Gender Differences in Pain

Thuan T. T. Dao, DMD, MSc, Dip Prostho, PhD
Associate Professor
Faculty of Dentistry
University of Toronto
Toronto, Ontario, Canada

Linda LeResche, ScD
Research Professor
Department of Oral Medicine
University of Washington
Seattle, Washington

Correspondence to:
Dr Thuan T. T. Dao
Faculty of Dentistry
University of Toronto
124 Edward Street
Toronto, Ontario
Canada M5G 1G6
Fax: 416-979-4936
E-mail: thuan.dao@utoronto.ca

A review of the literature on gender and clinical pain reveals a disproportionate representation of women receiving treatment for many pain conditions and suggests that women report more severe pain, more frequent pain, and pain of longer duration than do men. Gender differences in pain perception have also been extensively studied in the laboratory, and ratings of experimentally induced pain also show some sex disparity, with females generally reporting lower pain thresholds and tolerance than males. However, there is little consensus on whether these apparent differences reflect the way men and women respond to pain, differing social rules for the expression of pain, or biologic differences in the way noxious stimuli are processed. In this paper, our working hypothesis is that the higher prevalence of chronic orofacial pain in women is a result of sex differences in generic pain mechanisms and of as-yet unidentified factors unique to the craniofacial system. We will review the evidence concerning gender differences in the prevalence of pain conditions, with a focus on orofacial pain conditions. Evidence and hypotheses concerning biologic and psychosocial factors that could influence prevalence rates will also be discussed.
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With the obvious anatomic and genetic differences between males and females, many people intuitively believe that the sexes differ in their predisposition toward and responses to pain. This belief may have been perpetuated by the disproportionate representation of women receiving treatment for many pain conditions, and by studies that suggest that women report more severe pain, more frequent pain, and pain of longer duration than do men.[1-3] However, there is little consensus on whether these apparent variations reflect the way men and women respond to pain, differing social rules for the expression of pain, or biologic differences in the way noxious stimuli are processed. While several studies have attempted to address this controversy, the different patterns of sex-specific prevalence reported for various clinical pain disorders and the inconsistencies in the findings across experimental studies, as reviewed in this paper, highlight the fact that the gender issue is still unresolved and needs further exploration. This article will review the evidence concerning gender differences in the prevalence of pain conditions, as well as evidence and hypotheses concerning biologic and psychosocial

factors that could influence prevalence rates. Specifically, we will focus on chronic orofacial pain conditions, most of which show a significantly higher prevalence in women than in men.

Statement of Position

Our working hypothesis is that the higher prevalence of chronic orofacial pain in women versus men is a result of sex differences in generic pain mechanisms and as-yet unidentified factors unique to the craniofacial system.

Clinical Pain

Epidemiology

The volume of literature on clinical pain and gender is impressive. Overall, the information reveals some sex differences in the prevalence and manifestations of signs and symptoms of a variety of pain disorders. For instance, as summarized by Berkley,[4] several conditions in which chronic pain is a prominent component appear to be associated with a higher female prevalence. The number of such conditions is more than twice that of disorders that have a male predilection. Interestingly, many of the pain conditions that primarily affect women are still of unknown origin. Some involve the cardiovascular system (carotidynia, Raynaud's disease, chronic venous insufficiency, and migraine headaches, especially migraine without aura) and gastrointestinal structures (irritable bowel syndrome, esophagitis, reflux esophagitis with peptic ulcer, proctalgia fugax, chronic constipation), while a large number are expressed in the head and neck region. These include temporomandibular disorders (TMD), various types of headaches (with the exception of cluster and post-traumatic headaches, which have a male predilection), occipital neuralgia, hemicrania continua, chronic paroxysmal hemicrania, atypical odontalgia, burning mouth syndrome, and probably trigeminal neuralgia. With regard to pain induced by dental treatments, the perception of general pain intensity, analgesic consumption, pain when eating, and the influence of discomfort on daily life were all significantly greater in girls than in boys who received orthodontic treatments.[5] Most studies of musculoskeletal pain indicate that women are more likely to report musculoskeletal pain than men. However, some studies of neck, shoulder, back, and knee pain indicate equal prevalence among the 2

sexes, or, in a few cases, a higher rate in males than in females.[6] These conditions may be more strongly related to occupation than to gender.[2] However, it is important to note that pain disorders do not always have a female predilection. In fact, if we rely on the list provided by Berkley,[4] the disorders with no sex predilection added to those with higher male prevalence outnumber those associated with higher female predilection. This is consistent with the extensive review on gender and clinical pain experience published recently by Unruh.[2]

It is also important to point out that the prevalence of most pain disorders varies greatly with age, as well as with gender (eg, the probability of experiencing migraine headache is similar for boys and girls at age 12, whereas a 30-year-old woman is much more likely than a 30-year-old man to experience this kind of pain). Thus, the fact that there are gender differences (across all age groups) in the prevalence of a given pain condition may not be as informative as data on the overall sex- and age-specific prevalence pattern of that pain.[7] An analysis of prevalence by both age and sex allows us to identify factors that vary across the life span (eg, hormonal state, occupational role) that may possibly interact with gender to increase the risk of developing particular pain conditions.

Gender Differences in the Epidemiology of Chronic Orofacial Pain Conditions

Temporomandibular disorder pain is the most common chronic orofacial pain condition. It is rare in children prior to puberty.[8] Prevalence rates found in population-based epidemiologic studies range from about 8% to 15% for women and from about 3% to 10% for men. Given differences in definitions and in populations examined in the different studies, these rates are remarkably consistent. In nearly every study, TMD pain is found to be 1.5 to 2 times more common in women than in men. Also, in all studies where there is a clear pattern for age-specific prevalence, the age of peak prevalence is around 35 to 45 years.

Population-based data on trigeminal neuralgia come primarily from 2 studies that measured the rates of seeking treatment for these conditions in 2 defined areas of the United States.[9,10] To the extent that people with trigeminal neuralgia consistently seek treatment for their problem, rates found in these "treated incidence" studies approximate true population-based incidence (onset) rates. However, if not all cases come to treatment, the rates and gender patterns may differ from those that

would be found in a survey of the general population. Overall incidence rates are on the order of 3 to 5 onsets per year per 100,000 people (about 1/500 to 1/1,000 the rate of onset of TMD pain). The incidence rate rises with age in both studies, but one study shows a large sex difference, with higher rates in women, while the other shows a much smaller difference.

Burning mouth pain has been investigated in a handful of population-based studies. These investigations have employed different definitions of the problem, so the absolute rates vary greatly, from a low of 1% in a large study of the U.S. household population[11] that inquired about "a prolonged unexplained burning sensation in your tongue or any other part of your mouth," to a high of almost 15% in a study of Finns over 30 years of age that asked about smarting and tickling sensations, as well as burning, due to any cause.[12] A third study, which used a definition of burning pain from any cause, found an intermediate rate of 4.5%.[13] Both increasing age and female gender appear to be risk factors for burning mouth pain. Prevalence rates in women are about twice those in men.

Clinical studies of atypical odontalgia and atypical facial pain indicate that women are much more likely than men to seek care for these conditions, and that the mean age of persons seeking care is around 40 to 55 years. Unfortunately, there are no population-based studies of these conditions, and the extent to which these clinic populations reflect the underlying distribution of the conditions in the population is unknown.

Sex Differences in Symptom Expression

In addition to the data on pain prevalence by gender, there is also evidence suggesting that for several diseases, the presentation of illness may differ significantly by gender, with certain signs and symptoms being much more common in one sex than in the other. For instance, disc degeneration has been reported to be associated with neck pain in men but not in women.[14] Migraine without aura is twice as prevalent in women as migraine with aura, while the opposite is true for men.[15] Similarly, among patients diagnosed with acute myocardial infarction, men were significantly more likely than women to complain about neck, back, or jaw pains and nausea.[16] Different risk factors and predictors of diseases have also been observed for the 2 genders. For example, risk of low back pain increases with height among men but not among women.[17] For acute appendicitis, previous abdominal surgeries, rectal digital tenderness,

rebound, and elevated body temperature are significant predictors for men, but not for women, whereas the absence of renal tenderness is a good predictor for women but not for men.[18] Similarly, chest pain is a much poorer predictor of coronary artery disease in women with abnormal angiography[19] or positive thallium-20 scans than it is in men with these findings.[20]

Taken together, these data show that some pain disorders may not affect women and men the same way. Since gender is only 1 of the multiple factors that have a profound impact on clinical pain reports, inference about its specific role is at best tentative.

Methodologic Issues

While epidemiologic studies sometimes show an uneven sex distribution of pain disorders, they do not usually explain the nature of the differences and the causes for observed discrepancies. Most epidemiologic literature to date has been descriptive, and reports of gender differences are often presented as secondary findings in studies that were not originally designed to address the gender issue. Sometimes the gender distribution is reported only as part of the sociodemographic description of the study population, and prevalence rates are not reported by gender (or age). Clinical studies may also neglect to analyze outcomes by gender.

Other problems become evident when studies that report gender differences as incidental findings are reviewed (see Unruh[2]). In studies in which the gender composition of the sample is represented in percentages without statistical analysis, it is difficult to appreciate the significance of any apparent disparities. Gender differences found during the review process may be inflated since they are based on incidental findings on this topic, and these are more frequently reported when they can be statistically substantiated. The review may be similarly biased during the electronic retrieval of published papers, since those that use gender (or a synonym) as a keyword are more likely to surface, and these keywords are listed mostly when gender is considered an important aspect of the study or when gender differences have reached statistical significance.

On the other hand, clinical studies that focus specifically on the issue of gender and pain are often observational and may not be designed to provide explanations for the differences being investigated. The interpretation of the extensive literature on clinical pain prevalence is further
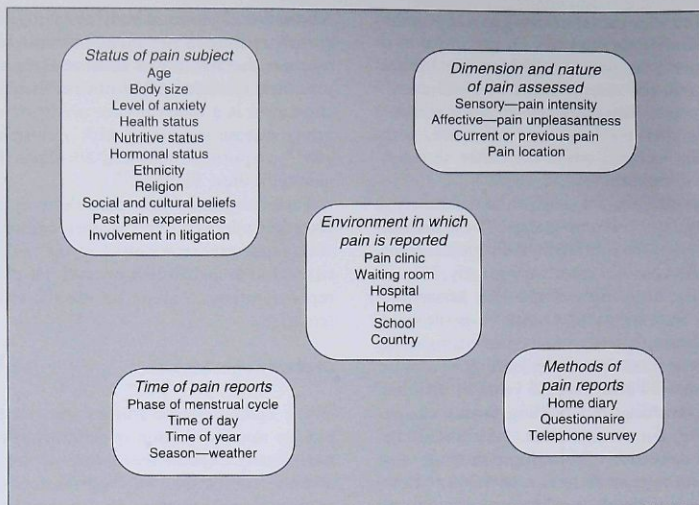
Fig 1 Interacting variables that influence clinical pain reports.

complicated with other methodologic issues, including the validity and reliability of pain measurement methods[21] and representativeness of study samples. The issue becomes more complex since pain assessment relies on perceptions and reports (from both the patients and the investigators) that are shaped by many variables other than gender. Some of these interacting variables are listed in Fig 1.

Data on gender prevalence may also vary across studies due to characteristics of the study samples. Data collected from population-based studies are less prone to bias than those obtained from clinical samples, industrial settings, occupational groups, or databases of insurance companies, since they are less influenced by factors that are specific to the nature of the sample. For instance, it has been argued that the overrepresentation of women with chronic orofacial pain in clinical samples does not necessarily reflect the true gender ratio of these pain conditions, but may instead reflect the possibility that female patients more readily seek treatment.[7] Although the data on gender differences in health care utilization for orofacial pain conflict,[13,22,23] Unruh's review suggested that for a variety of health problems, women report more visits and more return visits than do men.[2] This is

consistent with the results of a survey showing that among chronic pain patients, women used health care services more often than men.[24] Similarly, Linton et al also reported that when spinal pain was at its worst, men took sick leave, whereas women sought health care.[25] These data highlight the possibility that clinical samples may generate biased findings on gender prevalence in pain; the importance of using population-based samples to study gender differences in pain is thereby reinforced.

Experimental Pain

Gender differences in pain have also been studied extensively in the laboratory, where standardized protocols allow control for some variables that can influence pain reports. Fillingim and Maixner[26] reviewed a large number of psychophysical studies (ie, studies of the relationship between the physical properties of a pain stimulus and the sensory and behavioral responses of the subject). They concluded that, overall, females exhibit greater sensibility to laboratory pain compared to males. In a review,[4] Berkley also concluded that women have lower thresholds, rate similar stimuli as more

painful, and have less tolerance for intense stimuli. However, both papers pointed out that findings are not always consistent across studies. While mechanical pressure, electrical stimuli, and cold pressor stimulation are more reliable in producing higher pain ratings in females, studies using thermal stimuli (other than cold pressor) have generated conflicting data. This variability is not surprising, given the differences in experimental protocols, the diversity of noxious stimuli that have been employed (see Fillingim and Maixner[26]), and reports that sex differences in responsiveness to painful and non-painful stimuli are dependent on the stimulation method.[27] For instance, the duration and temporal sequence of application of the stimulus are important factors that affect study outcomes. For a stimulus of a given intensity, prolonged and repeated applications induce greater pain than a single, brief stimulus; in addition, they are more likely to activate temporal summation mechanisms, and temporal summation of thermal pain has been reported to be greater in females than in males.[28] The size of the stimulating tip is another important factor. If spatial summation is more pronounced and reaches a ceiling sooner in females than in males, sex differences in response to thermal stimuli may occur with small thermodes but not with larger ones.[27] Failure to find a gender disparity in many studies may also be a result of small sample size, which results in a lack of power to detect the difference being sought.[29]

Results may also differ depending on the dimension of pain being assessed and the environment in which the experiment takes place, since pain is a multidimensional experience with both sensory/discriminative and cognitive/emotional components. As discussed by Fillingim and Maixner,[26] it is possible that gender has a selective influence on these dimensions, while these, in turn, may be differently affected by various methods of pain induction. While the selective effect of gender on the sensory and affective dimensions of experimental pain has not been thoroughly investigated, it is well known that threshold and tolerance measures are susceptible to social environmental factors, including the gender of the experimenter,[30] the presence of other people, subjects' status and pain attitudes, instructional set,[31–33] and the clinical relevance of the laboratory settings.[34] In addition, responses to threshold and tolerance tests may be modulated by the subject's anxiety[35–38] and expectations of pain tolerance, both of which have been shown to differ between males and females.[39] Other psychophysical techniques, such as signal detection and magnitude matching procedures, allow the investigator to estimate separately both the sensory abilities of the subjects to discriminate different levels of stimuli and their willingness to report stimuli as painful (emotional or response bias). By normalizing responses to painful stimuli against ratings of standard stimuli in both painful and non-painful ranges, clinicians can control response bias. Although these approaches may be influenced less by attitudinal variables and represent a significant improvement over the threshold and tolerance measures, their results are still inconsistent across studies.[26] This is not unexpected, given the numerous factors that may influence responses to experimentally delivered noxious stimuli. Some of the biologic, psychosocial, and cultural factors are already listed in Fig 1; other variables more specific to a laboratory setting are included in Fig 2.

Overall, ratings of experimentally induced pain do show some sex disparity, and females generally report lower pain thresholds and tolerance than males. However, these differences are often small and observed inconsistently, most likely because of differences in the methodology employed and the numerous variables that influence pain reports in a laboratory environment. In this context, the clinical relevance of these findings remains limited. What remains to be determined is the extent to which the contrast observed reflects a response bias phenomenon shaped by various psychologic, social, and cultural factors or biologic differences in pain-processing mechanisms.

Possible Mechanisms Underlying Gender Differences in Pain

Biologic Factors

While the debate continues over the controversies about the various aspects of sex disparity in pain, it is difficult to disagree with the vivid remark made by Berkley[4] that ". . . females and males do differ virtually absolutely and unarguably in three aspects of their reproductive biology. Their pelvic reproductive organs differ and their hormonal conditions differ chronobiologically and compositionally." The potential impact of those biologic differences on pain will be discussed below.

Effect of Gonadal Hormones on Pain. An obvious gender difference is the characteristic temporal fluctuations of hormonal states in females and the frequent occurrence of pain associated with the reproductive cycle, ie, menstruation and ovulation. In addition to these non-pathologic pains, many
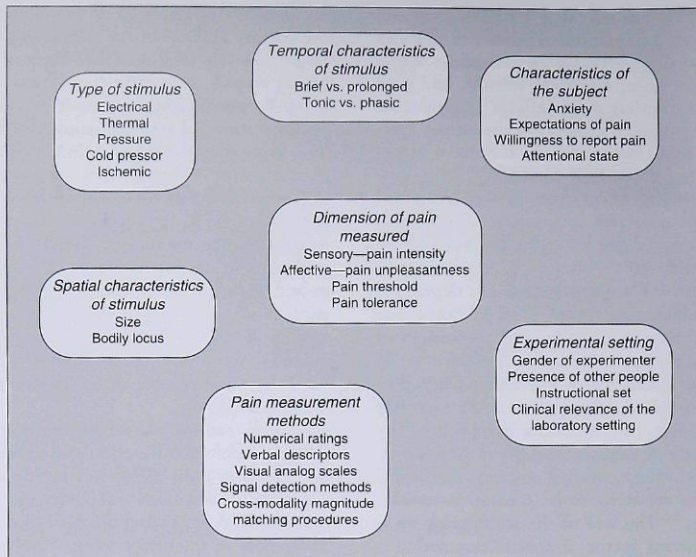
Fig 2 Factors that contribute to variability in responses to experimentally delivered noxious stimuli.

disorders have been reported to fluctuate with the menstrual cycle, including pain at the trigeminal level, ie, recurrent headaches,[40] myofascial pain,[41] and various medical conditions such as rheumatoid arthritis and other autoimmune diseases.[42,43] As an example, for approximately 60% of migraine sufferers, headache worsens around the premenstrual phase of the menstrual cycle, and 14% of women with migraine experience headache only with menses.[40] Estrogen replacement therapy can exacerbate migraine during menopause,[44,45] while oral contraceptives can change its character and frequency by inducing, changing, or even alleviating the headache crises.[45] Since fluctuations in hormonal levels have been suspected to account for the cyclic changes in some chronic conditions (eg, asthma, irritable bowel, and diabetes), medical suppression of ovulation through the use of gonadotropin-releasing hormone agonists has been proposed for both the diagnosis and treatment of these conditions.[43,46] Another example of possible pain modulation by hormonal states is illustrated in a recent paper showing that pain levels in myofascial patients who used oral contraceptives were significantly

more stable over time than those reported by non-users.[47] The connection between reproductive hormones and pain is also highlighted by data that suggest that the risk of TMD pain and low back pain increases with the use of exogenous hormones.[48–51]

The influence of hormonal changes on pain sensitivity has also been evaluated with various experimental techniques, including thermal stimuli, cold pressor, ischemic pain, electrical stimuli, and pressure pain. However, the patterns vary considerably across experiments (Table 1). Some studies reported greater sensitivity at ovulation[52–55] or during the premenstrual,[55–58] menstrual,[55,59–61] or luteal phase,[54] while others failed to show significant changes in pain thresholds across the menstrual cycle.[62–64] Many of these studies of pain and menstrual cycle phase suffer from limitations in study design. For example, some studies that failed to find differences across the cycle had small sample sizes. Many of the studies did not determine when, or even whether, ovulation occurred, making it difficult to assess accurately the phase of the cycle. Nevertheless, most studies found some variability in pain response across the menstrual cycle.

Table 1   Effect of the Menstrual Cycle on Pain Sensitivity

Study	Stimulus	Phase of cycle associated with greatest pain
Herren, 1933[56]	Pressure	Premenstrual
Kenshalo, 1966[57]	Cold	Premenstrual
Procacci et al, 1973[58]	Electrical	Premenstrual
Tedford et al, 1977[59]	Electrical	Menstrual
Kuczmierczyk and Adams, 1986[60]	Pressure	Menstrual
Hapidou and De Catanzaro, 1988[61]	Cold pressor	Menstrual
Goolkasian, 1980/1983[52,53]	Heat	Ovulation
Fillingim et al, 1997[54]	Ischemia	Ovulation and luteal phase
Veith et al, 1984[62]	Electrical and cold pressor	No identified pattern
Amodei and Nelson-Gray, 1989[63]	Pressure	No identified pattern
Giamberardino et al, 1997[55]	Electrical	Periovulatory for skin, menstrual/premenstrual for muscle
Hapidou and Rollman, 1998[64]	Pressure	No identified pattern

Interestingly, the periodic fluctuations in pain thresholds detected during the normal hormonal cycle are not observed during oral contraceptive therapy.[57,58,61] Similar results have been obtained in animal studies. As an example, in the female rat, nociceptive thresholds (as assessed by the tail flick test) appeared lowest during estrus and metestrus.[65] The nociceptive cycle was halted by ovariectomy,[65] while the pain threshold was elevated in the presence of high levels of sex steroids, ie, during pseudopregnancy[66] or in hormonally treated animals after ovariectomy.[67]

In summary, both endogenous and experimentally delivered pains seem to show cyclic changes with the unaltered estrous cycle, but not when hormonal fluctuation has been relatively stabilized with exogenous hormone supplementation. Although these clinical and experimental observations appear to support the role of gonadal hormones in the modulation of pain, they also highlight the lack of consensus regarding which phase of the menstrual cycle is associated with greater or lesser pain sensitivity. Nevertheless, given the marked difference in the relative composition of sex hormones between men and women, the periodic fluctuation of some pain disorders across the hormonal cycle, the large variation in levels of estrogen and progesterone across the menstrual cycle, and the interaction between these hormones and various neuroactive agents implicated in pain-processing mechanisms, it is not unreasonable to assume that sex hormones may play an important role in generating gender differences in pain.

Interaction Between Neuroactive Agents and Gonadal Hormones. Although the exact mechanism by which the gonadal hormones modulate menstrual headaches is still unclear, their interactions with various neuroactive agents implicated in pain mechanisms have been described. For instance, serotonin has been shown to play an important role in the pathophysiology of headache, and its levels vary positively with plasma estradiol, estrone, and estrogen.[68] The interaction of serotonin with female sex hormones is further illustrated by reports that the number of available serotonin receptors, their binding capacities, and their functional status are all associated with changes in estrogen levels.[69,70] Norepinephrine, another neurotransmitter important in the development of headache, has also been reported to be linked to sex hormones, both anatomically and functionally. Heritage et al[71] reported that brain stem catecholamine neurons, which contain primarily norepinephrine, are target sites for estradiol, and catecholamine nerve terminals are co-localized with steroid hormone target neurons in the midbrain and diencephalon. Moreover, norepinephrine levels and functions have been shown to change with the estrous cycle and with experimental alterations of the levels of sex hormones in the rat. The interactions between serotonin, norepinephrine, and sex hormones have been thoroughly reviewed by Marcus.[40]

The association between estrogen and nitric oxide (NO) has also been suggested as a possible source of gender differences in pain,[47] and the release of NO following estrogen intake has been the focus of numerous studies. For instance, a randomized, placebo-controlled, crossover study showed that the production of NO increased significantly in women of reproductive age who used exogenous estrogen for 8 days.[72] Similar results

were obtained in other controlled clinical trials: endogenous levels of NO and its stable substrate (nitrite/nitrate) increased significantly in peri-menopausal women after 8 weeks of estrogen supplementation[73] and in postmenopausal women undergoing 21 days of hormone replacement therapy.[74] While these data confirm that exogenous estrogen can increase circulating levels of NO, the involvement of NO in pain processing has also been thoroughly reviewed.[75,76] At the trigeminal level, NO supersensitivity has been proposed as a possible molecular mechanism of migraine pain.[77–79] Continuous intravenous infusion of a NO donor (nitroglycerin) caused a dose-dependent and reproducible headache in control subjects and patients with migraine and tension-type headaches during their remission phases, for the duration of the infusion.[77,80] A decrease in pain thresholds in the temporal region has also been observed following a systemic administration of nitroglycerin.[81] These data suggest NO as a possible molecule implicated in the pathophysiology of facial pain in women using exogenous hormone supplementation.

The Link Between Estrogen and Nerve Growth Factor. The nerve growth factor/estrogen link has been proposed as a possible mechanism for masticatory myalgias.[82] Nerve growth factor (NGF) is actively involved in many aspects of nociception, including the development and maintenance of the pain system, inflammation, and hyperalgesia.[83] Intravenous or subcutaneous injections of recombinant human NGF in healthy human volunteers caused muscle pain in the jaw, bulbar, and truncal musculature in a dose-dependent manner. Interestingly, women appeared to be more susceptible than men to NGF.[84] The possible gender difference in the action of NGF is further supported by reports that estrogen can affect the efficiency of NGF binding and regulate NGF sensitivity in neurotropin targets of adult dorsal root ganglia. In addition, estrogen receptors co-localize with receptors for NGF in cholinergic neurons of the basal forebrain,[85] and estrogen differentially regulates NGF receptor mRNA in adult sensory neurons.[86,87]

Contribution of the Sympathetic Nervous System. In addition to the interaction between neurochemical agents and gonadal hormones, sex differences in the structural organization and function of the sympathetic nervous system may also explain, in part, observed gender differences in pain. Berkley[4] pointed out that differences in afferent input from internal structures to the central nervous system could not only produce different forms of visceral pain in females and males, but could also result in different emotional consequences of pain experiences, assuming that visceral input is important in the perception of emotion. Many functions of the sympathetic nervous system have been reported to be influenced by gender, including lower levels of resting sympathetic activity to skeletal muscles in women than in men,[88,89] higher sympathetic output to the skin in women,[90] and sex differences in cardiovascular responses to various stressors.[91] Other autonomic activities that are strongly influenced by the menstrual cycle and may be related to cutaneous and muscle pains include sweating,[92] skin blood flow,[93,94] and postural vasoconstriction reflexes.[95] In addition, plastic changes in the autonomic nervous system may occur differently in females than in males. This is supported by data showing that the sprouting of sympathetic fibers into the hippocampus following neural injury is more restricted in male than in female rats.[96] Since plastic changes in neural structures are a phenomenon associated with the development of chronic pain, extrapolation of these data to humans may explain the large female predominance in the occurrence of chronic pain disorders associated with the sympathetic nervous system, such as sympathetically maintained pain, causalgia, or reflex sympathetic dystrophy.[4]

Opioid and Non-opioid Analgesia. As part of the neural mechanisms that modulate pain signaling and modify emotional reactions to pain, intrinsic descending pain inhibitory systems such as those inducing opioid and non-opioid analgesia also appear to be influenced by both gender and the action of estrogen and other gonadal hormones.[97–99] For example, sex differences in the distribution and binding capacities of steroid receptors have been identified in many regions of the central nervous system that contribute to the transmission and modulation of nociceptive information.[71,100–102] Female rats display less analgesic response than male rats to central acting agents such as morphine,[38] and their sensitivity to the antinociceptive actions of these drugs varies with the phases of the estrous cycle.[103] The sexual dimorphism in response to opioid analgesics has also been observed in human studies. However, the gender differences in humans tend to be opposite to those found in animals, since the administration of opioid analgesics that act on the kappa-opioid receptor produced better analgesia in women as compared with men.[104–106] While the reason for this contrast between animal and human data remains unclear, it is possible that the overall gender differences may be a result of the modulation of the opioid circuitry by hormonal

status and chronobiologic factors such as the female estrous/menstrual cycle.[107] Mogil and Kest[108] suggest that analgesic mechanisms in each sex may also have distinct and independent neuronal circuitry, since non-opioid stress-induced analgesia is mediated by N-methyl-D-aspartate receptors in male but in not female mice,[99] and an autosomal genetic locus that accounts for 25% of the overall variance in the trait in female mice has been identified.[109] The neuroanatomic, neurochemical, and neurophysiologic gender differences in opioid and non-opioid analgesia have been thoroughly reviewed by Fillingim and Maixner.[26]

Psychosocial Factors

In addition to the biologic factors mentioned above, gender differences in pain report may be attributable to a number of psychologic and social factors.

1. Males and females may differ in their sensitivity to physiologic signals. Once signals are perceived, there may be sex differences in whether or not the signal is labeled a symptom.
2. Differences in the rearing of boys and girls may influence the readiness of the sexes to express pain.
3. Different occupational roles for men and women carry with them exposure to different risks for developing a variety of pain conditions.
4. Stress may exacerbate pain, and it is possible that men and women are exposed to different types and levels of psychosocial stress.
5. Opportunities for different pain experiences may provide different opportunities for learning about pain.

In this section, we review the evidence for each of these factors.

A number of lines of evidence suggest that women may be more sensitive to painful stimuli than men. Several excellent recent reviews by pain researchers from different disciplines[2,4,26] all find support for this conclusion. Women seem to show greater sensitivity and/or greater physiologic responsiveness to stimuli in a number of other sensory modalities (eg, visual, auditory, tactile)[110,111] as well as pain. Thus, it is plausible that an increased sensitivity to pain in women is simply a result of women having a more sensitive perceptual apparatus than men. Whether or not this perceptual sensitivity is attributable to hormonal causes remains to be investigated.

There is some evidence that men and women differ in their cognitive and emotional experiences of pain. Once a change in physiologic signals is detected, the change may be labeled as a symptom or simply as a change. Some evidence indicates that women are more likely than men to perceive physical sensations as indicative of illness.[112] Furthermore, given that a sensation is classified as a symptom, ways of coping with that symptom may differ by gender. Specifically, women may be more likely to regard pain as serious and attend to pain sooner, in an effort to minimize its intrusiveness, because they have multiple primary role obligations, from household management to child care and increased social responsibilities.[2] Prevention of multiple role disruption may also motivate women to use more social and professional support and to use short-term disability to avoid long-term disability. The same review describes different coping strategies for men, including denial, talking the problem down, and using tension-reducing activities such as alcohol consumption, smoking, or drug abuse, unless pain interferes with work responsibilities.

There is, however, some contradictory evidence concerning whether health care use for pain differs in males and females. In the only study we could identify that examined predictors of treatment-seeking specifically for pain,[23] the major predictors of use of health care in both genders were pain severity and persistence. That is, persons with more severe, persistent pain were more likely to seek care. For some pain conditions, such as TMD pain, women in the community experience pain of greater average severity than do men. If it is true that pain severity drives treatment-seeking and that women, on average, experience more severe pain than men, we would expect that the levels of pain and pain-related symptoms among men and women seeking pain treatment would be fairly comparable, although women could outnumber men in treatment settings. One study examined this question for TMD and, in fact, found that pain levels, pain-related signs and symptoms, and psychosocial profiles were roughly comparable for male and female patients seen in the same treatment setting.[113]

The observation that boys and girls are reared differently and given different expectations for pain-related behavior (eg, "big boys don't cry") is so obvious that there has been little research that actually documents these socialization patterns and their influences on adult behavior. However, there is a body of research concerning the nonverbal expression of emotions (including some studies of the expression of pain). A systematic review of these studies of nonverbal behavior[114] indicates

that sex differences in expressiveness are small among preschool children but are much greater in adults. This finding is certainly compatible with the hypothesis that the reinforcement of different pain behaviors in boys and girls can result in different patterns of pain expression among adult men and women.

Despite recent changes in some societies, men and women still tend to fulfill somewhat different occupational roles, as well as different social roles within the family. To the extent that different exposures are associated with traditionally "male" or "female" occupations, different pain conditions would be more likely to occur in males or females. For example, persons in jobs involving lifting are at higher risk for back pain, whereas keyboard operators are at higher risk for carpal tunnel syndrome.

In addition, the different occupational and role situations of men and women may be associated with different stress levels. One aspect of the psychosocial work environment that has been receiving increasing attention in health research is the concept of job strain, which is defined as the combination of high job demands and low latitude in making decisions. Job strain has been found to be associated with myocardial infarction in men[115]; with a range of measures of poor health status, including low vitality, poor mental health, and pain in women[116]; and with musculoskeletal pain of the neck, shoulders, and back in both men and women.[117,118] In addition, high job strain has been associated with increases in blood pressure in some studies, and one recent investigation found that among white-collar women, the combination of high job strain and large family responsibilities was associated with significant increases in diurnal blood pressure measurements.[119] If persons of one sex or the other are more likely to be employed in occupations with high job strain, this factor might interact with gender to increase the probability of developing or maintaining a pain condition.

Finally, men and women may have different benchmarks for reporting pain, related to their prior pain experience. For example, boys, at least in earlier generations, were more likely to experience pain from sports injuries than girls. On the other hand, after puberty, women's monthly menstrual cycles provide them with a set of physiologic signals from their bodies that are not experienced by men. These physiologic signals (sometimes of a painful nature) could have a sensitizing effect on pain perception[4] or result in behavioral and social role responses (eg, taking medication, staying in bed) that can generalize to other types of pain.

These hypotheses concerning gender differences in pain emerge from the concept that men's and women's responses to pain may be shaped differentially by psychologic and social factors. We regard these hypotheses as testable scientific questions, for which there are currently varying degrees of research evidence. Unfortunately, because pain complaints are symptoms and frequently cannot be substantiated by "objective" clinical findings, a higher prevalence of pain or higher reported levels of pain in women can reinforce negative stereotypes of women held by some health care professionals. A study evaluating the contention that physicians have prejudicial attitudes toward female patients reported the physicians' belief that women have more psychosomatic illnesses, more emotional lability, and more complaints due to emotional factors.[120] Clearly, the evidence reviewed above indicates that both biologic and psychosocial factors are likely to play a part in gender differences in pain. Not only are a range of biologic, psychologic, and social factors likely to be involved, but these factors probably interact in ways that are as yet unclear. To suggest that observed differences between men and women are "all in the head" (ie, the fault of the patient) is simplistic from a scientific point of view and not constructive in terms of patient care.

Possible Additional Mechanisms Underlying Gender Differences in Orofacial Pain

Biologic Factors

In addition to the role of female reproductive hormones in pain modulation already discussed, it has been suggested that the female predisposition to TMD may be due to the effect of the reproductive hormones on the temporomandibular joint (TMJ) complex. In animals, sexual dimorphism in the distribution of estrogen receptors in the TMJ has been reported in studies showing that estrogen receptors were found in female[121] but not male baboons.[122] In the rat, sex hormones can modulate the collagen and protein content of TMJ discs; this sex difference in the collagen content of TMJ discs was eliminated by castration of both the male and female animals.[123] Estrogen receptors have also been found in the TMJ discs of both asymptomatic male and female subjects and TMD patients.[124] More recently, an in vitro study showed that estrogen can modulate the effect of relaxin on the expression of tissue-degrading enzymes and their

inhibitors in fibrocartilagenous cells of the TMJ.[125] Although these findings suggest that the TMJ disc may be a potential target for sex hormones, their clinical significance remains unclear. It is interesting to note that relaxin has been implicated in systemic joint hypermobility,[125] a condition that seems to be more prevalent in women[126] and that has been reported (but not proven) to be associated with TMD.[127–130]

Sex differences in the perception of orofacial pain have also been attributed to dysregulation of the pain modulation system. In addition to the data showing sex differences in temporal summation of thermal pain,[28] there is evidence that TMD patients have enhanced responses to noxious stimuli[131] and greater thermal temporal summation than pain-free subjects.[132] The neural mechanisms underlying these phenomena are as yet unknown. Proposed mechanisms include impairments in central inhibitory mechanisms, disorders in pathways modulated by peripheral baroreceptor afferent input, and alteration in central nervous system processes that regulate the temporal processing of pain.[132] Whether these mechanisms are generic or specific to orofacial pain also remains to be determined.

Psychosocial Factors

There is little evidence that the psychosocial factors involved in chronic orofacial pain conditions are qualitatively different from those involved in other chronic pain problems. In contrast, there is evidence that, although TMD pain is on average less disabling than back pain and headache, levels of psychologic distress in persons with a TMD are similar to those of persons with other common chronic pain conditions.[1] There is also no a priori reason to suspect that perceptual differences between the sexes, cognitive differences in symptom labeling and pain coping, or gender differences in pain expression would take different forms depending on the site of pain. It is possible that different occupational and social role exposures for men and women could influence the prevalence of specific orofacial pain conditions. However, we know of no research that specifically addresses this question. Thus, at this time, it appears that causes of the higher female-to-male prevalence ratio for head and face pain than for pain elsewhere in the body are best sought in the biologic rather than the psychosocial realm.

Summary and Conclusion

An analysis of the literature indicates that for endogenous pain, women tend to report higher pain levels and pain in more bodily regions than men. For no apparent reason, there are also sex differences in the manifestations of signs and symptoms of various pain disorders. Systematic investigation of gender differences in pain is a relatively new field. It is not yet known why some chronic pain conditions are predominant in men, while others (in particular those disorders that involve the craniofacial area or are modulated by the sympathetic nervous system) are more common in women. It is also unclear why some types of pain vary with hormonal fluctuations. Nevertheless, several interesting hypotheses reviewed in this paper are under active investigation.

Laboratory experiments have substantiated the gender disparity in responses to noxious stimuli. However, differences exist only for certain types of stimuli, mean differences between the sexes are generally small, and results are often inconsistent between studies. Therefore, the relevance of these laboratory findings to clinical conditions has been questioned. There are also other reasons why these data should be interpreted with caution. First, experimental pains are induced under acute conditions and do not reflect the persistent or recurrent nature of chronic pain conditions. Thus, they do not constitute a threat to the subject's health or cause a state of distress or disability that may affect the subject's perception and description of the pain signals. Second, the majority of experimental stimuli are delivered to the skin, while chronic endogenous pains are felt mostly in deep structures such as muscles, joints, or visceral organs. Third, it is difficult to attribute the differences to gender only, given the numerous interacting variables that may shape the responses to pain, as listed in Figs 1 and 2. Fourth, the experiments are often carried out in healthy asymptomatic subjects, in whom changes in the peripheral and central nervous systems potentially induced by chronic pain have not taken place. In other words, as we have noted elsewhere,[34] to understand the whole spectrum of pain response in male and female humans, pain must be studied in populations, not only in persons seeking treatment for pain, and not only in those who typically participate in laboratory pain research.

While evidence for sex differences in pain has not been established beyond doubt, distinct anatomic and hormonal features in women and men provide compelling clues that their pain might

be modulated in a differential manner by a number of biologic factors. The cyclic fluctuations of various pain disorders across the menstrual cycle, along with gender differences in the composition of gonadal hormones, give rise to a number of hypotheses related to the actions of estrogen, progesterone, and testosterone. These hypotheses have been substantiated with clinical and experimental data on the interactions of the gonadal hormones with various neuroactive agents and on their effect on both opioid and non-opioid analgesia. In addition, sex differences in the structural organization and operation of the sympathetic nervous system may account, in part, for the apparent gender differences in pain. More recently, direct evidence for gender differences in pain processing has been reported. For instance, Mogil et al[133] presented evidence illustrating the role of genetic background in the perception of pain. Gender differences in forebrain cerebral activation patterns of the brain during pain perception have also been reported.[134]

Several hypotheses concerning differential psychosocial influences on pain in women and men—notably, differences in perception, appraisal, pain-related behavior, and environmental influences—have also been reviewed here. Although information supporting the observation of sex differences in pain continues to emerge, it is still fragmented. While debates about the biologic or psychosocial nature of gender differences in pain continue, the answer is unlikely to be one or the other, since these aspects are undoubtedly interrelated. Yet it is alarming to see how clinical decisions, probably influenced more by personal beliefs than by scientific data on gender differences, may lead to inadequate treatment of pain in women. For instance, nurses' choices of initial doses of analgesic after appendectomy may be affected by the patient's gender, potentially causing inadequate analgesia in women.[135] Cleeland et al[136] reported that being female was a significant predictor of inadequate pain management in patients with metastatic cancer. Although coronary artery disease is the number one cause of mortality in women, those women with new-onset chest pain who present with similar symptoms as men are approached, diagnosed, and treated less aggressively than men.[137] Similarly, in an emergency setting, women with acute non-pleuritic and non-traumatic chest pain were evaluated and managed less aggressively than men.[138] These data strongly suggest that the available information on gender differences should be interpreted with caution. In other words, simply because women are more likely to report pain than men and on average they report higher levels of pain than men, does not mean that women's pain reports should be discounted. Rather, evaluation and treatment of pain patients should be performed on an individual basis. In the treatment context, whether gender differences in pain exist is perhaps not the main issue; rather, our ultimate objective is to use all the available information about a patient, including his or her gender, in a judicious manner to improve treatment strategies and the quality of life of those who experience pain.

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CRITICAL COMMENTARY 1

GENDER DIFFERENCES IN PAIN

Ilana Eli, DMD
Associate Professor
Department of Occlusion and Behavioral Sciences
School of Dental Medicine
Tel Aviv University
Tel Aviv, Israel
Fax: +972-3-6409250
E-mail: elilana@post.tau.ac.il

The comprehensive review by Drs Dao and LeResche[1] concerning gender differences in pain is a valuable addition to those recently published in the scientific literature.[2–4] As yet, there are no definite conclusions regarding the interactions between pain and gender-related factors in this relatively recent and rapidly expanding area of research. The uniqueness of this focus article lies in the attempt of Dao and LeResche to summarize the existing knowledge with regard to orofacial pain conditions. The multiple biologic and psychosocial factors that contribute to gender differences in pain are reviewed. I would like to add several comments on the psychosocial nature of those differences.

Pain (acute and chronic) is a complex experience of a multidisciplinary nature, which is always subjective and always associated with emotional and cognitive factors. The mere activity in the nociceptor and nociceptive pathways by a noxious stimulus is not pain, which always encompasses a psychologic state.[5] Pain is strongly affected by stress, fear, anxiety, mood, control, attention, expectations, modeling, suggestions, and sociocultural factors. Men and women differ in their pain perception and reaction according to their accepted social roles and individual cognitive and emotional factors. Moreover, one may react differently to similar pain stimulation under different conditions.