences in pain intensity/severity and depression but acknowledge potential for bias. A retrospective study of cancer patients referred for pain treatment found no sex differences in pain intensity or disability.⁴¹⁶ Miaskowski²⁷⁶ published a review on sex differences in chronic cancer pain, concluding sex differences were inconsistent. Two studies, one of patients 2 to 3 weeks after their last hospitalization³⁵⁰ and another of oncology outpatients with bone metastasis,¹⁰⁰ did not find sex was related to cancer pain. Another study that followed patients with inoperable lung cancer reported that women were more depressed at baseline than men but no differences were found in pain ratings.²⁵⁶ One month after diagnosis, chest pain was reported as more intense by men, whereas women reported more intense pain in areas outside of the chest and arm/shoulder. Schmidt et al³⁶⁶ found that women reported greater pain in the abdomen before rectal cancer surgery, at discharge, and at 3 months after surgery; however, there were no sex differences in pain at later time periods. Valeberg et al⁴²¹ reported that among outpatients at a large cancer hospital in Norway, females were more likely to have comorbid cancer pain and noncancer pain than males, and these authors also found that women were at increased risk for more severe pain.⁴²⁰

We have identified two studies that used population-level sampling. Reyes-Gibby et al³²³ reported that among adults ages 50 and older with cancer from the United States, females were more likely to have the symptom cluster of pain, depression, and fatigue than males by a factor of 1.2. A study from the Netherlands found that sex was not associated with prevalence or severity of cancer pain.⁴²³ These findings provide little evidence for sex differences in cancer pain; however, greater depression among women with chronic cancer pain has been reported.

Neuropathic Pain—Neuropathic pain is a complex pain state in which the nerve fibers may be damaged, dysfunctional, or injured.²⁷⁵ Until recently, there was little epidemiological data on chronic neuropathic pain at the population level because of the lack of an appropriate assessment instrument to identify the characteristics of neuropathic pain in community samples.⁴⁴ However, studies have examined sex differences in the epidemiology of specific neurological conditions that are painful.⁴⁰⁹ These studies report greater disease frequency among females.^{85,176,358}

Recently, questionnaires have been developed based on the analysis of the characteristics of pain (ie, pain descriptors) that discriminate pain due to a definite neurological lesion. Torrance et al⁴⁰⁹ estimated the prevalence of pain of predominantly neuropathic origin using a random sample of 6000 adults from family practices in three United Kingdom cities using a 5-item neuropathic pain scale developed by Bennett.²⁸ Females (6%) showed greater prevalence of neuropathic pain (lasting longer than 3 months) compared with males (3%). Using a large representative sample of the French population, Bouhassira et al⁴⁴ assessed neuropathic pain using their symptom-based screen for pain with neuropathic qualities⁴³ and found higher 3-month prevalence in females (8%) compared with males (6%). Neither study reported sex differences in the effects of age, pain intensity, or depression. Consequently, it appears that women are at greater risk for neuropathic pain than men.

Musculoskeletal Pain

Many studies have investigated the prevalence of musculoskeletal pain in men and women, with some assessing chronic musculoskeletal pain irrespective of the site, whereas others have been site specific. In a previous review, Rollman and Lautenbacher³⁴¹ concluded that women have greater frequency of musculoskeletal pain than men. A number of recent studies have tested for sex differences in chronic musculoskeletal pain at any site. In a study spanning 17 countries across 6 continents with a total sample size of 85,052 adults, the prevalence of any chronic pain condition was higher among females (45%) than males (31%), and females had a higher prevalence of depression comorbid with chronic pain than males.⁴¹⁵ Other studies from Australia,⁴¹ Europe,⁴⁷ France,⁴⁴ the Netherlands,⁴⁴² Norway,³⁵¹ Sweden,^{30,158} and the United Kingdom³⁷⁷ also indicate chronic musculoskeletal pain is more common in females than males (Table 1). In one study, women reported significantly higher ratings of worst and current pain intensity but there were no differences on the rating for least pain.³⁵¹ We review evidence regarding several specific types of musculoskeletal pain, including back pain, widespread pain/fibromyalgia, and osteoarthritis.

Back Pain—Several investigators have examined sex differences in back pain prevalence and severity, including a number of studies in European samples. A higher point-prevalence of back pain was reported in Swedish females (24%) than males (21%), and women reported greater pain severity than men on the SF-36 bodily pain scale.³⁹ Ihlebaek et al¹⁹² tested for sex differences in lifetime, 1 year, and point prevalence of low back pain among working persons in two neighboring regions in Norway and Sweden. Females had a higher prevalence of low back pain than males for both areas across all time periods with the exception that males living in the Norwegian region had a higher lifetime prevalence of low back pain. A German study reported the 7-day prevalence was 40% for women versus 32% for men,³⁶⁸ and another found that sex differences in back pain diminished as the time period lengthened (current, F = 39%, M = 35%; 1-year prevalence, F = 77%, M = 75%; lifetime prevalence, F = 86%, M = 85%), and more men reported low ratings of back pain than women.³⁶⁷ A study using a national representative sample from Spain estimated the current prevalence of low back pain as 18% for females and 11% for males.⁵⁹ Webb et al⁴³⁴ estimated the prevalence of back pain in over 5000 patients from three general practices in the city of Manchester, England. Twenty-five percent of women and 21% of men reported back pain for at least 1 week in the last month. Interestingly, female sex was no longer a significant predictor following adjustment in multivariate models that included age, body mass index, and several socioeconomic variables. No sex differences were found for pain intensity.

Data are available from other regions as well. In a sample of nearly 14,000 adults from a rural region of China, the 1-year prevalence of low back pain was higher among females than in males across all age groups below 60 years of age.²³ In a representative random sample from Turkey, the 2-month prevalence of back pain was consistently higher in women than in men

in all age groups with the overall values of 17% for females and 14% for males.³⁰¹ Two recent studies have reported on sex differences in the 12-month prevalence of back pain from Nigeria. Omokhodion³⁰⁴ reported a higher prevalence for males than females (45% and 36%, respectively), whereas a second study found no sex differences in chronic back or neck problems (F = 17% and M = 16%).¹⁷² A population-based postal survey study in Australia⁴²⁹ found few sex differences in current, 1-month, and 12-month prevalence of back pain in females (26%, 55%, 70%) versus males (25%, 50%, 68%). Significant sex differences were not found on pain intensity.

Two studies addressed sex differences in the chronicity of back pain. Thomas and colleagues⁴⁰⁴ followed 180 patients for 12 months after consultation with acute back pain. After 1 year, 41% of females and 24% males were classified as having both low back pain and disability. Other factors associated with persistent back pain included employment dissatisfaction and history of widespread pain. The predictors of poor outcome were the same for men and women. In a population-based cohort of over 2100 participants in a back pain survey, women with chronic back pain at baseline were more likely than men to still have chronic back pain 4 years later.³⁷⁷ However, the association lost significance in a multivariate model that included age, health history variables, and social factors. Women without back pain at baseline were no more likely to have developed chronic back pain than pain-free men. Thus, on balance, the recent evidence suggests higher prevalence of back pain in women, but there is limited evidence that females are at greater risk for chronicity.

Widespread Pain and Fibromyalgia—Sex differences in the prevalence of widespread musculoskeletal pain have also been documented. These studies typically include a pain drawing to identify the painful sites. The most common definition is pain present in both the left and right side of the body as well as above and below the waist. Multiple studies from various geographic regions indicate higher prevalence rates across all age groups in women compared to men (see Table 2). In contrast, Gupta and colleagues¹⁷¹ reported no sex differences in 15-month incidence of chronic widespread pain (females = 11% and males = 10%). In a 3-year follow-up of a previous study,³⁰ women without chronic pain or women with regional chronic pain did not develop persistence of chronic widespread pain more often than men.³¹ Another study also failed to show a sex difference in persistence of chronic widespread pain.³¹¹

Other studies have specifically screened for fibromyalgia syndrome (FMS). FMS is a common, chronically painful, soft tissue pain condition. Affected individuals exhibit persistent, widespread pain and tenderness to palpation at anatomically defined tender points located in soft tissue musculoskeletal structures.⁴⁰ Several studies have used self-report of FMS diagnosed by a health care professional and found similar findings in community samples from North America (F = 2%, M < 0.5%),²⁷³ the Netherlands (F = 2%, M < 0.5%),³¹⁵ and Spain (F = 4%, M < 0.5%).⁵⁹ Another study that was part of the London Fibromyalgia study has used direct evidence from clinical examinations as the case definition and found a point-prevalence among Canadian adults of 4.9% for women and 1.6% for men.⁴⁴⁰

Osteoarthritis—A recent meta-analysis on sex differences in osteoarthritis using clinical markers as the case definition (not pain) indicated that females are at significantly increased risk for osteoarthritis (OA) in the knee and hand compared with males.³⁸² Several studies have documented sex differences in pain prevalence, ratings, and depression in OA, and we will review selected studies below.

Two papers have reported sex differences in the prevalence of OA related pain (pain on most days for the past 6 weeks) based on representative samples of adults 60 years and older from the United States. The prevalence of persistent knee pain was estimated as 24% for females

and 18% for males¹¹ and 16% for females and 12% for hip pain.⁷⁰ In contrast, data from a community-based sample in the United Kingdom aged 50 years and older found that females in the 65+ group had a lower 12-month prevalence of knee pain than males (F = 22%, M = 33%), but there were no differences in the 50- to 64-year group.²³⁴ Another study of individuals registered with three general practices in the United Kingdom found a 12-month prevalence of pain in and around the knee of 49% for females and 44% for males.²⁰⁰

Jinks²⁰⁰ assessed pain severity using the Western Ontario and McMaster University Osteoarthritis Index (WOMAC)²⁷ and found higher ratings of pain for females than for males in the 50- to 64-year and 65- to 74-year age groups whereas pain scores were higher for males in the 75+ age group. Jinks et al²⁰¹ followed a prospective cohort of 2982 persons without knee symptoms at baseline for 3 years. At follow-up, sex was not a risk factor to develop mild or severe knee pain. However, in a second analysis, females were more likely than males to have developed severe knee pain at 3-year follow-up. Data from an Italian community based cohort also using the WOMAC found females had significantly greater hip and knee pain than males.³⁵⁵

Several studies have examined sex differences in depression among persons with OA. Data from a large sample of German primary care patients indicated that sex was not a predictor of the depression among patients with OA of the hip or knee as diagnosed by a general practitioner.³⁴³ This is in opposition to findings that older Chinese women with knee OA tended to have greater depressive symptoms than men, and the association between sex and pain intensity was moderated by depression.⁴¹⁴

Taken together, these findings from studies of musculoskeletal pain indicate that regardless of site or time frame, females consistently are more likely to report musculoskeletal pain than males, though these differences may be less consistent for low back pain. There is limited evidence for increased pain intensity among women with the possible exception of OA, where greater pain severity among women is more common. There is limited evidence that women with musculoskeletal pain are more likely to be depressed than men.

Oral Pain—LeResche²⁴³ reviewed several studies of temporomandibular joint pain that demonstrated a higher prevalence in women than men across the lifespan. Studies from Finland,^{322,352} Germany,¹⁵⁹ Sweden,²⁶⁷ Turkey,³⁰⁹ the United States,³²⁶ Nigeria,³⁰² and Brazil²⁵ have drawn similar conclusions for tooth pain, jaw joint pain, and other orofacial pain conditions. Riley and colleagues³²⁶ found that for most orofacial pain symptoms, significant sex differences in pain ratings were found within the middle aged (45- to 64-year-old) cohort but not the older (65+) group.

Abdominal Pain—Unruh⁴¹⁸ reviewed several epidemiological studies and concluded that most studies report a higher prevalence of abdominal pain for women. Several recent population-based studies of abdominal pain of unknown etiology generally support increased prevalence among females. For example, data from the Netherlands indicated point-prevalence was higher for women than men,³¹⁵ whereas no sex difference emerged in a Spanish study.⁶⁰ Gerdle¹⁵⁷ and Bassols²⁴ reported higher female prevalence across longer time periods, and United States estimates indicate higher prevalence of chronic abdominal pain among females.¹⁷⁹

Irritable bowel syndrome (IBS) is currently defined as a chronic syndrome characterized by recurring symptoms of abdominal discomfort or pain and alterations in bowel habits in the absence of detectable organic disease.²⁶¹ Population-based studies have reported a female-to-male ratio of approximately 3:1 in the diagnosis of IBS in populations from the United States.^{99,357} In Asian countries, the sex differences have been smaller than in Western countries.

173,258 Some evidence suggests similar prevalence rates for pain-related symptoms in IBS, but a greater female predominance in non-pain-associated symptoms of constipation, bloating, and extra intestinal symptoms.^{376,402,406} Lee et al²³⁹ also found no sex difference in the prevalence of painful visceral symptoms or severity of patients' intensity ratings of abdominal discomfort and pain. However, a study of IBS among Japanese university students found that women reported greater abdominal pain than men.³⁷⁴

Headache—Headache is one of the most common pain conditions.³⁰⁸ Unruh⁴¹⁸ reviewed findings from over 60 studies and concluded that the prevalence of headaches and migraines is higher for women than men. Migraine is a severe recurring vascular headache and can occur with and without aura. Estimates of the 1-year prevalence of migraine range from 3% to 33% for women and 1% to 16% for men.²⁵² The American Migraine Study II, a study of over 29,000 adults, has estimated the 1-year prevalence of migraine in the United States as 18% in women and 7% in men.²⁵³ A meta-analysis suggests that migraine is most common in North and South America, followed by Europe, and lowest in Africa and Asia.³⁶⁵ Although these regions may vary in overall 1-year prevalence^{79,174,185,210,253,385,399,431} they show similar female-male differences, with the exception of one study from Saudi Arabia⁹⁰ (see Table 3).

Tension-type headache is the most common form of headache.³⁹² A recent comprehensive review of headaches summarized prevalence by sex for current and lifetime tension-type headache.³⁹² For both sexes, the prevalence peaks between the ages of 30 and 39 years. Unlike for migraine, women (current = 44%, lifetime = 49%) are only slightly more affected than men (37%, 42%). Several studies have disaggregated tension-type headache into episodic and chronic and report a similar female-male ratio for prevalence, with women being at significantly greater risk.^{188,349,370} Thus, the headache literature consistently shows increased prevalence of headaches and migraine among women.

Pain in Children and Adolescents—The epidemiology of chronic pain in children has been reviewed by McGrath,²⁷² but differences between boys and girls were only briefly discussed. We will review several large studies that compared the prevalence of headaches, musculoskeletal pain, and abdominal pain in children and adolescents.

There is considerable literature on headaches in children. Migraine begins earlier in males than in females, with peak onset between ages of 5 and 10 years and 12 and 17 years, respectively, but new cases of migraine were uncommon in men once they reach their twenties.³⁹⁰ Before puberty, the prevalence of migraine is higher in boys than in girls; however, as adolescence approaches, incidence and prevalence increase more rapidly in girls than in boys.³⁹⁰ Data from the American Migraine Study II estimated that among adolescents 12 to 17 years of age, 7% of girls and 5% of boys reported at least one severe migraine headache in the previous 12 months.²⁵³ A meta-review by Stovner and colleagues³⁹² placed the mean point-prevalence for migraine among children/adolescents at 9% for females and 7% for males.

Kroner-Herwig and others²³¹ assessed the distribution and characteristics of headache in German children aged 7 to 14 years using International Classification of Headache Disorders-II criteria to classify headaches into migraine or tension-type. They found that, similar to migraines, boys have an earlier onset to nonmigraine headache than girls. The prevalence of nonmigraine headache was similar for girls and boys of elementary school age years with increasing prevalence for girls during adolescence. There were no significant differences between girls and boys regarding type of headache; however, they did find that girls experience recurrent headaches more than boys. Other studies, however, find the prevalence of tension-type headaches to be higher in girls. For example, in a sample of children from Sweden, Laurell et al²³⁶ reported the 1-year prevalence of tension-type headache among girls as 12% and 8%

for boys. The prevalence increased with age for both sexes with greater increases for girls. By 13 to 15 years of age, the prevalence was 21% for girls and 9% for boys.

Several authors have reported pain prevalence for multiple sites within the same sample and allow a less biased opportunity to compare the magnitude of sex differences across pain sites. A nationwide study of Swedish students in grades 3, 6, and 9 compared the 7-day prevalence of headache, abdominal, and musculoskeletal pain.⁴⁹ Girls were more than twice as likely as boys to suffer from headaches (17%, 8%). Abdominal pain was experienced weekly by 10% of the girls and 5% of the boys with sex differences significant only in grades 6 and 9. There were no sex differences for musculoskeletal pain, but prevalence increased with age for girls.

A study of third- and fifth-grade children in Finland found that 32% reported a weekly musculoskeletal pain with significantly more girls reporting pain in chest (7%, 4%) and in the upper back (8%, 5%) compared with boys.²⁷⁸ Sex-related differences were not found for the lower back and neck pain. The pain-free children were reassessed 1 year later, and new-onset nontraumatic musculoskeletal pain was reported in 23% of the girls compared with 16% of the boys.¹¹⁰ There was no sex difference in traumatic-related musculoskeletal pain. Also, females developed pain at multiple sites more often than boys.

A study of more than 700 German school children aged 10 to 18 years old also found that sex differences were increased among adolescents.³⁴⁷ The 3-month prevalence of any pain was significantly higher for girls than for boys at both the 13- to 15-year (F = 98%, M = 92%) and 16- to 18-year (F = 93%, M = 76%) age groups, whereas there was no sex difference among 10- to 12-year-olds (F = 78%, M = 76%). Headache and back pain followed the same pattern, but significant differences between girls and boys only occurred in the oldest group for abdominal pain. There was no sex difference in the duration of any pain symptom at any age group.

Other studies have examined sex differences in chronic pain among children and adolescents. In a study examining the prevalence of chronic pain in a sample of Dutch children (up through 18 years of age), the overall prevalence was 30% in girls compared with 20% in boys.³¹³ Chronic pain increased with age, and sex differences began to appear between 12 and 14 years of age. Girls also rated their chronic pain as more intense on a VAS than boys, but the ratings were not different for non-chronic pain. Among schoolchildren ages 8 to 16 years living in Catalonia, Spain, the overall prevalence of chronic pain was higher for girls than for boys (47%, 29%).¹⁹¹ Chronic pain at multiple sites was more common among girls than boys (50%, 22%), but lower limb chronic pain was more common among boys than girls (57%, 20% respectively). No sex differences were found for any of the other locations. Petersen et al.³¹⁴ examined pain in schoolchildren ages 6 to 13 living in Sweden. Sex differences in recurrent pain, defined as pain occurring more than once a week for 6 months, were not found for headache, stomach-ache, or backache. However, girls had a higher prevalence of multiple weekly pain symptoms than boys. The most consistent finding across the studies of pain in children and adolescents reviewed above is that sex differences emerge or become larger around puberty.²⁴⁵

Post Procedural Pain—Surgery and other invasive procedures are accompanied by acute pain, and some surgical procedures confer substantial risk for the development of chronic pain.²¹⁴ Several studies have reported on sex differences in acute pain following a variety of surgical procedures (see Table 4). Unfortunately, there is little standardization in the pain measures used or the time frame for assessing postoperative pain. There are no population level studies of postoperative pain; consequently, we review selected studies in clinical populations.

Two large studies of postoperative pain following out-patient general surgery found conflicting results. Chia and colleagues⁶⁷ investigated the influence of patient characteristics on

postoperative pain at rest and pain on movement in a large sample of Chinese patients. Male sex was associated with increased postoperative pain and morphine requirements. However, a study of 2732 outpatients at a hospital in Finland that included children and adults found that females were more likely to have pain immediately after surgery than males.²⁶⁹ Likewise, greater pain among women has been reported in heterogeneous surgical populations.^{16,62} These studies included multiple surgical procedures, which often differ across sex (eg, gynecologic surgery vs prostate surgery), which could contribute to sex differences in postoperative pain.

Mixed findings are found in studies of orthopedic surgery. A study that assessed pain in patients who underwent arthroscopic anterior cruciate ligament (ACL) reconstruction at an outpatient facility in the United States did not find sex differences in pain at the immediate postoperative evaluation.³⁹⁸ However, on the first day after surgery, females had higher mean VAS pain scores than males. Rosseland^{345,346} assessed pain immediately after and 1-year after an arthroscopic ACL procedure. Two hours after the procedure, 84% of the females reported at least moderate pain compared with 57% for men. There were no sex differences on the VAS among those with pain. One year later, there also was no sex difference in pain ratings. However, more females (33%) reported reduced activities of daily living due to pain compared with males (15%). Ritter et al³²⁹ followed a large sample of patients that received a total knee arthroplasty for 5 years. Men reported less pain than females before and at all time points after surgery, but the pre-post change in pain did not differ between men and women for any time period. Nikolajsen and others²⁹⁷ found no difference between men and women in the prevalence or intensity of chronic hip pain in 1231 patients who had undergone total hip arthroplasty 12 to 18 months previously.

Mixed findings are also reported for gastrointestinal procedures. Vetthus⁴²⁵ found that 27% of patients that underwent gallbladder surgery had pain 60 months later. There was no difference in the percentage of males or females reporting pain; although females were more likely than males to report the pain as diffuse. A study of acute pain following endoscopic hernioplasty found that pain scores at rest were significantly higher in females than males.²³⁵ Two studies of postoperative pain after cholecystectomy both indicated that female patients had higher VAS pain scores than males.^{82,417} Females undergoing colonoscopy reported greater abdominal than men.²⁴¹ Liem et al²⁵⁰ found that sex was not associated with chronic pain 1 year after a laparoscopic hernia repair. Thus, acute postprocedural pain shows a tendency toward greater intensity among females.

This review of recent clinical and epidemiologic findings generally indicates that women are at increased risk for many chronic pain conditions, and women tend to report higher levels of acute procedural pain. These sex differences appear smaller (or nonexistent) in children and appear to emerge or increase in magnitude during adolescence. Inevitably, these sex differences in clinical pain are driven by multiple biopsychosocial factors, which will be discussed below. We have previously suggested that sex differences in nociceptive processing, which would be manifested in responses to experimentally induced pain, represent one potentially important contributing factor. Next, we will review recent findings regarding sex differences in experimental pain sensitivity.

Sex Differences in Responses to Experimental Pain

Multiple studies have examined sex differences in experimentally induced pain, and previous qualitative and quantitative reviews by members of our research group concluded that women display greater sensitivity to multiple pain modalities compared with men.^{127,327} The current review will extend the findings from these reviews by examining a representative sample of studies published since that time. Sex differences in experimental pain have been evaluated

using a wide range of stimulus modalities including pressure, electrical, ischemic, thermal, and other models of experimental pain (eg, chemical). Dynamic models of experimental pain have been used to engage systems underlying summation and inhibition of pain. Pain sensitivity has been assessed by a number of different outcome measures including behavioral 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 reviews have concluded that females are more sensitive to pain compared with males.^{127,327} The following review will determine whether more recent studies continue to support this conclusion.

Pressure Pain Stimuli

The results from 9 studies that examined sex differences in experimental pressure pain are presented in the upper portion of Table 5. In the meta-analysis by Riley et al,³²⁷ pressure pain was determined to produce the largest sex difference. The studies published since that time support the conclusions of the meta-analysis. Females showed lower pain threshold and tolerance compared with men with the exception of one study²⁹⁵ in females had lower pain thresholds than males, but this difference was not significant, likely due to the sample size (12 F, 12 M). One study found that females provided higher ratings of suprathreshold pressure pain than males, with the sex difference increasing in magnitude with greater stimulus intensity.¹¹¹ In summary, the recent literature continues to provide strong support for the hypothesis that females are more sensitive to pressure pain.

Electrical Pain Stimuli—The results from 3 studies that examined sex differences in perceptual responses to electrical pain are presented in the middle portion of Table 5. Pain threshold and tolerance for electrical stimuli were significantly lower in healthy women compared with men. Even though electrical pain was reported for only 3 studies, it strongly favors the hypothesis that women are more sensitive to this pain modality in comparison to men. These recent findings present a more consistent picture than the 5 studies reviewed by Riley et al,³²⁷ who found that electrical stimuli produced inconsistent findings and a moderate effect size for the sex difference.

Ischemic Pain Stimuli—The results from 7 studies that examined sex differences in experimental ischemic pain are presented in the lower portion of Table 5. Studies used several variations of the submaximal effort tourniquet test to induce ischemic pain. Overall, a majority of the studies reported no sex differences in threshold (6 studies), tolerance (5 studies), or pain ratings (2 studies) to ischemic pain. Two studies reported that males displayed higher pain threshold and tolerance.^{128,161} Despite large sample sizes for several studies,^{107,124,132,133,161} sex differences in ischemic pain have not been statistically significant due to their small effect sizes.

Heat Pain Stimuli—The results from 22 studies that examined sex differences in experimental heat pain are presented in the upper portion of Table 6. All of the studies used some form of contact heat with the exception of one study that used hot water immersion.³⁶⁰ Also, the forearm was the most common site for stimulus application. The vast majority of studies reported that females were more sensitive to heat pain than males. For the studies examining behavioral measures of heat pain sensitivity, 81% (12/17), and 94% (15/16) of the studies reported lower thresholds and tolerances, respectively, in females. Females were also found to rate heat pain as more intense and unpleasant in the majority of studies that included a suprathreshold protocol (7/9, 78%), and one study found that females required lower temperatures to evoke moderate pain.⁴¹¹ Overall, the hypothesis that heat pain sensitivity differs as a function of sex has been supported.

Sex differences were not universal across all heat pain measures within a given study. For example, in a secondary review of unpublished and published studies, Jensen and Petersen¹⁹⁸ noted that heat pain thresholds were comparable between males and females, but females reported higher peak pain produced by a prolonged 45.0°C (1 minute) stimulus. The authors also mentioned that the total pain as indicated by area-under-the-curve was larger in females but failed to reach statistical significance. Two studies^{156,205} reported sex differences for tolerance but not thresholds, whereas others reported equivalent ratings of heat pain in males and females, and differences were observed with lower thresholds and tolerance in females.^{128,405}

Cold Pain Stimuli—The results from 22 studies that examined sex differences in experimental cold pain are presented in the lower portion of Table 6. Most studies have used some form of the cold pressor test in which subjects immerse their arm or hand in circulating cold water for a defined period of time, and their results support the hypothesis that cold pain sensitivity is more pronounced in females. Sex differences in cold pain were observed in 67% (6/9) of studies reporting cold pain threshold, 93% (14/15) of studies reporting cold pain tolerance, and 81% (13/16) of studies reporting continuous or retrospective subjective pain ratings to cold water immersion. Overall, each study reported sex differences in at least one pain outcome, but, similar to heat pain, discrepancies among pain outcomes occur between indices of cold pain within studies. For example, Jones et al²⁰⁵ observed sex-related differences for cold pain tolerance but not threshold. Based on the present set of studies, it appears that sex differences in cold pain are consistent, particularly for suprathreshold measures such as tolerance and pain ratings.

Sex-Related Differences in Dynamic Models of Experimental Pain

A number of investigators have used more dynamic models of pain to evaluate sex differences. One could argue that such pain assays, including temporal summation of pain and tonic pain induced via intramuscular administration of chemical stimuli, may provide more clinically relevant information. These studies generally support the conclusion that sex differences will be more robust with a painful stimulus that produces a deep, tonic sensation of pain.¹²⁷ Given the recency of these studies, they were not included in the previous meta-analysis³²⁷ but will be reviewed below.

Temporal Summation of Pain—The results from 4 studies that examined sex differences in temporal summation of heat pain are presented in the upper portion of Table 7. Temporal summation of heat pain is a commonly used to evaluate differences in the central processing of nociceptive signals (eg, temporal integration of pain). In this model, brief painful heat pulses are repetitively delivered to the skin at intervals at or less than 3 seconds. The temporal response to repetitive thermal stimuli is characterized as a gradual increase in subjective pain ratings associated with C-fiber input (eg, second pain) but not A δ fiber input (eg, first pain).^{130,318,338} Females exhibit a more pronounced temporal summation of heat pain,^{130,338,363} though one study revealed no sex differences.³⁸⁴ Although the authors did not speculate about this observation, differences in testing methodology (eg, preheated thermode with intermittent contact versus Peltier-based thermode) and small sample size may have contributed to the lack of sex-related effects. In addition, sex differences in temporal summation could be influenced by a number of psychological factors. For example, Robinson et al³³⁸ reported that sex differences in temporal summation of heat pain were mediated by gender roles and anxiety. Temporal summation of mechanical pain has also been more robust among females than males in most studies,^{361–363} with one exception.²⁹⁵ Again, differences in methodology (eg, temporal summation of cutaneous vs deep tissues) and site of stimulation (eg, temporal summation of hand vs leg) may be responsible for the discrepant results.

Finally, sex differences in temporal summation have also been demonstrated in clinical samples. Two studies reported that sex differences in temporal summation to heat¹⁵⁶ and mechanical³⁶¹ stimulation persisted in clinical pain populations with low back pain and temporomandibular disorders, respectively. Thus, on balance, the evidence supports the conclusion that temporal summation is greater among females than males.

Spatial Summation—Table 7 also presents information about 3 studies that examined sex differences in spatial summation. Unlike temporal summation, no differences have been observed between males and females with spatial summation of heat pain^{88,238} or cold pain.²⁶⁸ Lack of sex differences might be related to the fact that spatial summation was either measured or reflected only for pain threshold in these studies, and sex differences in suprathreshold measures are often more robust than for threshold. Moreover, sample sizes were relatively small in all of these studies, which may have reduced the ability of these studies to detect sex differences. Nonetheless, the currently available data suggest no sex differences in spatial summation of pain, though additional studies with larger sample sizes would increase confidence in this conclusion.

Capsaicin—Responses to the TRPV1 agonist capsaicin have been compared across sexes, and three of these five studies reveal significant sex-related differences in subjective pain ratings, suggesting higher sensitivity in females (Table 8). These sex differences may be due to increased activation of C-fibers among women, as vasomotor responses (eg, axon flare) produced by capsaicin were more pronounced in females.¹⁴³ Also, sex differences in capsaicin pain appear to be dependent on the menstrual cycle. Females reported less pain during the luteal versus the follicular phase.¹⁴³ Jensen and Petersen¹⁹⁸ used a model with both heat and capsaicin found that females exhibited greater dynamic tactile allodynia but responded similarly to males in subjective ratings of capsaicin pain and secondary hyperalgesia. In response to intraoral capsaicin, women using oral contraceptives provided lower pain ratings than men, whereas normally cycling women and men did not differ.²⁰ Thus, capsaicin-evoked pain does not differ consistently across sex.

Hypertonic Saline and Glutamate Muscle Injections—Table 8 also presents data from studies evaluating the effect of intramuscular injections of glutamate and hypertonic saline. Since muscle pain is more prevalent in females, these experimental models may provide clinically relevant information regarding sex differences in pain. Fillingim and Maixner¹²⁷ suggested that differences in pain sensitivity between men and women would occur most consistently with nociceptive stimuli associated with deep, tonic pain since these stimuli imitate sensations of pain an individual experiences naturally. All nine of the identified studies involving intramuscular injections of glutamate and hypertonic saline found that females reported more pain than males, providing strong support for the hypothesis that females are more sensitive to muscle pain.

Sex Differences in Physiological Measures of Experimental Pain

The studies reviewed above have examined sex differences in self-reported pain, which may be influenced by reporting biases or differences in interpretation or application of pain scales. However, several studies have also examined sex differences in physiological responses to pain, such as pupil dilation,¹¹¹ muscle reflexes, and cerebral activation.

RIII Reflex—The RIII reflex is a spinal nociceptive reflex detected in the biceps femoris muscle following electrical stimulation of the sural nerve. Three studies observed lower thresholds to elicit the RIII response in females^{1,137,371} in addition to two studies reporting greater pain ratings after stimulation of the reflex in females.^{1,137} Two studies reported no

sex differences in the RIII reflex,^{2,136} but one of these studies was conducted in patients with osteoarthritis pain, which may have influenced the results.¹³⁶

Brain Imaging—Differences in cerebral activation between males and females have been evaluated in a number of studies. Studies have examined brain activity through a number of methods including positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) in response to different pain modalities. Given the reported sex differences in experimental pain perception, the use of neuroimaging is a promising tool that may reveal sex differences in central representations of pain. Table 9 lists several studies that have compared the central processing of pain between males and females. These studies have revealed a number of common cortical and subcortical areas activated by pain, but they have also observed sex-specific areas of activation. This suggests sex differences in central processing of nociceptive information.

Two PET studies reported that males and females process thermal pain differently, though both the methodology and the pattern of results differed substantially between studies. Paulson et al³¹² found that females reported more pain than males in response to a 50 °C contact heat stimulus, with an accompanying higher level of activation in the contralateral thalamus and anterior insula. Derbyshire et al⁹¹ tailored a laser heat stimulus to produce comparable pain levels in men and women and found that males showed greater activation in some brain regions (eg, parietal cortex, SII, PFC, insula), whereas females showed greater activation in others (eg, perigenual cortex, cingulate cortex). A more recent study of using fMRI to determine cerebral activation to contact heat reported sex differences in several brain regions, including the somatosensory cortex, insular cortex and dorsolateral prefrontal cortex (DLPFC).²⁸⁵ Interestingly, rather than sex differences in activation, these authors found that the sex differences were due to greater deactivation in these brain regions among females. Others have reported sex differences in cerebral responses to aversive visceral pressure among patients with IBS²⁹² and healthy controls,³⁴ whereas a study using magnetoencephalography and cortical-evoked potential found no sex differences in brain responses to electrical stimulation of the esophagus.¹⁸⁹ Overall, these studies suggest that there may be sex differences in cerebral responses to painful stimulation; however, the pattern of results varies across studies, likely due to differences in the stimulation method and in the approaches to brain imaging. Clearly, additional studies are needed to further characterize differences in pain-related brain activity between males and females.

Endogenous Pain Modulation

The experience of pain is endogenously modulated, and several experimental approaches to engaging pain modulatory systems are reviewed in this article. One experimental model of endogenous inhibition is diffuse noxious inhibitory controls (DNIC). Other forms of pain inhibition have included stress-induced analgesia (SIA), in which a laboratory stressor is used to reduce experimental pain, and exercise-induced analgesia. Finally, limited research has addressed sex differences in placebo analgesia. Assuming that basal pain sensitivity may reflect the activity of endogenous pain modulatory systems, it would be expected that females and males may also differ in endogenous pain modulation. The available evidence addressing this possibility is reviewed below.

Diffuse Noxious Inhibitory Controls—Diffuse noxious inhibitory controls (DNIC) refers to a form of endogenous pain modulation in which the perception of one painful stimulus (the test stimulus) is attenuated by a heterotopically applied conditioning stimulus at a remote site. Some investigators have speculated that DNIC may be of substantial clinical relevance, because dysfunction in endogenous pain inhibitory systems is believed to contribute to certain chronic pain conditions.^{101,384,453} Sex differences in DNIC have been evaluated in a number

of studies (Table 11). Approximately half (6/13, 46%) of the studies suggest that DNIC is more pronounced in males than females, based on psychophysical^{147,165,321,384,438} and neurophysiological³⁷¹ responses. In contrast, five studies have found that males and females inhibit pain equally during exposure to a conditioning stimulus.^{20,106,137,268,319,411} Inconsistent findings across studies may be a consequence of methodological differences among the studies; however, no clear pattern emerges when comparing methodological characteristics of studies that have shown a sex differences to those that have not. Most studies used the cold pressor as the conditioning stimulus, whereas a variety of test stimuli have been used. The timing of the conditioning stimulus may also affect the ability to detect inhibition, with the conditioning stimulus producing greater inhibition when administered before the test stimulus compared with weaker inhibition with concurrent administration.²⁶⁸ Additional factors, including sex-specific psychological mediators, may also contribute to the presence or absence of sex differences in DNIC. For example, Weissman-Fogel et al⁴³⁹ found that sex differences in DNIC were no longer significant after controlling for catastrophizing, which suggests a potential mediating role for psychological factors in sex differences in DNIC.

Conclusions related to sex-related differences in DNIC remain tentative pending additional studies. Future research investigating sex differences in DNIC should attend to characteristics of pain induction (eg, stimulus intensity, duration), stimulation site, and possible role of biological (eg, hormonal, genetics, autonomic) and psychological (eg, anxiety, catastrophizing, coping) mediators.

Other Forms of Endogenous Pain Modulation—Several studies have addressed whether physical or psychological interventions differentially influence pain responses in men versus women, and these studies are summarized in the lower portion of Table 10. The majority of these studies (5/6, 81%) indicate that females exhibit more efficient pain inhibitory responses compared with males. For example, using an isometric handgrip exercise, pressure pain threshold was elevated in females but not males, suggesting that exercise-induced analgesia was greater in females.²²⁶ However, sex-related differences in pain modulation may be dependent on the type of stressor and pain modality. For example, in response to a laboratory public-speaking stressor, males exhibited a greater stress-related reduction in heat pain, whereas females showed a greater reduction with ischemic pain.⁴⁵ Sternberg et al³⁸⁷ reported that cold pain was reduced in males during video game competition, whereas pain was more substantially reduced by physical exercise in females.

Another form of endogenous modulation that may be sensitive to sex differences is placebo analgesia. This section was not included in Table 10 since only a limited number of studies have addressed this issue. Sex differences in placebo response are often not discussed or reported, although these differences may contribute to the large variability in the magnitude of placebo responses.^{145,225} Clinical studies have generally reported no sex differences in placebo responses.^{18,153} Regarding laboratory findings, one study reported that men exhibited a greater increase in cold pain tolerance with placebo compared with females.⁷² Another study reported greater placebo and morphine responses in females as indicated by increase cold pain thresholds and lower pain ratings compared with men.³²⁰ The ability of placebo to reduced pain outcomes in males and females was not different in psychophysical studies comparing alfentanil³⁰³ and topical lidocaine³³⁴ to placebo. However, all of these studies were conducted in typical “clinical trial” fashion, which can reduce the magnitude of placebo responses.⁴²⁴ One study that included a placebo manipulation demonstrated that males who were informed that a “powerful pain reliever” had been administered showed significant increases in ischemic pain tolerance, but there was no effect in females.¹³⁵ On balance, these studies of endogenous pain modulation suggest inconsistent sex differences, which may not be surprising given the variety of methods used to engage pain modulatory systems and to assess their effects.

Since our two previous reviews^{127,327} a large number of studies using widely varying methodologies have investigated sex differences in experimental pain sensitivity. Based on the overall findings, it can be concluded that females are more sensitive to painful stimulation as assessed in the laboratory. From the pattern of results, it is difficult to pinpoint any specific mechanism(s), because the sex differences appear relatively consistently across multiple stimulus modalities. However, the recently developed literature on pain in response to intramuscular injections of algescic substances reveals robust and unanimous differences, suggesting that deep, tonic stimuli that mimic clinical musculoskeletal pain may be particularly sensitive to sex differences. Moreover, the inconsistency of findings from brain imaging studies can be attributed not only to the vast methodological differences across studies but also to their small sample sizes. Sex differences in endogenous pain modulation have received more limited attention, but the available evidence suggests that males and females may differ in this regard as well, though the direction and magnitude of the effects are quite variable. The mechanisms and practical importance of these sex differences merit further investigation in future studies.

Sex Differences in Responses to Pain Treatment

Gender Bias in Pain Treatment

Another important issue to consider is the possibility of sex and gender differences in the context of pain treatment. One topic that has received attention is the possibility of gender bias in the provision of pain treatment. Although the use of both prescription and nonprescription analgesics is significantly higher among women than men,^{109,115,193} there is concern that women are at greater risk for undertreatment of pain.¹⁹⁰ It has been observed that women presenting with chest pain are less likely than men to receive both invasive and noninvasive diagnostic and interventional cardiac procedures,^{80,339,369} though sex differences in symptom presentation and diagnostic test results may contribute to these disparities in management of chest pain.^{163,447} A frequently cited study reported that after cardiac surgery, women were more likely than men to be prescribed sedatives, whereas men were more likely to receive analgesics.⁵⁷ More recently, in the emergency department, women were less likely than men to receive analgesics for abdominal pain.⁶⁵ In contrast, in the hospital setting, more women than men received analgesics, although differences in the reasons for hospitalization could have contributed.⁴²² It has also been reported that women with temporomandibular disorders were treated more frequently by surgical intervention than men, which may have been due to self-selection or an increased tendency for clinicians to recommend surgery for women.²⁶⁴ Vignette studies have also explored gender biases in pain treatment. Using this approach, Hamberg and colleagues¹⁷⁷ found that when the neck pain case was a woman, female and male medical students were more likely to provide nonspecific somatic diagnoses, address psychosocial variables in the history, and to prescribe analgesic and psychoactive medications. Another vignette study showed an interaction between physician and patient sex, in that female physicians prescribed higher doses of opioid pain medication for women than men with low back pain, whereas the reverse pattern emerged for male physicians.⁴³⁷ Subsequently, male but not female physicians were more likely to recommend activity restrictions for female than male medical patients.³⁵⁴ However, nurse anesthetists showed no gender bias in pain treatment in a vignette regarding patients who had undergone orthopedic surgery.⁷⁸ Thus, while not unanimous, evidence suggests potential gender biases in pain treatment; however, the clinical characteristics of the patient and the sex of the provider may influence the magnitude and direction of the effect.

Sex Differences in Analgesia: Clinical Studies—In addition to gender differences in the provision of pain treatment, some investigators have examined whether females and males respond differently to pain treatment. For example, sex differences in responses to analgesic medications have been explored, and these findings have been reviewed previously by several

authors.^{74,122,221,277} While not a direct measure of analgesic response, studies of self-administration of opioids using patient-controlled analgesia (PCA) have revealed lower postoperative opioid consumption among women than men in several studies, as previously reviewed by Miaskowski and Levine.²⁷⁷ Of course, this lower opioid consumption among women could be driven by factors other than pain relief, such as increased adverse effects, which have been well documented among females.^{38,63,132,457} Additional findings emerging since that review provide a mixed picture of sex differences in opioid analgesia (see Table 11). Lower postoperative opioid consumption among women versus men has been reported in several studies.^{67,187,202} One study indicated lower opioid consumption among women for lower abdominal surgery, but opioid use was similar across sexes for all other surgical subtypes.⁶⁴ Other PCA studies have reported no sex differences in opioid consumption.^{202,140} Others have indicated higher opioid requirements to achieve pain relief when medication was administered by providers rather than via PCA.^{16,62} More recently, women were found to consume significantly more tramadol, a weak μ -opioid, than men after cholecystectomy, and women also reported greater postoperative pain.⁸⁶ In multivariate analysis, the sex difference in pain remained significant, whereas the sex difference in tramadol consumption did not. Other studies of clinical pain have reported no sex differences in morphine analgesia for cancer pain,²⁰⁶ acute pain in the emergency department,^{38,280} or pain after oral surgery.^{164,206}

In addition to the above findings addressing sex differences in responses to μ -opioid agonists, others have investigated analgesic responses to mixed-action opioid agonist-antagonists among women relative to men. In several studies of pain after oral surgery, women have shown more robust and longer lasting analgesic responses than men in response to pentazocine, nalbuphine, and butorphanol.^{150,152,153,164} Interestingly, these investigators have shown that low dose nalbuphine actually increases pain in men, an effect that can be reversed with a subanalgesic dose of morphine.¹⁵¹ After endodontic surgery, women showed significantly greater pain relief with a pentazocine/naloxone combination compared with men.³⁵³ In contrast, no sex differences in butorphanol analgesia were observed among patients treated in the emergency room for trauma-related pain.²⁸⁰ Clinical data regarding sex differences in response to nonopioid analgesics is limited; however, analgesic responses to ibuprofen after dental surgery were similar in women and men.^{17,353} Taken together, these clinical findings suggest more robust analgesic responses to mixed-action opioids among women, particularly with dental pain models; however, sex differences in μ -opioid analgesia have been inconsistent. Combining the data from Table 11 with the studies reviewed by Miaskowski and Levine,²⁷⁷ there is some suggestion that when using PCA women consume lower doses of morphine. Interestingly, the two studies showing lower morphine requirements for men involved provider administered morphine.^{16,62} It is tempting to speculate that men may be less willing to report pain or request analgesics from a provider, which would explain their lower opioid consumption in the provider-administered settings. Alternatively, one could argue that women benefit more from the increased sense of control that accompanies self-administration of opioids. Additional research will be required to confirm or refute these possibilities.

Sex Differences in Analgesia: Experimental Studies—In recent years, several investigators have examined sex differences in analgesic responses using experimental pain models, and these studies are summarized in Table 12. As with clinical pain, most of these studies have examined μ -opioid analgesia, and overall the findings suggest minimal sex differences. The vast majority of studies have reported no sex differences analgesia with a variety of opioids. One exception was a study using electrical pain, which reported longer lasting and higher peak morphine analgesia among women than men; however, this study did not include a placebo condition.³⁶⁴ This may be important, because Pud and colleagues³²⁰ recently found that women showed greater increases than men in cold pain threshold and tolerance after oral morphine; however, women also showed greater analgesia in response to

the placebo. Therefore, when placebo responses were controlled for, no sex difference in morphine response emerged. The effects of some nonopioid pain medications have been compared for women versus men. Analgesic responses to ibuprofen produced greater analgesia for electrical pain among men than women.⁴³⁰ In a study of another NSAID, no significant sex differences the effects of ketorolac on cold pressor pain tolerance were found.⁷² Inspection of the means indicates that males showed substantially increased tolerance in response to both placebo and ketorolac, whereas females showed no placebo response and a very modest increase in response to ketorolac. Also, using pressure pain, Robinson et al³³⁴ reported that lidocaine produced greater cutaneous anesthesia in men than women. Thus, experimental pain models provide no consistent evidence of sex differences in analgesic responses to opioid or nonopioid medications; however, two of the studies indicate the importance of a placebo condition in the experimental design.^{72,320}

Sex Differences in Responses to Nonpharmacologic Interventions

In contrast to research on sex differences in responses to pharmacologic treatments, whether nonpharmacologic interventions for pain produce differential effects in women and men has received relatively little attention. Some research has addressed this issue in the context of experimentally induced pain. For example, a cognitive intervention in which subjects were instructed to focus on the sensations of pain they experienced was effective for reducing pain intensity in men but not women.²¹⁹ In another experimental study, women but not men reported lower ratings of cold pressor pain after exercising on a treadmill, whereas men but not women showed reduced pain ratings after playing video games.³⁸⁷ In another study, pleasant odors significantly reduced the intensity and unpleasantness of heat pain in females but not in males.²⁶⁵ It has also been reported that ingestion of sucrose produced a longer-lasting suppression of the R3 reflex in males than in females.³⁷

Limited clinical research has addressed sex differences in outcomes from physical medicine or interdisciplinary treatments. Several studies have examined potential sex differences in outcomes of treatments for back pain. For example, conventional physical therapy was more effective for men, whereas intensive dynamic back exercises produced better pain reduction among women.¹⁷⁸ Similarly, women but not men with back pain undergoing cognitive behavioral treatment with or without physical therapy exhibited improved health-related quality of life.¹⁹⁷ Moreover, women in active treatment showed reduced likelihood of permanent disability than women in the standard care control group, but no such effect emerged for men. In contrast to these results, other findings indicate similar treatment gains for women and men after active rehabilitation for chronic low back pain.^{155,208,263} In a study of conservative multidisciplinary treatment for orofacial pain, women showed significant reductions in pain 2 years after treatment, whereas men showed no pain improvements.²³⁰ Keogh and colleagues²²⁰ recently reported that men and women showed similar reductions in pain intensity and pain-related distress after interdisciplinary pain management, but men maintained their treatment gains 3 months later, whereas women did not.

Importantly, even when men and women show treatment responses of similar magnitude, the determinants of outcome may be sex-related. For example, anger expression was associated with functional and mood improvements among men but not women undergoing interdisciplinary pain treatment.⁵¹ Another study of responses to interdisciplinary pain treatment found that pretreatment pain tolerance more strongly predicted reductions in pain severity and pain-related interference among women than men.¹⁰⁴ Also, in a study evaluating responses to three physical therapy interventions for acute back pain, baseline levels of pain and disability as well as duration of symptoms predicted outcomes in women, whereas type of treatment and fear avoidance beliefs were significant predictors among men.¹⁵⁵ This somewhat limited literature suggests the possibility of sex differences in responses to

nonpharmacological pain treatment and the predictors of treatment response, but additional research is needed to further explore these issues.

Mechanisms Underlying Sex Differences in Pain and Responses to Treatment

The preceding review clearly demonstrates the presence of sex differences in pain responses, and some evidence suggests that endogenous and exogenous modulation of pain may vary in women versus men. However, the mechanisms underlying these sex differences have yet to be fully uncovered. Importantly, as in other fields of pain research, mechanisms underlying sex-related variability in pain responses are often portrayed as either psychosocial or biological. This dualistic conceptualization should be recognized as artificial and based primarily on the level of analysis rather than the actual mechanism of action. For example, at a psychosocial level, gender differences in expression of pain are often attributed to the effects of stereotypic sex roles. However, from a more biological perspective, hormonal and neurobiological factors are inevitably associated with and influenced by masculine versus feminine sex roles, and these underlying neurobiological processes can directly affect nociceptive responses. Thus, when considering the putative mechanisms underlying sex differences in pain, the terms “psychosocial” versus “biological” are used for convenience, but it is recognized that these terms may actually refer to the same underlying processes described at different levels of analysis. Previous reviews have addressed potential “biological” contributions to sex differences in pain, including gonadal hormones,^{7,75,77,131} endogenous pain modulation,^{73,127} as well as “psychosocial” influences including gender roles^{35,289,335} and other psychosocial factors.^{203,289,335} We will briefly discuss each of these issues: “biological” mechanisms and gonadal hormones and pain.

In addition to their reproductive role, gonadal hormones produce far-reaching effects throughout the peripheral and central nervous systems, and these hormones likely contribute importantly to sex differences in pain. The concentrations and temporal characteristics of estrogens, progesterone and testosterone differ substantially between sexes. For women, hormone levels change during and after pregnancy, after menopause, and monthly throughout most of the female’s reproductive lifetime (menstrual cycle), whereas men are exposed to less impressive fluctuations in hormone levels across the lifespan, with the most significant change being the reduction of testosterone with aging. After a brief overview of findings regarding hormonal effects on clinical and experimental pain in humans, we will highlight several pathways whereby gonadal hormones can influence pain.⁷⁵

Hormonal Influences on Clinical Pain

Abundant evidence suggests hormonal contributions to many clinical pain conditions. For example, as noted previously, prepubertal girls and boys have an approximately equal prevalence of migraine; however, the lifetime prevalence of migraine increases to 18% for women and 6% for men after puberty, suggesting a hormonal link between female sex and migraine.^{253,391} Similar prevalence patterns have been observed for temporomandibular disorders, with no difference between boys and girls in childhood and higher prevalence in women after puberty.²⁴² In addition, the prevalence of one or more common pain complaints was similar among girls and boys before puberty but increased more dramatically in girls as puberty progressed.²⁴⁵ The severity of symptoms appears to vary across the menstrual cycle for several pain conditions, including irritable bowel syndrome,^{180,181} TMD,²⁴⁴ headache,^{13,213} and fibromyalgia.^{9,10,310} However, data suggesting no menstrual cycle effect are also available.^{240,300} Additional support for hormonal modulation of pain comes from findings that during pregnancy migraine frequency declines and TMD pain is reduced.^{46,75,247} Interestingly, as the estradiol level sharply declines postpartum, frequency of migraine attacks increases.³⁵⁶

Exogenous hormone use has also been associated with clinical pain. Postmenopausal women using hormone replacement have shown increased risk for back pain^{50,288,397} and TMD,²⁴⁶ and oral contraceptive use has been related to increased risk for TMD²⁴⁶ and carpal tunnel syndrome.¹¹⁶ Moreover, Wise and colleagues⁴⁴⁵ found that postmenopausal women on hormone replacement seeking treatment for orofacial pain reported significantly more severe pain compared to facial pain patients not using hormones. However, other research suggests no association of exogenous hormone use with clinical pain.²⁶⁰ Moreover, discontinuation of hormone replacement therapy in postmenopausal women was associated with higher levels of reported pain or stiffness,²⁹⁹ and after sustained estradiol administration, estradiol withdrawal has been shown to precipitate migraine headaches.^{249,381} Finally, a study of transsexuals undergoing hormonal treatment to acquire somatic characteristics of the opposite sex revealed a change in response to pain.⁶ Approximately one-third of the male-to-female subjects undergoing estradiol/antiandrogen treatment developed chronic pain, whereas about half of the female-to-male subjects treated with testosterone reported a significant improvement of the chronic pain (headache) already present before the start of treatment. Taken together, these data provide evidence for hormonal contributions to clinical pain, in that both administration and withdrawal of estrogens have been shown to increase risk for pain.

Hormonal Influences on Experimental Pain—Studies of laboratory pain provide additional evidence of hormonal influences on pain responses. In a meta-analytic review of 16 publications related to pain perception across the menstrual cycle, Riley and colleagues concluded that pain thresholds for mechanical, thermal, and ischemic muscle pain were higher during the follicular phase of the menstrual cycle (low to moderate levels of estradiol and progesterone) than during perimenstrual phases of the cycle (decreasing levels of estradiol and progesterone), and the effect sizes were generally small to moderate.³²⁸ Since this systematic review, additional studies have yielded conflicting results. Electrical pain thresholds were lower in the luteal versus the follicular phase in one study,⁴⁰¹ but two other studies reported no menstrual cycle effects on electrical pain thresholds.^{305,408} Three studies reported no menstrual cycle effects on heat pain perception^{83,166,380} and another reported lower heat pain thresholds only on the abdomen during the ovulatory phase.²¹ In several studies, pressure pain thresholds generally did not vary across the menstrual cycle in healthy women or women with TMD,^{71,373,426} one study reported lower thresholds during the perimenstrual versus luteal and follicular phases,¹⁹⁴ others reported that PPT tested on the back was lower during the ovulatory phase,²¹ and temporalis PPTs were higher in the menstrual than the follicular phase.⁹⁸ Cimino and colleagues⁷¹ found that masseter and temporalis PPTs were lowest during the periovulatory phase. Two studies reported no menstrual cycle effects on ischemic pain.^{373,393} Cold pressor pain threshold showed menstrual cycle effects in two studies, with lower thresholds in perimenstrual¹⁸³ and luteal³⁸⁶ phases; however, these authors reported no menstrual cycle effects on pain ratings or pain tolerance, and others have reported no menstrual cycle effect on cold pressor pain.²²⁹ Gazerani et al¹⁴³ reported greater capsaicin-induced pain, allodynia, and mechanical hyperalgesia during the menstrual versus the luteal phase. In addition to subjective pain responses, pain-related cerebral activation,^{68,84} laser evoked potentials,¹⁶⁶ and nociceptive muscle reflexes have varied across the menstrual cycle.⁴⁰¹ As previously noted^{328,372} these inconsistent menstrual cycle effects are likely related to the tremendous variability in how investigators have defined cycle phases, along with other methodological inconsistencies, including varying pain modalities and testing sites.

Additional evidence of hormonal contributions to pain sensitivity has been reported. For example, in pre-menopausal women, higher estradiol levels were associated with increased pain in response to thermal stimuli.¹²⁹ In contrast, higher progesterone levels were associated with increased cold pressor pain sensitivity, and this association was attenuated in the presence of higher estradiol levels.³⁸⁶ Further, we reported that postmenopausal women taking hormone replacement therapy (HRT) displayed lower thermal pain thresholds and tolerances than

postmenopausal women not taking HRT, whose pain responses did not differ from men.¹²⁰ Thus, menstrual cycle and hormonal influences on pain sensitivity have been reported, but the direction and magnitude of these associations is highly variable.

The exact mechanisms whereby hormones influence pain remain complex and poorly understood, because hormonal effects vary in both magnitude and direction based on numerous factors, including (1) the dose and timing of hormonal exposure; (2) the type of pain under consideration; (3) the entire hormonal complement (ie the presence of multiple hormonal factors); (4) the target tissues (eg peripheral vs spinal vs supraspinal). Moreover, gonadal steroids exert both organizational and activational effects, which refer to long-term developmental influences versus transient effects in adulthood, respectively. The impact of sex hormones on pain responses can be broadly dichotomized into peripheral versus central nervous system effects, which are discussed below.

Peripheral Effects of Sex Hormones—Sex hormones can affect disease pathophysiology, which can affect disease-related pain. For example, the effects of estrogens on bone deposition and cartilage homeostasis could influence the development of articular pathology and pain.⁴⁰⁰ Of more direct relevance to pain are the hormonal contributions to inflammation. In general, women show a heightened inflammatory response compared with men.³⁹⁴ Although beneficial for wound healing and response to infection, this more robust inflammatory response places women at significantly greater risk for a variety of painful inflammatory autoimmune conditions, including rheumatoid arthritis, osteoarthritis, and systemic lupus erythematosus. The inflammatory response to various triggering events involves plasma extravasation, chemotactic attraction of leukocytes, and, in turn, stimulated release of inflammatory cytokines and growth factors. Additional peptides are released from C fibers, and spinal N-methyl-D-aspartate (NMDA) receptor activation and nitric oxide production occur.⁴⁵⁰ This cascade of events can alter the transduction properties of nociceptors, lowering their activation thresholds, and this peripheral sensitization could ultimately lead to central sensitization. For example, stress-induced activation of the sympathoadrenal system attenuated the inflammatory response (ie plasma extravasation) to bradykinin in male but enhanced plasma extravasation in female rats.¹⁶⁷ The effects of estrogens on inflammatory responses are highly complex and depend on the level of estrogens, the cell type being examined, the specific inflammatory factor, the type of tissue that is inflamed, the time course of the inflammatory response (eg acute vs chronic), and the time point at which estrogen exposure occurs.³⁹⁴ For example, very high estrogen concentrations tend to inhibit inflammation, whereas lower levels of estrogens produce either no effect or a proinflammatory effect.^{56,394} Regarding inflammatory pain, systemically administered estradiol reduced formalin-induced nociceptive behaviors in gonadectomized male and female rats,^{142,233,262} whereas centrally administered estradiol heightened formalin-induced nociceptive responses in male rats.^{8,61} Thus, peripheral and central effects of estrogens may be divergent.⁷⁵ A complete review of the literature regarding hormonal effects on inflammation is beyond the scope of this manuscript, and interested readers are referred to other recent reviews for more detail.^{56,75,281,394} Suffice it to say that hormonal effects on inflammation represent one important albeit complex pathway whereby gonadal hormones can influence pain responses.

Another peripheral mechanism whereby gonadal hormones can affect pain responses is through their effects on peripheral afferents. Indeed, estrogen receptors are found on primary afferents,²⁹ and estradiol has been shown to increase trigeminal afferent discharges evoked by injection of NMDA.⁹⁶ Also, estrogen increased C-fiber activity evoked by uterine cervical distension, and this enhanced afferent activity was reversed by administration of a TRPV1 receptor antagonist.⁴⁵² However, another group recently demonstrated that estrogen reduced capsaicin-induced TRPV1 activation of lumbosacral afferents.⁴⁵¹ Thus, estrogenic influences on

peripheral afferent junction have been reported, though the direction of the effects can be variable.

Gonadal steroids exert wide-ranging effects in the central nervous system, including direct and indirect effects on pain processing. Sex hormones may influence multiple central nervous system pathways, including effects on the functioning of endogenous opioid systems, dopaminergic function, serotonergic activity, and other endogenous components involved in the nociceptive processing, as discussed below.

Endogenous Opioid Systems—The most studied of the endogenous pain modulatory systems is the endogenous opioid system, and sex differences in the functioning of this system could arise based on several different mechanisms. First, sex differences could result from differences in the distribution, expression or sensitivity of opioid receptors in regions of the central nervous system involved in nociceptive processing. At rest, women have shown higher μ -opioid receptor binding in various cortical and subcortical brain regions than men,⁴⁵⁶ whereas men exhibited greater μ -opioid receptor binding in several brain regions than women in response to experimentally induced muscle pain. These sex differences in both resting and pain-related μ -opioid receptor binding may contribute not only to sex differences in basal pain perception but also to differences in sensitivity to opioid medications.

Sex differences in opioid function could be partially mediated by the well-known interaction between gonadal hormones and the opioid system.⁴² In rodents, estradiol site-specifically modulates peripheral and supraspinal but not spinal μ -opioid receptor activity.¹⁹⁹ In the brain, intact and estradiol-treated ovariectomized female rats had significantly fewer opioid-binding sites than their untreated ovariectomized counterparts.⁴³⁵ Women in low estradiol states show decreased μ -opioid receptor availability. Smith et al³⁷⁹ showed that women in a high estradiol, low progesterone state, reported less pain and displayed increased pain-related brain μ -opioid receptor binding than women in a low estradiol state.

Additional evidence of hormonal modulation of opioid function comes from studies investigating responses to exogenous opioids under different hormonal conditions. For example, hormonal manipulations affect opioid antinociception in rodents, though the magnitude and direction of these effects can depend on multiple factors.^{77,131} We have previously concluded¹³¹ that the preclinical evidence suggests that conditions characterized by relatively high estradiol levels are associated with reduced sensitivity to opioid agonists. However, the influence of gonadal steroids on responses to opioids in humans has not been determined.

Dopamine—Another neurotransmitter system that could contribute to sex differences in pain responses is the dopaminergic system. Recent insights indicate a central role for dopaminergic neurotransmission in modulating pain perception,⁴⁴⁸ and evidence suggests that there are sex-specific differences in the dopaminergic function, and estrogens play an important role in maintaining the integrity and modulating the functional activity of the dopamine system in the CNS.^{270,271} Estrogens and progestins have complex effects on dopamine turnover, which vary across brain regions and depend on the dose and time course of administration.^{255,271} Also, some data indicate sex differences in dopamine transporter (DAT) function. This transporter plays a critical role in regulating dopaminergic function.^{139,448} The density of DATs are greater in female versus male rats,^{330,448} and clinical reports have shown greater densities of DATs within healthy adult women versus men.^{286,383,448} Moreover, assays of DAT function indicate a more active DAT system within females versus males.^{36,448} Such sex differences may be related to estrogens.

Although these studies do not confirm that dopamine influences sex differences in pain perception, it seems plausible that hormonal influences on dopaminergic function could contribute to sex differences in pain. Some have suggested that dysfunction of dopaminergic neurotransmission may explain the primary clinical symptoms of fibromyalgia (ie, chronic widespread pain and generalized hyperalgesia); therefore, dopamine represents an important and physiologically relevant target for the treatment of fibromyalgia.⁴⁴⁹ Additional research is needed to determine the role of the dopamine system in sex-related influences on pain.

Serotonin—Serotonin represents another potential contributor to sex differences in pain. Serotonin (5-hydroxytryptamine [5-HT]) influences pain processing in complex fashion, depending on the site of action and receptor subtype. In the CNS, 5-HT generally has been associated descending pain inhibition, whereas peripheral 5-HT is an inflammatory mediator and is generally pronociceptive. Although peripheral effects of serotonin are thought to contribute to sex-related pain conditions, such as migraine and IBS, serotonin's contribution to sex differences in pain processing is primarily associated with its CNS actions. For example, compared with male rats, female rats have demonstrated higher serotonin levels and/or synthesis in multiple brain regions.^{94,175,209,433} A similar sex difference in rat brain serotonin turnover, an indication of serotonergic activity, has also been reported.⁵⁸ Furthermore, brain serotonergic function is modulated by ovarian hormones.^{270,271} Clinical research also suggests that the greater brain 5-HT synthesis in female IBS patients versus controls may be related to the visceral hypersensitivity that characterizes IBS patients, the female predominance of the disorder, and the sex difference of the efficacy of the 5-HT₃ antagonist in treatment for this syndrome.²⁹¹ Thus, it seems plausible that central serotonin function may contribute to sex differences in pain.

NMDA Receptor Function

Sex differences in pain modulation may also be influenced by NMDA receptor function. NMDA receptors are expressed in the dorsal horn and their sustained activation by the release of glutamate from tonically active primary afferents enhances the excitability of the second-order neurons on which they are expressed, producing enhanced nociceptive responses. McRoberts and colleagues²⁷⁴ recently reported that the application of agonists (NMDA and glycine) to cultured dorsal root ganglion (DRG) neurons from female animals produced significantly larger currents compared with DRG neurons from males, and the addition of estradiol increased the NMDA receptor currents more in females than males. Moreover, NMDA antagonism can enhance opioid anti-nociception, and this effect has shown sex dependence, with generally greater enhancement in male versus female animals,^{169,254,294} although these effects depend on the particular NMDA antagonist used, its site of action, as well as its dose.⁷⁶ It seems plausible that estrogenic enhancement of NMDA receptor excitability could contribute to more robust central sensitization among women than men.¹⁸⁶ These sex-related influences on NMDA receptor function could help explain sex differences in temporal summation (or “windup”) of pain.^{130,338,362,363}

“Psychosocial” Mechanisms

Gender Roles and Pain—Within gender studies, sex has generally been seen as a biological marker, used to categorize human beings into males and females based on physical characteristics such as chromosomes, hormones, external genitalia, and secondary characteristics.^{35,87} The assignment of a sex category involves social processes whereby a human being is classified as man or woman based on socially agreed-on biological criteria (eg, genitalia at birth, chromosomal typing); however, biological characteristics are often inferred based on social characteristics, such as how people dress or present themselves.³⁵ Some investigators argue that the use of the dichotomous variable sex as a proxy for presumed biologic aspects of being female or male may obscure the contribution to sex-correlated

differences that could be ascribed to the ways in which women and men are socialized.²⁸⁹ Thus, the terms “sex” and “gender,” while related, are not interchangeable. Sex refers to biological distinctions characterizing male and female, whereas gender reflects sex-related social roles with which an individual identifies that presumably reflect learned femininity and masculinity.^{289, 446}

The differences that exist between males and females in the perception, expression, and tolerance of pain are likely influenced by a variety of social and psychological processes.²⁷⁹ Gender roles have been associated with pain response, with the masculine gender norm dictating increased tolerance of pain among males, whereas feminine gender norms accept pain as a normal part of life and are more permissive of pain expression.^{289,418} Using standardized measures of gender roles, several studies have investigated the association of masculinity and femininity to experimental pain responses. In one study, higher masculinity relative to femininity was associated with higher mechanical pain thresholds among men but not women, whereas greater masculinity relative to femininity predicted higher mechanical pain tolerance in both sexes.³⁰⁷ Similar findings were reported for cold pain tolerance in a more recent study.²⁹⁰ Sanford and colleagues³⁵⁹ reported that higher levels of femininity predicted lower cold pain tolerance, whereas masculinity was not associated with pain response. Subsequently, these investigators reported that higher masculinity relative to femininity was associated with higher cold pain tolerance and lower cold pain ratings.⁴⁰⁷ In two of these studies, sex differences in pain responses remained significant after controlling for gender roles^{290,307} whereas gender roles partially mediated the sex difference in pain tolerance in the other two studies.^{359,407}

In addition to these studies using general measures of gender roles, Robinson and colleagues have developed a pain-specific gender role measure, the Gender Role Expectations of Pain (GREP).³³⁶ Their findings indicate that both women and men consider women more sensitive to pain, less enduring of pain, and more willing to report pain compared with men.^{336,338, 444} Willingness to report pain was significantly associated with heat pain threshold and heat pain tolerance, and sex differences in pain threshold were not significant after controlling for willingness to report pain, whereas sex differences in pain tolerance remained significant.⁴⁴⁴ These authors also found that sex differences in temporal summation of heat pain were partially mediated by willingness to report pain.³³⁸ Using a different measure of pain-related gender norms, Nayak and colleagues²⁹³ found that females viewed overt pain expression as more acceptable than did males, and these beliefs predicted cold pain tolerance, which was lower in females than males. Pool et al³¹⁷ found that both men and women agreed that the ideal man should tolerate more pain than the ideal woman, suggesting that gender norms are indeed associated with pain tolerance. They then assessed the degree to which participants identified with these gender norms and demonstrated that strong identification with the male gender norm was associated with higher electrical pain tolerance in men, whereas gender norm identification was not associated with pain tolerance among women.

Experimental manipulations have also been used to examine the influence of gender roles on pain perception. Levine and DeSimone²⁴⁸ reported that men reported less cold pressor pain in the presence of a female versus a male experimenter, whereas pain ratings for females were not influenced by experimenter sex. Similar findings were reported by Gijbbers and colleagues,¹⁶⁰ who found that males showed a higher pressure pain threshold when tested by a female versus a male experimenter, whereas females' pain threshold was not influenced by the sex of the experimenter. Interestingly, experimenter gender effects for both of these studies may have been enhanced, as one study stated that “experimenters were dressed in a manner that emphasized their gender roles,”¹⁶⁰ and the other reported that “to evoke gender-related motives, experimenters were selected for their attractiveness.”²⁴⁸ Aslaksen et al¹⁵ also reported an interaction between participant and experimenter gender, such that males tested by a female experimenter provided lower heat pain ratings and lower ratings of arousal

compared with those tested by a male experimenter, whereas experimenter gender did not influence the pain or arousal ratings of female participants. Another study demonstrated that cold pain tolerance was higher for both males and females when tested by an experimenter of the opposite sex.²⁰⁷ On balance, these studies indicate that males report less pain in the presence of a female experimenter; however, other investigators have failed to show any effect of experimenter gender on pain responses.^{52,112,290,307} Based on these findings, Greenspan and colleagues¹⁶⁸ recommend documenting and reporting experimenter sex in the experimental pain setting because such factors may influence pain report in the laboratory and clinic setting.

Additional research has attempted to manipulate other gender-related variables. Fillingim et al.¹¹⁹ provided instructions designed to manipulate females' and males' perceived ability to tolerate ischemic pain, hypothesizing that enhancing perceived ability would produce greater effects in females, because males report higher perceived ability to tolerate pain at baseline. Surprisingly, the group with the highest pain tolerance was males who had been informed that females tolerate the procedure better. In contrast, Robinson and colleagues³³³ found that sex differences in cold pain tolerance were nonsignificant when participants were given gender-specific expectations for pain tolerance. The findings appear to indicate that females exhibited an increase in their pain tolerance when given the expectation that women would tolerate the pain for a longer time, whereas males showed similar pain tolerance regardless of expected tolerance time. Another study examined the effects of high versus low monetary incentives on pain tolerance among females and males, anticipating that high external incentives would produce stronger effects among females, because males possess higher endogenous motivation to tolerate pain.²⁵⁷ However, the incentive manipulation had no effect on pain tolerance for females or males.

More limited research has addressed the contribution of gender roles to clinical pain, and the results have been mixed. For example, higher scores on one aspect of masculinity were associated with lower pain-related symptoms among patients with rheumatoid arthritis.⁴¹³ Also, higher femininity scores in college aged males predicted an increased number of pain complaints 30 years later, whereas the masculinity-femininity scale did not predict future pain complaints among females.¹² In contrast, Helgeson¹⁸² reported that higher masculinity predicted greater chest pain after myocardial infarction among men and women, and others have reported no association between gender role measures and clinical pain.^{121,232}

The available research indicates a potentially important contribution of gender roles to sex differences in responses to experimentally induced pain, with masculinity and femininity predicting higher and lower pain sensitivity, respectively. Findings regarding clinical pain are more limited and less consistent. The exact mechanisms mediating the association of gender roles and pain responses have yet to be elucidated. An important question is whether these findings simply reflect gender-related response biases (ie, men under-report and/or women over-report pain) or might they reflect gender-based differences in endogenous pain modulation? More research is needed to further characterize the contribution of gender roles to the relationship between sex, gender, and pain.

Cognitive/Affective Variables—Cognitive/affective factors are important determinants of pain responses and likely contribute to sex differences in pain.^{289,335} The cognitive and affective mechanisms that have been investigated most widely in the context of sex and gender differences include coping processes, catastrophizing, and affective factors (eg, anxiety, depression). The following sections discuss the evidence regarding sex differences in the associations among psychological factors and pain report.

Coping and Catastrophizing—Coping refers to cognitive and behavioral efforts to manage demands judged to tax or exceed one's resources, and this might be one factor contributing to gender differences in responses to pain.¹⁹⁵ It seems plausible that biological and psychosocial influences may predispose males and females to utilize different coping strategies, and several studies have demonstrated sex differences in pain coping. In a sample of patients with musculoskeletal pain, Jensen et al¹⁹⁶ found that women reported higher levels of catastrophizing and increasing behavioral activities compared with men, and higher catastrophizing was associated with poorer perceived health status among women. In a telephone survey, Unruh⁴¹⁹ found that women reported having more intense pain and used more coping strategies than men, including positive self-statements and the use of more social and emotional support than men, but men and women did not differ in catastrophizing. Among patients with osteoarthritis, Keefe and colleagues²¹² found that women reported higher levels of pain, disability, and pain behavior. Also, women reported higher levels of catastrophizing, which mediated the sex differences in pain-related outcomes. In a daily diary study, these investigators also found that women with osteoarthritis reported greater use of problem-focused coping than men.²¹¹ Also, catastrophizing was more strongly related to negative mood among men than women. In children and adolescents with chronic pain, girls reported greater use of social support-seeking as a pain coping method, whereas boys made greater use of distraction.²⁵⁹ Another study in adolescents revealed that girls used more social support, positive statements, and internalizing/catastrophizing, whereas males reported more behavioral distraction, and the authors reported that internalizing/catastrophizing mediated sex differences in clinical pain.²¹⁷ Sex differences in coping have also been reported in healthy populations. Several investigators have reported higher levels of catastrophizing among healthy women compared with their male counterparts.^{107,134,306} In one of these studies, catastrophizing mediated sex differences in reports of recent daily pain but did not affect the sex differences in heat pain sensitivity.¹⁰⁷ Thus, sex differences in pain coping have been widely reported and have mediated sex differences in pain in some studies.

Affective Distress—Anxiety represents a negative emotional response to an anticipated threat, and higher levels of anxiety have been associated with increased clinical pain and heightened experimental pain sensitivity.^{325,331,337} Sex differences in anxiety have been reported, such that women tend to report higher levels of anxiety and are at increased risk for many anxiety disorders,^{26,410} and anxiety has been suggested as a potential mediator of sex differences in pain sensitivity.³⁴⁰ However, increasing evidence suggests that anxiety may be more strongly associated with pain responses among males than females.²⁰³ Several studies of laboratory pain have indicated that anxiety is positively associated with pain sensitivity among males but not females.^{125,204,205} In patients with chronic low back pain, Robinson and colleagues³³² demonstrated that anxiety was more strongly related to both ongoing clinical pain and pain induced via low back exercise among men than women. Edwards and colleagues¹⁰² also reported that anxiety was more strongly related to clinical pain severity among male versus female patients with chronic pain, and they subsequently found that higher pretreatment anxiety predicted greater pain reductions after interventional therapy for men but not women.¹⁰³ Thus, anxiety is more strongly related to experimental and clinical pain and to treatment-related pain reductions among men.

Another anxiety-related construct is anxiety sensitivity, which refers to the fear of anxiety-related bodily sensations.^{388,405} Sex differences in anxiety sensitivity have been reported, such that females report higher levels of anxiety sensitivity, especially for the physical concerns component of the construct (ie, fear of the physical sensations associated with anxiety, such as rapid heartbeat, shortness of breath).³⁸⁹ Measures of anxiety sensitivity have been associated with both clinical^{97,218,388} and experimental pain responses.^{215,388,405} Moreover, anxiety sensitivity was more strongly related to pain among women than men with chest pain, and the authors found that the association of anxiety sensitivity to pain severity in

women was mediated by the tendency to negatively interpret bodily sensations.²¹⁸ Sex differences in the associations of anxiety sensitivity to experimental pain have also been reported. Specifically, in a study of responses to cold pressor pain higher anxiety sensitivity predicted lower pain threshold and tolerance only among men, whereas higher anxiety sensitivity was associated with greater sensory and affective pain ratings among women.²¹⁵ Taken together, these findings suggest that anxiety sensitivity may contribute differently to pain responses among women and men.

Depression

Another component of affective distress that is relevant to pain is depression. Abundant evidence demonstrates that depression and pain are highly comorbid,^{92,287} and depression is more prevalent among women than men,²⁸⁷ especially somatic depression.³⁷⁵ Moreover, among individuals with depression, women are more likely to report pain complaints than men,²⁶⁶ and some of the evidence reviewed above suggests that women with some forms of chronic pain (eg, cancer, OA) may be more likely to experience depression compared to men. Although depression has been associated with experimental pain sensitivity,^{22,237,316} whether depression influences pain perception differently among women versus men is not yet known.

Conclusions and Recommendations

We have attempted to thoroughly, if not comprehensively, review the recent literature regarding sex differences in clinical pain, experimental pain sensitivity, and response to pain treatment, and several conclusions can be confidently drawn from the available evidence. First, the prevalence of most common forms of pain is higher among women than men, and women report greater pain after invasive procedures than men, though these findings are less consistent. Second, compared with men, women display enhanced sensitivity to most forms of experimentally induced pain (with the exception of is-chemic pain). Although this has been noted in previous reviews,^{127,327} a substantial increase in the number of studies has occurred, some of which have used more clinically relevant experimental pain models. For example, findings indicate that women show more robust temporal summation of pain and experience higher levels of pain after intramuscular injection of algescic substances, such as glutamate and hypertonic saline. Also, only recently has evidence emerged indicating that men may exhibit greater DNIC than women, and recent findings suggest that DNIC may be particularly predictive of clinical pain.^{101,108,453} Additional data regarding sex differences in responses to analgesic medications have been quite mixed and general conclusions are difficult to draw. We have also discussed multiple “biological” and “psychosocial” mechanisms that may contribute to sex differences in pain and analgesic responses, including gonadal hormones, endogenous pain modulatory systems, gender roles, and cognitive/affective factors.

Although research regarding sex, gender, and pain has continued to expand and generate novel findings, to date there has been limited clinical impact of this new knowledge. We would like to highlight several issues, consideration of which could promote more rapid progress in the field. First, without compelling scientific justification limited research to one sex or the other, both preclinical and human studies should routinely include subjects of both sexes. The NIH requires this for human studies; however, nonhuman pain research continues to eschew females.^{32,283} Given that the clinical pain conditions to which preclinical research is intended to apply are female-predominant, one could argue that preclinical research that excludes females is incomplete at best and invalid at worst. Moreover, clinical studies, which typically include participants of both sexes, should consistently analyze for sex differences and report the findings, whether positive or negative. This would help overcome publication biases, which could overestimate sex differences based on the reduced likelihood of reporting negative findings. Another important conceptual and analytical concern is the distinction between qualitative and quantitative sex differences. Most of the studies reviewed above address

quantitative differences, which refers to whether females and males display different amounts of pain or analgesia. In contrast, qualitative sex differences are present when a given variable influences pain or analgesia differently in women versus men. Because qualitative differences may indicate sex-specific pain mechanisms they represent the most compelling rationale for the development of sex-specific pain treatments. Thus, even in the absence of quantitative sex differences, researchers should conduct analyses to uncover potential qualitative sex differences, which simply involves including sex as a moderator in the statistical model.

In this era of translational science, an important goal for future research in this area is to generate information that will enhance pain treatment for both sexes. Despite the challenges of translational research, several opportunities that could be exploited to enhance translation have previously been suggested.¹¹⁸ For example, human laboratory pain models and genetic research could both serve as translational bridges between laboratory findings from nonhuman animals and clinical populations. For example, Mogil and colleagues²⁸⁴ successfully translated a novel sex-related genetic association (ie, the melanocortin-1-receptor gene, *MC1R*) with analgesic responses across species using experimental pain models in both mice and humans. To complete the translational continuum, it is important to determine whether sex-related genetic associations such as these discovered in the laboratory setting will extend to clinical populations. Human brain imaging represents another methodology that holds promise for facilitating mechanistic and translational advancements, and increased application of imaging to enhance understanding of sex differences in pain and analgesia is strongly recommended. We would like to echo the important issues demanding future investigation as delineated in the recent consensus report from the IASP Special Interest Group on Sex, Gender, and Pain, including identifying hormonal versus chromosomal contributions to sex differences in pain/analgesia; understanding the contribution of local (versus gonadal release) hormonal effects; elucidating the role of psychological factors; understanding whether pain chronicity contributes to sex differences; distinguishing the roles of sexual dimorphism in ascending versus descending modulatory pathways; determining the cellular and molecular bases of sex differences in pain/analgesia; understanding sex differences across the lifespan; and considering whether diagnostic criteria for some pain disorders should be sex-specific.¹⁶⁸ Empirical attention to these issues will further advance knowledge regarding sex, gender, and pain and could lead to sex-specific enhancements in clinical pain management in the not too distant future.

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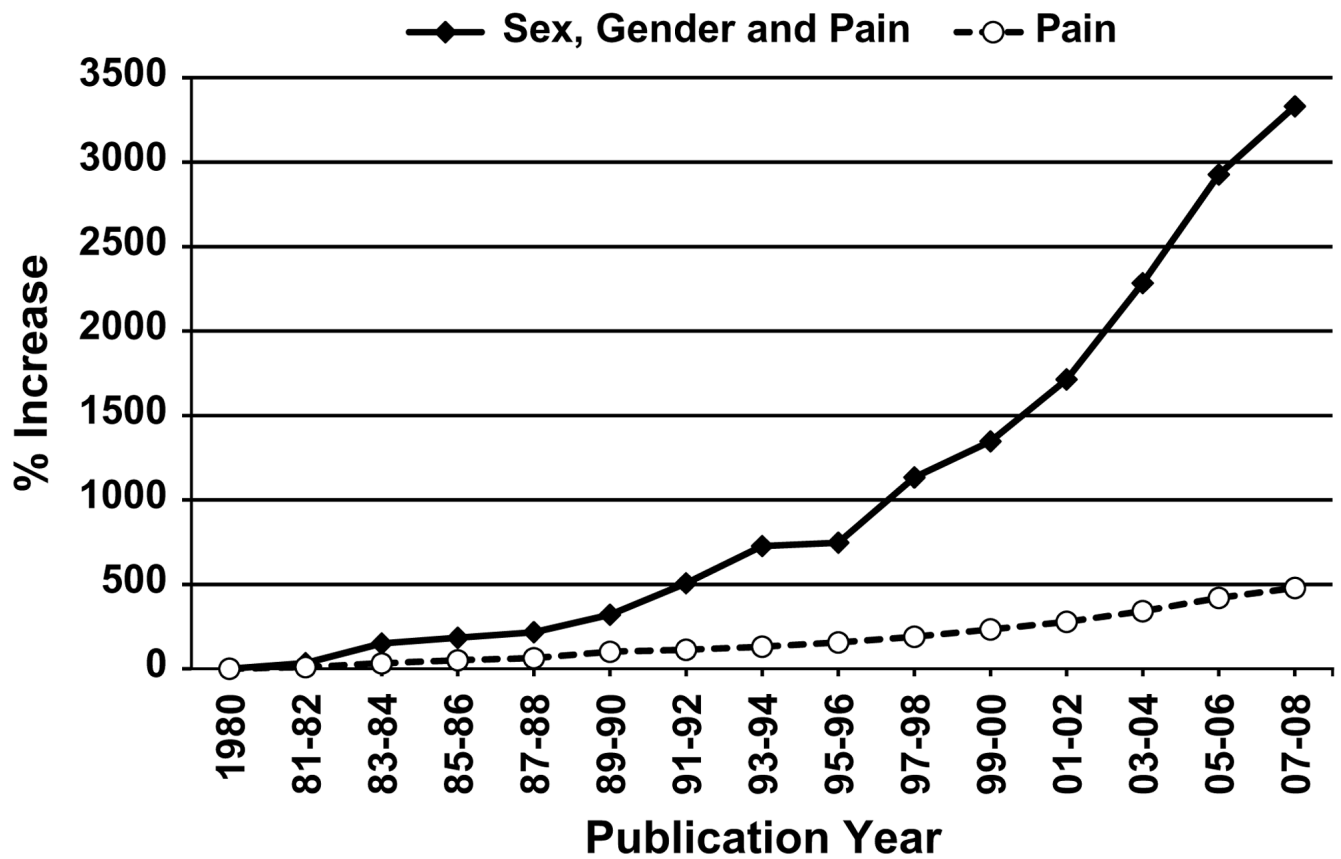


Figure 1. Average annual percentage increase in publications over each 2-year period after 1980, which served as the reference year. These percentages were computed by conducting literature searches using PubMed for every year since 1980. For 2008, the first 6 months was collected and doubled to obtain an annualized estimate. The PubMed search for Sex, Gender, and Pain was completed using the following Boolean combination (Sex differences OR Gender differences) AND Pain.

Table 1
Prevalence of Chronic Pain in Representative Samples

Study	Country	Prevalence	Female	Male
Bergman ³⁰	Sweden	12-month	38%	31%
Blythe ⁴¹ , *	Australia	6-month	20%	17%
Bouhassira ⁴⁴	France	Current	35%	28%
Breivik ⁴⁷	Europe	6-month	11%	10%
Gerdle ¹⁵⁸	Sweden	3-month	59%	48%
Rustoen ³⁵¹	Norway	Current	28%	23%
Smith ³⁷⁷	United Kingdom	Current	52%	49%
Tsang ⁴¹⁵	17 countries	12-month	45%	31%
Von Korf ⁴²⁷	United States	12-month	20%	18%
Wijnhoven ⁴⁴²	Netherlands	12-month	49%	41%

NOTE. **Bolded** numbers reflect significant sex differences in prevalence.

* Blyth et al did not indicate the significance of the difference.

Table 2
Prevalence of Widespread Pain in Representative Samples

Study	Country	Prevalence	Female	Male
Bergman ³⁰	Sweden	Chronic	15%	8%
Buskila ⁵³	Israel	Chronic	14%	3%
Gerdle ¹⁵⁷	Sweden	1-week	34%	22%
Hardt ¹⁷⁹	United States	1-month	4%	3%
Thomas ⁴⁰³	United Kingdom	1-month	5%	3%
Winjhoven ⁴⁴²	Netherlands	current	12%	6%
Winjhoven ⁴⁴²	Netherlands	1-year	20%	11%
Winjhoven ⁴⁴²	Netherlands	Chronic	4%	1%

NOTE. **Bolded** numbers reflect significant sex differences in prevalence.

Table 3
 One-Year Prevalence in National Representative Samples of Migraine Headaches

Study	Country	Female	Male
Dahlof ⁷⁹	Sweden	17%	10%
Deleu ⁹⁰	Saudi Arabia	6%	5%
Hagen ¹⁷⁴	Norway	16%	8%
Henry ¹⁸⁵	France	11%	4%
Kececi ²¹⁰	Turkey	17%	8%
Lipton ²⁵³	United States	18%	7%
Lipton ²⁵¹	United States	17%	6%
Steiner ³⁸⁵	England	18%	8%
Takeshima ³⁹⁹	Japan	9%	2%
Wang ^{431,*}	China	5%	1%

NOTE. **Bolded** numbers reflect significant sex differences in prevalence.

* Older population (65 years and older).

Table 4
Sex Differences in Postoperative Pain and Procedural Pain

Study Author	Surgical Procedure	Sample Size (F,M)	Time/Pain Measure, (Sex Difference)
Chia ⁶⁷	Outpatient surgery	1444, 854	VAS day 1 (F = M); D2 (F < M); D3 (F = M)
De Cosmo ⁸²	Cholecystectomy	49, 31	24 h post: VAS rest, F > M, VAS, cough F > M
Lau ²³⁵	Endoscopic hernia repair	18, 491	VAS rest, days 1, 3–5 (F > M), D2 (F = M); VAS cough D1–5 (F > M)
Lee ²⁴¹	Colonoscopy	431, 569	24 h post. Rated as mild, moderate, severe (F > M)
Liem ²⁵⁰	Hernia repair	48, 944	chronic pain 1-y post (F = M)
Mattila ²⁶⁹	Outpatient surgery	1394, 750	Week post surgery. VRS pain (F > M); headache (F > M); backache (F > M)
Mattila ²⁶⁹	Outpatient surgery	238, 320 ^a	Week post surgery. VRS headache (F > M)
Nikolajsen ²⁹⁷	Total hip arthroplasty	294 (total) ^b	12–18 mo post. Chronic pain (F = M); NRS (F = M); Constant pain (F > M); Disabling pain (F = M)
Ritter ³²⁹	Knee arthroplasty	4379, 2947	Pre-post. 0–100 VAS (F > M)
Rosseland ³⁴⁶	Knee arthroscopic repair	86, 133	2 h post. 5-point VRS (F > M), 0–100 VAS (F = M)
Rosseland ³⁴⁵	Knee arthroscopic repair	46, 54	1 year post. Prevalence of pain (F = M)
Smith ³⁷⁸	ICD implant	60, 180	1 day post. Pain severity (F > M)
Taenzer ³⁹⁸	Knee arthroscopic repair	186, 230	VAS day 1 (F > M), days 2, 3 (F = M)
Uchiyama ⁴¹⁷	Cholecystectomy	54, 46	VAS 24 h post (F > M) VAS 48 h post (F > M)
Vetthus ⁴²⁵	Gallbladder removal	214, 49	60 mo post. Prevalence (F = M)

Abbreviations: VAS, visual analogue scale; NRS, numerical rating scale; VRS, verbal rating scale.

^aKey: = children,

^b = Male/female composition not reported.

Table 5
 Studies Examining Sex Differences in Pressure, Electrical, and Ischemic Experimental Pain Models

Authors	Sample Size (M/F)	Stimulation Site	Method	Threshold*	Tolerance*	Ratings [†]
Pressure pain						
Ayesh et al ¹⁹	24/19	F	PA	F = M	M > F	—
Chesterton et al ⁶⁶	120/120	H	PA	M > F	—	—
Ellermeir and Westphal ¹¹¹	18/18	FNG	PA	—	—	F > M
Fillingim et al ¹²³	39/49	T, M, U	PA	M > F	—	—
Fillingim et al ¹³²	39/61	T, M, U	PA	M > F	—	—
Garcia et al ¹⁴¹	12/18	TP	PA	M > F	—	—
Komiyama and De Laat ²²⁷	16/16	M, H	PA	M > F	M > F	F = M
Komiyama et al ²²⁸	44/44	M, H, L	PA	M > F	M > F	F > M
Nie et al ²⁹⁵	12/12	H	CCPS	F = M	—	F = M
Electrical pain						
al' Absi et al ¹	59/40	FA	ES	M > F	M > F	—
Ashina et al ¹⁴	9/12	T, TM	ES	M > F	M > F	—
Ayesh et al ¹⁹	24/19	F	ES	F = M	—	—
Nyklicek et al ²⁹⁸	26/23	FA	ES	M > F	M > F	—
Ischemic pain						
Bragdon et al ⁴⁵	22/20	A	SETT	F = M	F = M	—
Edwards et al ¹⁰⁷	83/115	A	SETT	F = M	F = M	—
Fillingim and Maixner ¹²⁸	25/23	A	SETT	F = M	M > F	F = M
Fillingim et al ¹²³	39/49	A	SETT	F = M	F = M	—
Fillingim et al ¹³²	39/61	A	SETT	F = M	F = M	—
Girdler et al ¹⁶¹	40/37	A	SETT	M > F	M > F	F = M

Abbreviations for stimulation sites: A, arm; F, face; FA, forearm; FNG, finger; H, hand; L, Leg; M, masseter muscles; T, trapezius muscles; TM, temporal muscle; U, Ulna.

Abbreviations for methods: CCPS, computer controlled pressure stimulator; ES, electrical stimulation; PA, pressure algometry; SETT, submaximal effort tourniquet test.

* Lower levels of threshold and tolerance in females indicate greater pain sensitivity.

[†] Higher subjective ratings in females indicate greater pain sensitivity.

Table 6
Studies Examining Sex Differences in Thermal Experimental Pain Models

Authors	Sample Size (M/F)	Stimulation Site	Method	Threshold*	Tolerance*	Ratings [†]
Thermal pain – heat						
al' Absi et al ⁵	15/11	FA	CH	M > F	M > F	F > M
Bragdon et al ⁴⁵	22/20	A	CH	M > F	M > F	—
Edwards et al ¹⁰⁵	28/51	FA	CH	M > F	M > F	—
Edwards et al ¹⁰⁷	83/115	FA	CH	M > F	M > F	—
Fillingim and Maixner ¹²⁸	25/23	FA	CH	M = F	M = F	F > M
Fillingim et al ¹³⁰	22/27	FA, F	CH	M = F	M > F	M = F
Fillingim et al ¹²¹	92/117	FA	CH	M > F	M > F	—
Fillingim et al ¹²⁶	20/20	FA	CH	M > F	M > F	—
Fillingim et al ¹²³	39/49	FA	CH	M > F	M > F	—
Fillingim et al ¹³²	39/61	FA	CH	M > F	M > F	—
George et al ¹⁵⁶	16/17	A	CH	M = F	M > F	—
Girdler et al ¹⁶¹	40/37	A	CH	M > F	M > F	—
Jensen and Petersen ¹⁹⁸	44/41	FA	CH	M = F	—	F > M
Jones et al ²⁰⁵	69/75	FA	CH	M = F	M > F	—
Kim et al ²²³	194/306	FA	CH	—	—	F > M
Kim et al ²²²	248/369	FA	CH	—	—	F > M
Nielsen et al ²⁹⁶	78/110	FA	CH	—	—	M = F
Paulson et al ³¹²	10/10	FA	CH	—	—	F > M
Sarlanti et al ³⁶⁰	20/20		HWI	—	—	F > M
Thompson et al ⁴⁰⁵	37/88	H	CH	M > F	M > F	—
Toussignant et al ⁴¹²	42/41	H	CH	—	—	F > M ³
Wise et al ⁴⁴⁴	61/87	FA	CH	M > F	M > F	—
Thermal pain – cold						
al' Absi et al ⁴	31/34	H	CPT	—	—	F > M
al' Absi et al ³	72/80	H	CPT	—	—	F > M
al' Absi et al ⁵	15/11	H	CPT	—	—	F > M
Baad-Hansen et al ²⁰	20/34	H	CPT	—	—	M = F

Authors	Sample Size (M/F)	Stimulation Site	Method	Threshold*	Tolerance*	Ratings [†]
Dixon et al ⁹⁵	91/112	H	CPT	—	M > F	M = F
Edwards et al ¹⁰⁷	83/115	H	CPT	M > F	M > F	—
George et al ¹⁵⁴	32/34	H	CPT	M > F	M > F	—
Jackson et al ¹⁹⁵	34/57	H	CPT	—	M > F	F > M
Jones et al ²⁰⁵	69/75	H	CPT	M = F	M > F	F > M
Keogh et al ²¹⁹	50/50	H	CPT	M = F	M > F	—
Keogh et al ²¹⁶	31/31	H	CPT	M > F	—	—
Kim et al ²²³	194/306	H	CPT	—	M > F	F > M
Kim et al ²²²	248/369	H	CPT	—	M > F	F > M
Lowery et al ²⁵⁷	42/39	H	CPT	M > F	M > F	F > M
Mitchell et al ²⁸²	20/24	H	CPT	—	M > F	F > M
Myers et al ²⁹⁰	54/50	H	CPT	—	M > F	M = F
Nielsen et al ²⁹⁶	78/110	H	CPT	M > F	M > F	—
Pud et al ³²⁰	15/19	H	CPT	M = F	M = F	F > M
Sarlanti et al ³⁶⁰	20/20	H	CPT	—	—	F > M
Thompson et al ⁴⁰⁵	37/88	H	CPT	M > F	M > F	—
Toussignant et al ⁴¹²	42/41	H	CPT	—	—	F > M
Weisenberg et al ⁴³⁶	40/40	A	CPT	—	M > F	F > M
Zimmer et al ⁴⁵⁵	39/37	H	CPT	—	M > F	M = F

Abbreviations for stimulation sites: A, arm; F, Face; FA, forearm; H, hand.

Abbreviations for methods: CH, contact heat; CPT, cold water test; HWI, hot water immersion.

* Lower levels of threshold and tolerance in females indicate greater pain sensitivity.

[†] Higher subjective ratings in females indicate greater pain sensitivity.

[‡] Females required a lower temperature to produce moderate pain

Table 7
Studies Examining Sex Differences in Experimental Pain Models of Temporal Summation

Authors	Sample Size (M/F)	Stimulation Site	Method	Summation
Temporal summation – heat				
George et al ¹⁵⁶	16/17	A	CH	F > M
Fillingim et al ¹³⁰	22/27	FA, F	CH	F > M
Robinson et al ³³⁸	30/37	H	CH	F > M
Staud et al ³⁸⁴	11/22	H	CH	F = M
Temporal summation – mechanical				
Nie et al ²⁹⁵	12/12	L, H	CCPS	F = M
Sarlani and Greenspan ³⁶³	10/10	Fng	CCPS	F > M
Sarlani et al ³⁶²	25/25	Fng	CCPS	F > M
Sarlani et al ³⁶¹	36/27	Fng	CCPS	F > M
Spatial summation				
Lautenbacher et al ²³⁸	20/20	FA	CH	F = M
Martikainen et al ²⁶⁸	6/14	H	CPT	F = M
Defrin et al ⁸⁹	12/12	L	CH	F = M

Abbreviations for stimulation sites: A, arm; F, face; FA, forearm; Fng, finger; H, hand; L, leg.

Abbreviations for methods: CH, contact heat; CPT, cold water test; CCPS, computer controlled pressure stimulator; HWI, hot water immersion.

Table 8
Studies Examining Sex Differences in Experimental Models of Chemical and Muscle Pain

Authors	Sample Size (M/F)	Stimulation Site	Chemical	Pain Ratings
Capsaicin pain				
Baad-Handen ²⁰	20/34	IO	CAP	F < M*
Gazerani et al ¹⁴³	14/14	F	CAP	F > M
Gazerani et al ¹⁴⁴	14/14	FH, FA	CAP	F > M
Frot et al ¹³⁸	10/10	CK, ANK	CAP	F > M
Jensen and Petersen ¹⁹⁸	44/41	FA	CAP	F = M
Muscle pain (glutamate and hypertonic saline)				
Cairns et al ⁵⁴	18/20	M	GLU	F > M
Cairns et al ⁵⁵	11/13	M	GLU	F > M
Falla et al ¹¹³	9/9	T	HS	F > M
Gazerani et al ¹⁴⁵	15/15	FH	GLU	F > M
Ge et al ¹⁴⁷	11/10	T, PN	HS	F > M
Ge et al ¹⁴⁶	10/9	T	GLU	F > M
Ge et al ¹⁴⁸	14/14	T	GLU	F > M
Ge et al ¹⁴⁹	15/15	T, PN	HS	F > M
Svensson et al ³⁹⁶	18/17	M	GLU	F > M

Abbreviations for stimulation sites: ANK, ankle; CK, cheek; F, face; FA, forearm; FH, forehead; M, masseter muscles; IO, intraoral; PN, posterolateral neck muscles; T, trapezius muscles.

Abbreviations for methods: Cap, Capsaicin; GLU, glutamate; HS, hypertonic saline.

* For women using oral contraceptives only.

Table 9
Studies Examining Sex Differences in Brain Activation to Experimental Pain

Authors	Sample Size (M/F)	Imaging Method	Pain Stimulus	Findings
Berman et al ³⁴	7/6	fMRI	Visceral pressure	M > F: Insula F > M: deactivation in amygdala, mid-cingulate
Derbyshire et al ⁹¹	11/10	PET	Heat (laser)	M > F: Contra PFC, S2, S1, insula F > M: Ipsi perigenual & ventral cingulate
Henderson et al ¹⁸⁴	11/11	fMRI	Hypertonic Saline	M > F: Cerebellar cortex F > M: Mid-cingulate, DLPFC
Hobson, et al ¹⁸⁹	8/8	MEG/EP	Esophageal Electrical	No sex differences
Moulton et al ²⁸⁵	11/17	fMRI	Contact Heat	F > M: Deactivation in S1, lt anterior insula, DLPFC
Naliboff et al ²⁹²	19/23*	fMRI	Visceral pressure	M > F: Rt. DLPFC, Insula, PAG F > M: Lt. VMPFC, rt. ACC, lt. amygdala
Paulson et al ³¹²	10/10	PET	Heat (contact)	F > M: Contra PFC, Insula, thalamus
Straube et al ³⁹⁵	12/12	fMRI	Electrical	F > M, MPFC M > F, IC

Abbreviations for imaging methods sites: fMRI, functional magnetic resonance imaging; MEG/EP, magnetoencephalography/evoked potentials; PET, positron emission tomography.

Abbreviations for findings (F > M, female > male): ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; PFC, prefrontal cortex; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; VMPFC, ventromedial prefrontal cortex.

Table 10
Studies Examining Sex Differences in Experimental Models of Pain Inhibition

Authors	Sample Size (M/F)	Primary Testing Stimulus (Site)	Conditioning Stimulus	Pain Inhibition
DNIC				
Baad-Hansen et al ²⁰	20/34	Cap (IO)	CPT (H)	F = M
Edwards et al ¹⁰⁸	29/48	TS-CH (A)	CPT (H)	F = M
France and Suchowiecki ¹³⁷	39/44	TS-NFR (L)	ISC (A)	F = M
Ge et al ¹⁴⁷	11/10	HS (T)	HS (Trap)	F < M
Granot et al ¹⁶⁵	21/10	CH (A)	CPT (H)	F < M
Martikainen et al ²⁶⁸	6/14	CPT (H)	CPT (H)	F = M
Pud et al ³¹⁹	23/17	MS (H)	CPT (H)	F = M
Quiton and Greenspan ³²¹	32/30	CH (L)	E (A)	F < M
Rosen et al ³⁴⁴	15/15	P, E (Fng, F)	CPT (H)	F = M
Serrao et al ³⁷¹	16/20	TS-NFR (L)	CPT (H)	F < M
Staud et al ³⁸⁴	11/22	TS-CH (H)	HWI (H)	F < M
Tousignant et al ⁴¹¹	42/41	CH (H)	CPT	F = M
Weissman-Fogel et al ⁴³⁹	19/29	CH (H)	MP (H)	F < M
Miscellaneous				
al' Absi et al ³	72/80	CPT (H)	PS	F = M
Bragdon et al ⁴⁵	22/20	ISC (A), CH (A)	IS	F = M
Girdler et al ¹⁶¹	40/37	CPT	TSST	F > M
Koltyn et al ²²⁶	15/15	P (Fng)	Exercise	F > M
Rhudy et al ³²⁴	20/20	RH (Fng)	Noise	F > M
Sternberg et al ³⁸⁷	19/22	CPT (A)	VG, Exercise	F < M VG; F > M Exercise

Abbreviations for stimulation sites: A, arm; F, face; Fng, finger; H, hand; L, leg; IO, Intraoral; T, Trapezius muscle.

Primary test stimulus: Cap, Capsaicin; CH, contact heat; CPT, cold pressor test; E, electrical stimulation; HS, Hypertonic saline; ISC, ischemic; MS, mechanical stimuli; P, pressure; RH, Radiant heat; TS-CH, temporal summation of contact heat pain; TS-NFR, temporal summation of nociceptive flexion reflex (electrical stimulus). Conditioning stimulus: CPT, cold pressor test; E, electrical stimulation; IS, Interpersonal stressor; ISC, Ischemic; HS, Hypertonic saline; HWI, hot water immersion; MP, muscle pain by physical effort; P, pressure pain; PS, Public speaking stressor; TSST, Trier Social Stress Test; VG, Video game.

NOTE. F > M indicates greater pain inhibition among females than males.

Table 11
Clinical Studies Regarding Sex Differences in Analgesic Responses

Authors	Sample Size (F, M)	Type of Pain	Medication	Findings
<i>μ</i> -opioids				
Aubrun et al ¹⁶	1933, 2344	Multiple surgeries	iv morphine	F > M morphine dose for analgesia
Bijur et al ³⁸	211, 144	Acute pain in ER	iv morphine (0.1 mg/kg)	F = M
Cepeda and Carr ⁶²	423, 277	Multiple surgeries	iv morphine	F > M morphine dose for analgesia
Chia et al ⁶⁷	1444, 854	Multiple surgeries	iv morphine (PCA)	F < M morphine consumption
Gagliese et al ¹⁴⁰	120, 126	Multiple surgeries	iv morphine (PCA)	F = M
Glasson et al ¹⁶²	106, 44	Cholecystectomy	iv morphine or meperidine	F = M (when weight adjusted)
Hirasawa et al ¹⁸⁷	15, 15	Spine surgery	iv morphine (PCA)	F < M morphine consumption
Joels et al ²⁰²	246, 235	Colectomy	iv morphine or meperidine	F < M opioid consumption
Kaiko et al ²⁰⁶	422, 293	Cancer Pain	im morphine (8, 16 mg)	F = M
Miller and Ernst ²⁸⁰	22, 24	Acute pain in ER	iv morphine (2.5–5 mg)	F = M (trend for ↑ analgesia in M)
Mixed-action opioids				
Gear et al ¹⁵³	69, 62	Oral surgery	iv nalbuphine (5, 10, or 20 mg)	F > M analgesia at 5, 10 mg doses
Gordon et al ¹⁶⁴	22, 12	Oral surgery	iv pentazocine (30 mg)	F > M analgesia
Miller and Ernst ²⁸⁰	23, 25	Acute pain in ER	iv butorphanol (0.5–1 mg)	F = M
Ryan et al ³⁵³	16, 12	Dental surgery	50 mg pentazocine, 0.5 mg naloxone (oral)	F > M analgesia
Other analgesics				
Averbuch and Katzper ¹⁷	195, 119	Oral surgery	oral ibuprofen	F = M
De Cosmo et al ⁸²	49, 31	Cholecystectomy	iv tramadol (PCA)	F > M tramadol consumption
Ryan et al ³⁵³	15, 14	Dental surgery	600 mg ibuprofen (oral)	F = M

Table 12
Experimental Studies Regarding Sex Differences in Analgesic Responses

Authors	Sample Size (F, M)	Medication	Type of Pain	Findings
μ -opioids				
Filligim et al ¹³²	61, 39	iv morphine (0.08 mg/kg)	Heat, pressure, ischemic pain	F = M
Olofsen et al ³⁰³	8, 8 (E) 5, 5 (H)	iv alfentanil (30 min infusion to 150 ng/mL)	Electrical Heat Pain	F = M
Pud, et al ³²⁰	15, 19	Oral morphine (0.5 mg/kg)	Cold pressor	F = M (placebo controlled)
Romberg, et al ³⁴²	10, 10	iv M6 G (0.3 mg/kg)	Electrical	F = M
Sarton, et al ³⁶⁴	10, 10	iv morphine (0.13 mg/kg)	Electrical	F > M analgesia peak/duration
Mixed-action opioids				
Filligim et al ¹³³	41, 38	iv pentazocine (0.5 mg/kg)	Heat, pressure, ischemic pain	F = M
Zacny and Beckman ⁴⁵⁴	8, 8	iv butorphanol (0.5, 1, 2 mg/70 kg)	Cold pressor	F = M (M > F trend)
Nonopioid analgesics				
Walker and Carmody ⁴³⁰	10, 10	Oral ibuprofen 800 mg	Electrical	M > F
Compton et al ⁷²	25, 25	oral ketorolac 10 mg	Cold pressor	F = M
Robinson et al ³³⁴	23, 21	lidocaine iontophoresis	Pressure pain	M > F