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Studying sex and gender differences in pain and analgesia: A consensus report

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Abstract

In September 2006, members of the Sex, Gender and Pain Special Interest Group of the International Association for the Study of Pain met to discuss the following: (1) what is known about sex and gender differences in pain and analgesia; (2) what are the “best practice” guidelines for pain research with respect to sex and gender; and (3) what are the crucial questions to address in the near future? The resulting consensus presented herein includes input from basic science, clinical and psychosocial pain researchers, as well as from recognized experts in sexual differentiation and reproductive endocrinology. We intend this document to serve as a utilitarian and thought-provoking guide for future research on sex and gender differences in pain and analgesia, both for those currently working in this field as well as those still wondering, “Do I really need to study females?”

Keywords

Sex differences; Gonadal hormones; Estrogens

1. The case for studying sex and gender differences in pain and analgesia

The pain field has moved from debating whether sex differences in pain exist to recognizing the importance of these differences. Attention is now directed toward understanding (1) what conditions lead to the expression of sex and gender differences in pain experience and reactivity, (2) what mechanisms underlie these differences, and (3) how these differences can inform clinical management of pain.

As noted in a recent review, at least 79% of animal studies published in *Pain* over the preceding 10 years included male subjects only, with a mere 8% of studies on females only, and another 4% explicitly designed to test for sex differences (the rest did not specify) [142]. Given the substantially greater prevalence of many clinical pain conditions in women vs. men [20,199], and growing evidence for sex differences in sensitivity to experimental pain and to analgesics [21,41,213], *we recommend that all pain researchers consider testing their hypotheses in both sexes, or if restricted by practical considerations, only in females*. It is invalid to assume that data obtained in male subjects will generalize to females, and the best non-human model of the modal human pain sufferer – a woman – is a female animal. If only males are examined in a given study, it is important that a rationale for exclusion of females be provided and that the potential limitation in generalizability of the findings be addressed in the discussion, particularly when examining a pain phenomenon that occurs with greater prevalence or severity in females. In both preclinical and clinical studies, a comparison of both sexes will further our understanding of individual differences in sensitivity to pain and analgesia, thus improving our ability to treat and prevent pain in all people.

2. General considerations

Two issues of terminology are important. First, the term “sex” refers to biologically based differences, while the term “gender” refers to socially based phenomena. Although biological sex exerts a major influence on one’s gender identity, sex and gender are not equivalent, and the terms are not interchangeable. If subjects are categorized by anatomical features (chromosomes, reproductive organs), it is appropriate to describe the study as one of “sex differences”. In contrast, if additional measures of masculinity/femininity or gender identity are used to describe subjects, then the term “gender differences” is appropriate [88,216]. Gender is often conceptualized as a dichotomous variable, yet individuals differ in the degree to which they conform to the norms for masculinity and femininity in their particular culture. Thus, gender is most accurately regarded as a continuous variable (ranging from exclusively feminine to exclusively masculine), with most individuals falling somewhere along the

continuum of maleness to femaleness on a range of characteristics. Even within the same society, gender role expectations may differ for generations born at different times, and within an age-cohort, gender role expectations may change as a function of age. Finally, in any statistical analysis of human subjects, the dichotomous variable sex (male vs. female) is confounded with the social construct of gender. That is, in human studies in which the dependent measure is pain report, group differences are likely to be attributable to both sex and gender. *Therefore, both constructs should be examined when possible in order to understand their relative contribution to differences in pain between men and women.* For the sake of efficiency – and because most studies to date have classified subjects by sex rather than gender – the terms “sex” and “sex difference” will be used in this paper, except when gender is specifically discussed.

The second issue of terminology regards the use of the term “estrogen” to refer to any of a number of steroid hormones akin to estradiol. In fact, “estrogen” and “progestin” refer to *classes* of hormones, each specific hormone being “an estrogen” or “a progestin.” We encourage pain researchers to refer to the *specific* hormone used in their studies, whether it is estradiol, estrone, estriol, or others in the case of estrogens, or the naturally occurring progesterone or specific synthetic progestin in the case of progestins.

3. Experimental study of sex differences in pain and analgesia

Researchers studying sex differences in pain are strongly advised to consult a recent, comprehensive set of guidelines entitled “Strategies and Methods for Research on Sex Differences in Brain and Behavior” [17]. In addition, methodological issues that are specific to pain research are discussed below.

It is generally agreed that the first stage of any sex difference study should be a comparison of gonadally intact adult females and males. In the absence of previous evidence for large menstrual/estrous cycle-related variations in the measure of interest, it is not absolutely necessary to test females in specific stages. However, a failure to observe sex differences in pain can be interpreted in multiple ways: (1) no sex difference exists; (2) the observed sex difference occurs only when females are in a particular stage of the menstrual or estrous cycle (e.g., [193]), and the sex difference could not be discerned due to “averaging” across the cycle; (3) a sex difference in *mechanism* exists even though the magnitude of the phenomenon under study is similar in males and females (e.g., [126,127]); or (4) two sex-specific mechanisms exist that cancel each other out, resulting in no phenotypic sex difference [50,153]. Thus, in the case of a negative finding when comparing gonadally intact females vs. males, interpretations 2, 3, and 4 should be acknowledged.

When designing and interpreting studies on sex differences in pain or nociception, it is important to recognize that there are sex differences in a number of physiological systems that may directly or indirectly affect measures of pain/analgesia. For example, adult male rodents have greater percentage of body fat than females [124], while the opposite is true for humans [78]. This sexual dimorphism can affect the distribution of highly lipophilic drugs, and therefore influence analgesic drug potency, efficacy, and duration of action. Other aspects of pharmacokinetics, including liver metabolism and membrane transport, may differ between the sexes [139,144], possibly affecting analgesic potency, efficacy, and duration of action. Immune responses also differ between the sexes [21], which may contribute to sex differences in response to chronic inflammatory and neuropathic pain. The activity level of female rodents varies dramatically across the estrous cycle [24,74], which may introduce a confound on pain tests that allow subjects to locomote freely, such as the hot-plate test. Lastly, adverse effects of analgesics such as respiratory depression and nausea may occur differentially in females vs.

males [32,46,179], which is important to consider when comparing analgesic efficacy in females vs. males.

3.1. Are sex differences mediated by gonadal hormones?

As described by Becker et al. [17], if a sex difference is observed in gonadally intact adults, a logical next step is to determine whether the sex difference can be attributed to the actions of gonadal steroid hormones, either activationally (in adulthood) or organizationally (during development). Organizational effects can only be practically examined in animal studies. Several recent reviews have described the multiple ways in which estrogens, progestins, and androgens may modulate nervous system function related to pain and analgesia [5,6,41,43, 111,193].

3.2. Testing across the estrous cycle: animal studies

The value of testing female rodents at different stages of the estrous cycle is debatable. In rodents, an influence of estrous cycle stage is not necessarily indicated by larger observed variance [142]; therefore, large samples are typically required to adequately power studies examining females in specific stages of the estrous cycle. One of the most reliable and simple ways to determine stage of the estrous cycle in rodents, sampling vaginal cytology, requires that females be handled and probed daily for at least two cycles (approximately 8–10 days). Given that females and males often respond differently to acute stressors (e.g., [214]), it is not clear whether daily handling of males adequately controls for this potential confound. Obtaining repeated vaginal samples in rodents also may affect sensitivity to drugs [209]. An alternative to daily vaginal lavage is to measure motor activity (in the home cage), which peaks during proestrus [24]. Because rodent estrous cycles differ substantially from primate menstrual cycles (Fig. 1), one cannot readily extrapolate a cycle effect in a rodent to one in a human. Therefore, although estrous cycle fluctuations in a pain/analgesia measure suggest that reproductive hormones modulate the effect of interest, this hypothesis is more directly and efficiently tested using a hormone depletion/replacement approach (see Section 3.4), which is readily accomplished in rodents. If females in different stages of the estrous cycle are tested, it is imperative that the investigator explicitly state how the stages – particularly the stage of most dramatic hormone change, proestrus – are defined, as there is more than one way to designate stage of cycle. One study has shown significant differences in analgesic sensitivity between females in “early” vs. “late” proestrus [19].

3.3. Testing across the menstrual cycle and reproductive stages: human studies

In humans, while it may not always be important to test at different stages of the menstrual cycle, it is always important to *consider* whether such testing is appropriate. If menstrual cycle itself is not a factor to be evaluated, the investigator should plan to evaluate women in the same phase of their cycle. There is no one ideal phase of the cycle to choose. Both absolute and relative hormonal levels could influence pain. Times of rapid change in hormone levels (e.g., ovulation) or phases when subjective mood changes are thought to occur (e.g., pre-menstrual) may be of interest.

Start date of the last menstrual period can be reliably obtained from self-report, as can year and month of menarche [77]. A number of methods, including analysis of daily vaginal secretions, basal body temperature, and ovulation kits can provide information on the occurrence and approximate timing of ovulation, although some methods are more reliable than others [17] (p. 1663). Prediction of ovulation using urine-based home ovulation testing kits to assess leuteinizing hormone surge is a minimum standard in studies in which the menstrual cycle is of interest. These kits are relatively inexpensive, are easy for subjects to use, and have high sensitivity and specificity for detecting ovulation [138]. Additional measurement of blood or salivary levels of mid-luteal progesterone can confirm ovulation [183]. Although

serum-based measurements are still the most widely used and considered the gold-standard for clinical research, saliva-based methods can be an alternative. Saliva-derived hormone measures reflect the fraction of the hormone that exerts biological effects [158]. Furthermore, collection of saliva is non-invasive and pain-free; with appropriate instruction, the subject can collect saliva at home and store it in a home freezer without deterioration of the sample [66]. A serious drawback is that salivary hormone levels may be below detection levels. Additionally, standardization across laboratories can be a problem. It should be noted that both serum and salivary measures of estradiol and progesterone exhibit great between-subject variability within the range of normal. However, because menstrual cycle length varies between and within women [198], and hormone levels also vary from one day to the next in some phases of the cycle, if hormonal status is a critical variable in the research, it is best measured directly rather than inferred from self-report and ovulation measures of menstrual cycle phase.

The standard designations for stages of the menstrual cycle (menstrual, follicular, ovulatory, and luteal) are gynecological terms based on reproductive function. However, a woman's actual hormone levels within a phase vary radically. Thus, researchers must consider whether their interest is in reproductive function or in the relationship of hormone levels to pain. If the interest is in hormone levels, the gynecological nomenclature (and the lack of standardization with which it is applied) represents an obstacle to progress in the field [165,183]. We propose that use of the terms menstrual, follicular, ovulatory, and luteal be discouraged in human clinical pain studies, unless coupled with report of the actual days of the menstrual cycle, standardized to a 28-day cycle based on ovulation testing. One statistical standardization method is described by LeResche et al. [122]; however, other reasonable standardization methods are possible, and reaching consensus on the issue of how to standardize menstrual cycles of various lengths would facilitate comparison across studies. For these reasons, hormone levels should be reported when available.

If the research question is specifically *cycle*-related, as opposed to hormone-related, subjects with irregular cycles should be excluded. However, it is difficult to exclude irregularly cycling subjects based only on self-report; many subjects who describe their cycles as regular in fact have irregular cycles [198]. Even monitoring cycles before study enrollment may not solve this problem because there are no agreed criteria for distinguishing between a regular and irregular cycle. If the research question concerns the relationship between pain and hormone levels (or hormone variability) and hormones are measured directly, including irregularly cycling subjects may not be a problem, provided sufficient hormonal variability occurs. However, this approach assumes that the neurohormonal processes related to pain are comparable for women with regular and irregular cycles, which may not be the case. Finally, it is important to record dysmenorrheal status, as dysmenorrheic women may differ from those without dysmenorrhea in their responses to (non-menstrual) pain stimuli, especially during the perimenstrual period (e.g., [15,75]).

Circadian rhythms have been documented for steroid hormone levels [26,105], autonomic nervous system activity [27], and drug absorption [36]. These rhythms may be altered by menstrual cycle rhythms in women. For example, at the time of ovulation, decreased absorption of drugs such as aspirin and alcohol occurs and intestinal transit times are longer in the late luteal phase, during pregnancy and with hormone supplementation; these effects can influence drug onset time. With a few exceptions (e.g., [134]), the effect of circadian rhythms on pain and analgesia is largely unexplored.

Inclusion of non-cycling subjects may be of interest at specific life stages (pre-puberty, pregnancy, menopause). The conventional standard is to define puberty according to Tanner stages [196], based on clinical examination of development of secondary sex characteristics. Self-report measures with sufficient reliability and validity are available for use in studies

where direct examination is not feasible [25]. A woman is conventionally defined as “post-menopausal” one year after the last menstrual period, provided the cause of amenorrhea is not pregnancy, nursing, disease, or medical intervention [217]. Date of menopause is the date of the last menstrual period. Standardized criteria for stages of the menopausal transition are also available [83]. If pregnant women are studied, stage of pregnancy should be clearly noted, as pain responses are known to change dramatically over the course of pregnancy (e.g., [16, 121]). Reproductive history also may be important to document. For example, pain during breastfeeding in the first week postpartum is directly predicted by parity, with women who have given birth to more children experiencing more pain [87]. Conversely, in the laboratory (and not in close proximity to birth), multiparous women have higher pain thresholds than nulliparous women [82].

3.4. Hormone manipulations: animal studies

A useful approach for identifying effects of particular hormones on pain/analgesia in animals is gonadectomy with or without hormone replacement. However, it is important to keep in mind that hormone depletion via gonadectomy alters the physiological status of the animal in two significant ways. First, surgery can affect pain thresholds [93,173] and sensitivity to analgesics. Second, gonadectomy disrupts the normal feedback loop that sex steroids exert on the anterior pituitary and hypothalamus, leaving both males and females in a prolonged state of elevated (e.g., gonadotropin-releasing hormone (GnRH), leuteinizing hormone) or depressed (e.g., prolactin) circulating hormones [1,53,95,220]. The likelihood of unintended consequences due to altered hypothalamic/pituitary hormone secretion can be addressed by administering low (maintenance) doses of estradiol or testosterone rather than using gonadectomized animals with no hormone replacement. In the case of the female rat, daily s.c. injections of 1 µg estradiol benzoate are sufficient to reduce leuteinizing hormone and to elevate prolactin to diestrous levels without inducing receptive behavior [1,95].

Although there are “chemical castration” alternatives to gonadectomy, these have drawbacks and have not been fully characterized in terms of their possible effects on pain/analgesia. For example, continuous GnRH can be used to shut down the hypothalamo–pituitary–gonadal axis in both males and females. However, elevated GnRH may interfere with some aspects of opioid analgesia [160] and may cause long-term enhancement of glutamatergic post-synaptic activity [218]. Inhibitors of aromatase, the enzyme necessary for the synthesis of estrogens from androgens, can be used to substantially reduce synthesis of estrogens, and 5- α -reductase inhibitors can be used to reduce dihydrotestosterone synthesis; however, these inhibitors may also reduce synthesis of other steroid hormones within these metabolic pathways. The androgen antagonist flutamide can be used to block the effects of androgens, but it can also affect aromatase activity that is induced by androgens [23] and can act directly as an androgen agonist in some tissues [131]. The estrogen receptor antagonist tamoxifen, like other selective estrogen receptor modulators, has been shown to act as a partial agonist in some peripheral tissues [92]. ICI 182780 is a selective estrogen receptor antagonist, but it does not cross the blood–brain barrier [208]. Ultimately, convergent approaches to manipulate gonadal hormones will provide the most definitive testing of hypotheses that gonadal hormones modulate pain/analgesia.

When using a gonadectomy/hormone replacement approach, several issues must be considered. First, an effect of gonadectomy (relative to gonadally intact controls) implicates a role for gonadal secretions in pain/analgesia, but does not implicate any *specific* hormone. For example, one cannot conclude that testosterone mediates a given outcome based only on a castration effect in a male. Rather, studies in which testosterone is replaced in castrated males are also necessary. Second, to study the origins of sex differences, it is important to make the sex hormone levels as similar as possible in males and females at the time of testing. That is,

both sexes rather than just males should be tested with androgens, and *both* sexes rather than just females should be tested with estrogens. This approach enables one to assess whether the mechanisms in question are sexually differentiated. If both sexes respond similarly to the same hormone treatment – even if one sex does not normally experience that hormone state – it can be concluded that the mechanism is likely to be similar in the two sexes (that is, not sexually differentiated).

A third point regarding gonadectomy/hormone replacement approaches is that failure to obtain an ovariectomy effect in females does not necessarily mean that ovarian hormones do not modulate pain/analgesia, particularly if the comparison group of intact females is in unknown or low hormone stages (i.e., an ovariectomy effect in females may only be apparent if the intact control group is in proestrus or estrus, when gonadal hormones are at or near peak levels). Fourth, the timing of hormone administration may be critical: if hormone replacement begins weeks rather than days (or immediately) after gonadectomy, responsiveness to exogenous hormone administration may diminish, requiring higher doses or longer duration treatment to obtain comparable effects [38,51]. Moreover, for estradiol, the interval between the last injection and behavioral testing as well as the duration of hormone exposure may dramatically influence the outcome [42,128,150,171].

Another aspect of hormonal manipulations concerns the age at which they are done. In rodents, the effects of ovariectomy and estradiol replacement depend upon the age at which the surgery is done [33,203]. Furthermore, there are important species differences in the pattern of hormonal changes during the progression through reproductive senescence (sometimes called “estropause” [33]). Unlike mice and women, in whom both estradiol and progesterone levels fall to very low levels following reproductive senescence, when rats progress through estropause, their estradiol levels remain elevated [203].

In the absence of relevant data to guide the design of a hormone replacement protocol, administration of a dose that has been shown to maintain or reinstate sexual behavior is a reasonable starting point. However, the dose ranges of hormone replacement relevant to the reproductive system may not be equivalent to ranges that modulate pain/analgesia. Even within the reproductive system, tissue sensitivities to estradiol vary widely [99]. Thus, reasonable *starting* doses for estradiol in ovariectomized rats would be in the range of 2 µg estradiol benzoate s.c., with testing beginning 24–48 h later; this dose/test interval has been shown to mimic proestrus–estrus, both behaviorally and in terms of plasma hormone levels [13]. Likewise, 500 µg of s.c. progesterone is a reasonable starting point for progestin replacement, with testing beginning 4–6 h later [58]. Of course, these testing intervals assume a nuclear steroid receptor-mediated (genomic) effect, whereas recent reports indicate that gonadal steroids may modulate pain thresholds at considerably shorter intervals [57]. Thus, it is important to consider shorter treatment-test intervals as well. For *in vitro* preparations, $100\text{--}1000 \times K_d$ may be a reasonable starting dose to saturate a receptor [100], followed by decreasing the dose until the effect of interest disappears.

No obvious rationale exists for examining the influence of progesterone alone in a gonadectomized animal (other than as a control for progesterone + other hormone combinations), because gonadectomized humans are not exposed to progesterone alone under any known clinical treatment condition. However, it would be informative to test progestins and estrogens alone and in combination in *gonadally intact* animals, to model various clinical hormone treatments in humans (e.g., [48]).

3.5. Hormone manipulations: human studies

In human studies it is often impractical or unethical to manipulate hormones. However, women taking contraceptives for birth control or other reasons (and men taking androgens) can be

studied. Additionally, short-term hormone administration is feasible (e.g., [187]). Hormone replacement and supplementation therapies differ markedly in the particular androgens, estrogens, and progestins they contain; these should *always* be clearly specified, as the various hormones likely exert different effects.

3.6. What types of pain tests are appropriate? Animal studies

The model system that is most appropriate is entirely hypothesis-driven. In animals, although acute pain tests such as the tail-flick test may not model clinical human pain per se, many advances have been made in understanding mechanisms of pain using such models. Face validity is less critical than using the model that is most appropriate to studying the specific mechanism of interest. In other words, mechanism “translates” better than phenomenology. A variety of approaches (e.g., visceral vs. cutaneous pain, acute vs. chronic [inflammatory or neuropathic] pain, behavioral vs. electrophysiological vs. molecular measures) are all worth pursuing, because they may reveal sex differences that have not yet been observed. Many existing pain models have not yet been applied to females, and animal models for female-specific pain syndromes are needed. In any model, the intensity of the noxious stimulus should be carefully considered. High-intensity stimuli are likely to result in a ceiling effect in which all subjects (or cells, etc.) respond at the limit of their capacity, thereby potentially obscuring individual differences (e.g., sex differences). Examination of more than one stimulus intensity is valuable in determining the generalizability of the sex difference.

As noted in reviews, sex differences in acute pain models have been observed, but are often protocol-, species-, and strain-dependent [140]. Very few studies have investigated sex differences in chronic pain models such as nerve injury and persistent inflammation. Notable exceptions include nerve ligation [40,113,195] and arthritis studies [4,39]. This dearth of information makes it premature to suggest which protocols or animal species are most relevant to any particular human pain condition. One valuable approach involves parallel testing in the animal and human laboratory (e.g., [29]).

3.7. What types of pain tests are appropriate? Human studies

In contrast to the robust sex difference found in the prevalence and severity of many chronic pain conditions, reported sex differences in experimental pain responsiveness, while generally consistent in direction, are often subtle in magnitude and sometimes absent. Sex differences may be more consistently observed when using particular stimulus modalities or psychophysical protocols. Specifically, a meta-analysis reported that sex differences in threshold and tolerance measures were largest and most consistently found for pressure pain and electrical stimulation, while smallest and least consistently found for thermal pain stimuli [164].

With respect to visceral pain, a lower pain threshold to esophageal distension was demonstrated in females [149], whereas rectal stimulation studies showed no gender differences in mechanical thresholds [11,186], or higher thresholds in healthy women [34]. Additionally, women have shown larger referred pain areas to the mechanical and thermal stimulation of the esophagus [161]. Characterizing sex differences in visceral pain, even with the limited number of studies published, is complicated. As with sex differences in somatic pain, detailed evaluations of visceral pain will be necessary to determine the mechanisms responsible.

Studies should include a range of stimulus intensities, as assessments of threshold or only mildly painful stimuli could fail to reveal differences that are manifest with more intensely noxious stimuli. Similarly, different physiological and psychological mechanisms operate in acute vs. sustained pain, such that sex/gender differences may be more prominent in tests of sustained pain.

Studies of experimentally induced hyperalgesia have demonstrated robust sex differences [29,70,71], but not all aspects of pain show significant sex differences in these models. Such observations provide the opportunity to selectively evaluate different mechanisms of hyperalgesia, and identify those in which sex is a significant factor.

When testing pain sensitivity of persons with clinical pain, it may be informative to use quantitative tests that are closely related to and replicate the clinical pain, as well as stimuli that differ from it in location and/or quality. The decision on these options should be based on the questions posed. For instance, evaluation of pain sensitivity at asymptomatic body sites can reveal information about general pain-processing alterations, as has been shown for fibromyalgia [118,189], various types of headaches [182], and temporomandibular disorders (TMD) [175]. Additionally, experimental provocation of a patient's clinical pain allows separate assessment of that pathological condition, for instance evaluating pressure pain sensitivity of symptomatic muscles of fibromyalgia patients [188], or rectosigmoid distension of irritable bowel syndrome patients [34].

It is important to document as much of the experimental testing situation as possible. For example, experimenter (or clinician) sex should always be reported, as this variable may influence pain report in the laboratory (e.g., [14,76,94,125]) and in the clinic [133]. Other relevant factors to document include: (1) a detailed description of instructions to subjects and the training they received prior to data collection; (2) the history of subjects' pain experiences; and (3) the history of subjects' experience with similar experimental studies.

The goal of providing such information is to characterize the context of the experimental testing situation, and importantly, the subjects' reaction to the context. While it is relatively simple to document the environmental features of the testing situation, it is more complicated – but likely more relevant – to document the subjects' perception of and reaction to the testing environment. One example is the anxiety or stress that the subject feels in the testing environment. These states can vary substantially among subjects, and there is considerable evidence that stress or anxiety level influences pain perception, often in a sex-dependent manner [91]. Accordingly, it is valuable to document both the environmental conditions and the subjective state of the participants at the time of evaluation. Decidedly relevant factors are identified in Table 1 under "Context".

Many variables other than a person's sex or gender account for individual differences in pain sensitivity. Thus, sex differences may be more prominent in one sample than another due to differences in other sample characteristics. It is important to document the characteristics of the study population as thoroughly as possible; a list of relevant characteristics is presented in Table 1 under "Individual Factors." Many of these factors are also relevant to clinical pain research.

4. Clinical and psychosocial study of sex and gender differences in pain and analgesia

Clinical pain research is defined as observational or experimental research with human subjects who have clinical pain conditions. Psychosocial pain research is the study of the cognitive and affective aspects of pain experiences, as well as social and psychological variables that influence risk for experiencing pain, manifestation of pain conditions, and treatment outcomes. Clinical and psychosocial research on sex and gender differences in pain is important for the following reasons:

1. Findings from clinical research are more directly relevant to clinical pain – and the relief of clinical pain – than are findings from studies involving laboratory study of animals or healthy, pain-free humans.
2. Sex and gender differences in pain are generally more pronounced in the clinic than in the laboratory. The higher prevalence of a wide range of clinical pain conditions in women than in men, coupled with the predominance of a few specific pain conditions in men (Table 2; [20]), suggests that (a) different clinical pain mechanisms may operate in men vs. women, (b) different or additional risk factors are relevant in one sex, or (c) differences compound such that small differences in mechanisms become large differences in morbidity and mortality through interactions with pharmacological and interventional therapies.
3. A review of studies conducted to date indicates that psychological and social variables powerfully influence pain, and can often explain more of the variance associated with pain than do biological variables – not only in clinical pain conditions, but also in the human laboratory [168,169,215].

Basic science researchers often attempt to control a substantial number of individual differences (e.g., age, prior experience) in order to minimize “noise” when trying to identify and understand a specific mechanism underlying nociception or pain. In contrast, psychosocial research specifically examines these individual differences for their influence on pain. Research on sex and gender differences in clinical pain is necessarily complex because numerous factors that may influence the pain experience are themselves influenced by biological sex and by psychosocial factors. It is important to investigate how psychosocial variables differ in men and women, and how these variables interact with gender role and/or biological sex to influence the experience of pain in the two sexes. That is, to what extent are observed differences in clinical pain expression due to physiological differences, to differences in pathophysiology, and to psychosocial mediating factors? Factors to consider in planning clinical and psychosocial research on sex and gender differences in pain in human populations are described below.

4.1. Clinical and psychosocial factors of relevance to sex and gender influences on pain and analgesia

4.1.1. Age—The patterns of pain prevalence by age and sex differ for different pain conditions [120]. Many clinical pain conditions show no sex difference in prevalence before puberty, but show increased prevalence in one sex or the other (usually women) after puberty. Evidence suggests that the female prevalence in many common pain conditions increases across the pubertal period [123], and that the experience of multiple pain problems also becomes more common in girls as puberty progresses. Some of the differential in pain report among adolescents who seek care for chronic pain may be attributable to differences in coping strategies by gender, with females showing more catastrophizing, which is associated with higher pain levels [101]. Although it is assumed that the pain behaviors of males and females are learnt through early experience, there is little research that explicitly examines the general development of sex differences in pain across the rapidly changing period of childhood and adolescence.

Some pain conditions, such as migraine headaches [180] and TMD [54], decline in prevalence after the fourth decade of life, whereas others, such as interstitial cystitis [45], joint pain and fibromyalgia [120], appear to persist until later ages. However, few studies have directly examined the relationship of specific pain problems to menopause. In addition, little information is available on the influence of sex/gender on the development and presentation of clinical pain in middle-aged and older adults, an age group frequently presenting with pain in clinical practice.

4.1.2. Race/ethnicity/culture—Few research studies have examined the influence of culture on gender-specific response to experimental pain or on presentation of clinical pain conditions. Cultural differences in gender-specific pain patterns would suggest sociocultural mechanisms, or possibly racial differences, whereas similarities across cultures would suggest biological or biopsychological mechanisms (e.g., [181]). There is evidence that culture/race interacts with gender on the experience of pain [59,147]. Future cross-cultural studies could be useful for illuminating mechanisms underlying sex differences in pain, although cultural and genetic factors may be difficult to differentiate.

4.1.3. History—In female-predominant pain disorders, physical abuse and sexual abuse appear to be related to pain and mood disorders [163]. For example, abuse history is associated with increased rates of pelvic pain in women [116]. However, these relationships are complex, with only certain aspects of pain or mood showing such relationships [35]. Few studies have examined sex or gender differences in the relationship between abuse and pain sensitivity [60]; clearly, more research is needed on this topic. Women are more likely to get post-infectious irritable bowel syndrome (IBS) than men [148], and chronic stress may be a risk factor. The number of existing pain conditions is a strong predictor of onset of new pain problems (e.g., [205]), and women are more likely to report multiple pains. Thus, pain history should be recorded in clinical studies.

4.1.4. Health vs. disease—A wide range of diseases have different prevalence rates and/or different presentations in males and females of the same age [63,157]. When possible, studies should compare not only women with pain to men with the same pain condition, but also healthy women to healthy men and patients of each sex to sex-matched healthy controls. For example, differences in symptoms and/or in pain sensitivity in the intestinal tract have been found between women with IBS and healthy women, between women with IBS and men with IBS, and between healthy women and healthy men [34]. Similarly, exaggerated temporal summation of pain has been documented for women with TMD, but not for men with TMD [174,175]. Moreover, researchers should be alert to the possibility that differences in presentation of disease between men and women may result in different diagnoses. In fact, it may be appropriate to develop sex/gender-specific diagnostic criteria for some pain conditions.

4.1.5. Comorbidities—Comorbidities are defined as: (1) pathological conditions, both physical and psychiatric, that exist in the patient with a pain condition; and (2) other symptoms that co-occur with pain that are not a direct result of the same condition. Investigations of comorbidities are important because: (1) they frequently occur; (2) they increase the burden of illness, which may affect treatment outcomes; (3) some comorbid conditions, notably depression, may share common mechanisms with pain; and (4) there are few relevant animal models. Women have more comorbid mood disorders [185], comorbid physical conditions [154], and numbers of somatic symptoms [204] than do men. Such comorbidities likely affect treatment outcomes [185]. Specifically, depression and anxiety are more common in women than in men, and genetic risk factors for mood disturbance may be more likely to result in these psychiatric disorders in women than in men [79,211]. Women have a larger number of comorbid pain conditions [120,123], and specific pain conditions with high female-to-male prevalence ratios may be etiologically related (e.g., [2]). Research is needed to determine whether comorbidities influence sex/gender differences in the effectiveness and side effects of specific treatments. For example, selective serotonin reuptake inhibitors (SSRIs) are more effective for women than for men for depression [106,197]; research is needed to determine whether this difference holds when SSRIs are used for pain.

4.1.6. Disability—Women are more likely than men to experience disability from the same pain condition [206]. In addition, patterns of disability may differ by sex [44,102,199]. Research is needed on why chronic pain is more likely to be disabling for women than for men.

4.1.7. Medications—Sex differences in the pharmacokinetic and pharmacodynamic properties of drugs [67], as well as in mechanisms of pain and analgesia, suggest that different medications may be more effective in one sex and that side-effect profiles and side-effect tolerance may differ between men and women. These variables can affect treatment adherence. Currently, some drugs are approved for use only in specific age groups, and recently a drug for the treatment of heart failure (BiDil[®]) was found to have differential effectiveness by race and was approved only for a specific racial group by the U.S. FDA [201]. Similarly, analgesic drug trials need to be powered to detect sex differences in effectiveness and side effects.

4.1.8. Physical variables—On average, blood pressure, height and weight differ by sex and these differences may affect response to a pain stimulus, as well as responses to pain treatment [3,61]. Physical variables should be measured and controlled for as much as possible.

4.1.9. Beliefs—Gender role expectations differ between sexes and are related to pain [137, 169]. Studies of clinicians' and patients' perceptions/beliefs about pain and gender are needed.

4.1.10. Coping—Women with chronic pain seek more social support and use a wider range of coping strategies than men. They also report significantly more use of problem solving, positive self-statements, and palliative behaviors [200]. Female pain patients are more likely to catastrophize than male patients [96,101]. Studies are needed to assess the effectiveness of teaching male pain patients to use a range of additional coping strategies. Studies are also needed on the effectiveness of interventions to decrease catastrophizing in women with pain.

4.1.11. Mood—Women have higher levels of anxiety than men, and some studies suggest that anxiety and pain may be more closely related in men than in women [85,91]. However, there are exceptions. In clinic patients with pain, there are sex differences in level of mood disturbance (e.g., anxiety and depression symptom levels), but it is not clear whether they simply reflect the higher prevalence of mood disturbance among women in the general population. Possible mechanisms for the relationship of pain to mood and comorbidities include central sensitization and the balance of descending inhibition and descending facilitation [194].

4.1.12. Clinic vs. community—Sex and gender differences in pain may differ in clinical versus community populations. Although female-to-male ratios for pain may be substantial in the general population, these ratios are usually even larger among treatment seekers. However, treatment seeking is also related to pain level [207]. Women in the community report higher pain levels on average than men, which may explain the increased female-to-male ratio in clinical settings. In contrast, pain characteristics of men and women in treatment settings may not differ greatly [28,166]. Studies of community populations are needed to tease apart sex/gender-related risk factors for pain vs. treatment seeking.

4.1.13. Other psychosocial factors—A single cross-sectional study shows that the relationship of number of social roles and presence of pain differs by age and pain condition in women [119]. Studies are needed on gender differences in the effect of living arrangements, employment history, social support, marital status, and family composition on pain and pain outcomes (e.g., [68]).

5. Translational considerations for the study of sex differences in pain and analgesia

Translational research is an iterative process. While “translational” is generally regarded as applying knowledge from animal studies to human studies and eventually clinical practice, a more valuable model is presented in Fig. 2. Specifically, to complete the information flow, clinical experience and human experimental research findings should inform animal research. Such interactions exist for some recent studies of sex differences in pain, as demonstrated by the two examples that follow: temporal summation and opioid analgesia.

5.1. Examples of translational research

5.1.1. Temporal summation of pain—The physiological phenomenon of “wind-up” was originally observed in the feline spinal cord in response to electrical stimulation of primary afferents [135]. Subsequent studies elaborated the conditions necessary for wind-up (e.g., C-fiber stimulation, interstimulus intervals of 5 s or less, NMDA-receptor activation) and extended observations to thermal and mechanical stimuli. Although wind-up is a transient upregulation of post-synaptic responsiveness to C-fiber input, it shares some properties with central sensitization, which is a long-term upregulation of post-synaptic response to a wider range of inputs. Thus, one could envision wind-up as a gateway to central sensitization, a potential factor in several chronic pain conditions [162].

As a first step in translation, a psychophysical correlate of wind-up was sought, and referred to as the temporal summation (TS) of pain [156]. Like wind-up, it required C-fiber stimulation, short interstimulus intervals, and NMDA-receptor activation [202]. As TS was explored further, studies reported that women showed greater temporal summation of pain than men [62,176,178]. The sex difference in TS could be attributed to factors other than wind-up, as suggested by studies pointing to gender role expectations as associated factors [167].

In another translational step, TS was found to be significantly more enhanced in women with chronic pain conditions such as fibromyalgia [188–190] and TMD [132,175]. This phenomenon was observed even in asymptomatic body sites. Because fibromyalgia and TMD are significantly more prevalent in women than men, it has been suggested that the naturally greater TS in women put them in a position to be more easily upregulated into a pathological state [177]. While this concept remains speculative, it should direct attention to altered CNS processing of nociceptive signals as at least one factor underlying the chronic pain of conditions with higher female prevalence.

5.1.2. Opioid analgesia—Another translational example involves the identification of a sex-dependent genetic association with opioid analgesia. Based on mouse strain surveys and subsequent genetic linkage mapping in mice, Mogil and colleagues determined that mutations of the murine melanocortin-1-receptor gene (*Mclr*) influenced κ -opioid analgesia in a sex-dependent manner. Because most redheaded, fair-skinned humans show functional mutations of the human *MC1R* gene, a study of pentazocine analgesia was conducted in redheads. Consistent with the mouse data, women with two variant *MC1R* alleles displayed significantly greater analgesic responses to pentazocine on thermal and ischemic pain stimuli compared to women with either one or no variant *MC1R* alleles and men [143]. Thus, a novel sex-dependent genetic association with mixed action (κ/μ) opioid analgesia was successfully translated from mice to humans.

5.2. Future translational studies

Translational pain research could be aided by bringing tools and knowledge from other areas of neuroscience. Areas of particular value include affective, cognitive, and autonomic

neuroscience, as well as the fields of stress and addiction research. While these areas overlap with pain research to some extent, the sharing of translational models would be of value all around.

The discussion above hints at the significant gains that could be made from deliberate attempts at translational research. To assist in this effort, our field should promote increased communication among basic scientists, translational researchers, and clinicians dealing with pain patients. While pain research has developed such communication channels to some degree, as reflected in national and international scientific meetings, there is significant room for improvement. An important step would be organizing training programs (graduate, postgraduate, fellowships) to include substantive experience in all domains of the translational model [219].

6. Is there enough evidence to warrant sex-specific pain interventions?

The evidence does not appear strong enough to warrant sex-specific pain interventions in most situations. Initial studies [72,73] found that mixed action (κ/μ) opioid drugs produced greater analgesia after third molar extraction in women than in men. However, later human and animal research has produced equivocal results regarding sex differences in opioid analgesia [43]. Some evidence indicates that serotonergic agents (5HT₄ agonists, 5HT₃ antagonists) may be more efficacious in alleviating IBS symptoms in women than in men [30,97,145,151]. However, these clinical trials have been criticized because the higher frequency of IBS in females skewed the sex distribution. Studies with larger numbers of males should be conducted. Furthermore, research into the mechanisms by which these drugs produce their effects is needed in order to explain why a unique serotonin receptor pharmacology is specifically relevant to IBS, and also the significant influence of estrogens on this system [22]. There may be female-specific pain mechanisms that are yet to be elucidated, and these may lead to novel therapeutic approaches for pain in women. A prime example is the recent report that the antinociception resulting from the i.t. application of morphine requires the functional recruitment of spinal dynorphin in females, but not males [127].

Alongside studies of pharmacological interventions, a few non-pharmacological treatment studies have examined the potential for sex effects [90,103,109]. However, findings are mixed, and more studies are required that not only consider whether men and women respond differently to such interventions, but also compare effects for different pain conditions and treatment approaches. Including sex as a factor in clinical trials and reporting any differences in outcomes are paramount in addressing the lack of research in this area.

7. Future directions

The main goals of research on sex differences in pain/analgesia are to: (1) determine mechanisms that contribute to the generally greater prevalence of pain in females than males, (2) discover how sex-specific mechanisms of pain/analgesia can be exploited to improve pain management for both sexes, and (3) determine differences in outcome when similar treatments (pharmacological, interventional, behavioral) are applied. To attain this goal, a number of important issues remain to be addressed. These are listed below, in no particular order of importance:

What are the hormonal vs. genetic (sex chromosome) contributions to sex differences in pain/analgesia?

Mouse models now exist to test whether mice of the same gonadal sex (either males or females), which differ in sex chromosome complement (XX vs. XY), have different phenotypes reflective of pain or analgesia. If XX and XY males, for example, differ in their response to

pain, then one can conclude that Y chromosome genes present only in the XY mice, or X chromosome genes (present in different genomic doses in XX vs. XY, and with different parental genomic imprints), cause the difference [12,49,69,153]. The sex chromosome effect does not tell where the X or Y chromosome genes act to cause the sex difference, although direct actions of Y chromosome genes have been demonstrated in the brain [52]. These new mouse models offer the opportunity to discover previously unknown direct effects of specific X or Y chromosome genes, which influence phenotypes via mechanisms that are not mediated by sex hormones. The models also allow testing, for the first time, the interaction of effects between sex chromosome complement and gonadal hormones.

What is the contribution of local hormone effects to sex differences in pain/analgesia?

Many hormone effects on pain/analgesia that were initially thought to be due to gonadal release of hormone may actually be due to de novo hormone synthesis in tissues such as the brain and spinal cord (e.g., progesterone [136,184], estradiol [9,86,108]). For example, changes in spinal aromatase activity dramatically and immediately affected pain thresholds in the Japanese quail, without changes in plasma levels of gonadal steroids [56,57]. Future studies in which various steroidogenic enzyme inhibitors (or hormone agonists or antagonists) are locally infused would contribute to our understanding of how local changes in hormone action result in behavioral changes in sensitivity to pain and analgesia.

How do psychological factors such as stress, mood, and conditioning (expectation) contribute to sex differences in pain/analgesia?

Psychosocial factors contribute substantially to pain perception in humans and may differentially influence pain in men and women [64,101,159,167,172]. There are well-documented sex differences in stress responses in both animals and humans [112], and sex differences in mechanisms of stress-induced analgesia have been reported in rodents [141]. Because pain is a stressful experience in itself, it is likely that sex differences in stress responses contribute to sex differences in pain. For instance, housing conditions (isolated vs. grouped) significantly affect the onset of inflammatory responses in rats. Furthermore, sex differences in acute stress effects on the inflammatory response are dependent on the housing conditions of the animals [84]. Social factors can be examined in rodents, as in a recent study demonstrating modulation of pain sensitivity in mice as a function of witnessing their cagemates (but not strangers) in pain [114]. Further animal and human research is necessary to reveal the extent to which psychological and social factors contribute to sex differences in pain/analgesia, and the mechanisms by which they do so. Additional research is also needed on how observers' perceptions of pain are related to the sex/gender of the person experiencing pain.

How does pain chronicity contribute to sex differences in pain/analgesia?

For ethical and practical reasons, most animal studies to date have used acute painful stimuli, despite the facts that (a) the most robust and striking sex differences in pain in humans are the 2- to 6-fold greater prevalence and greater intensity of chronic pain syndromes in women compared to men [199], and (b) the most pressing need for research advances is for alleviation of chronic, severe pain. Because women are more likely than men to have a history of clinical pain experiences, and pain history influences current pain perception [170], chronicity of pain is most likely an important contributing factor to sex differences in pain/analgesia. Animal studies can be utilized to determine whether sex differences in pain/analgesia are amplified as the duration of persistent pain lengthens [39,89,210], or as subjects experience repeated episodes of pain over time. Repeated episodes of formalin testing engender adaptations in nociception that are gonadal hormone-dependent [7,31], suggesting that pain chronicity is indeed an important factor to consider in future preclinical studies of sex differences in pain/

analgesia. The extent to which chronic pain or analgesic use alters an individual's circulating gonadal hormones (e.g., [8,10,47,104]), which can in turn affect their pain/analgesic sensitivity, should also be considered.

To what extent are sex differences in pain or analgesia due to sexually dimorphic ascending (afferent) pathways vs. sexually dimorphic pain modulation?

Some pathological pain states might be attributable to inadequate tonic levels of endogenous analgesia rather than (or along with) sensitization of the nociceptive system. For example, a growing literature documents that human sufferers of complex pain disorders such as fibromyalgia are impaired in their ability to recruit endogenous pain inhibitory mechanisms [107,117]. Staud and colleagues [191] found that diffuse noxious inhibitory control (DNIC)-induced attenuation of experimental pain "wind-up" was absent in normal females and fibromyalgia patients, suggesting that women may be overrepresented among fibromyalgia patients precisely because of this deficiency. Moreover, hypertonic saline-induced muscle pain activates brain μ -opioid receptors less in women than in men [221], and brain μ -opioid receptor activation is estradiol-dependent in women [187]. The spinal cord endorphin/ μ -opioid receptor analgesic system is more robust and 'higher gain' in male vs. female rodents, which, if also true for humans, could be one mechanism underlying the greater female prevalence and intensity of chronic pain syndromes [81]. Sex differences in the anatomy and physiology of endogenous descending pain modulatory pathways have been reported in the rat [129,130]. These pathways are also sexually dimorphic in terms of their activation by persistent pain as well as in their responsiveness to exogenous opioids. Given that most previous studies characterizing the anatomical and physiological organization of pain pathways were conducted in males, these results highlight the necessity of including female subjects in all experimental paradigms, and further suggest the need for a reevaluation of conclusions based on the previous anatomical studies.

What are the cellular and molecular bases of sex differences in and hormonal modulation of pain/analgesia?

Investigators should focus studies on *qualitative* rather than simply *quantitative* sex differences, the former referring to whether mechanisms underlying pain-related responses are fundamentally different in females versus males. We know little about the cellular mechanisms of steroid action in the brain, especially with regard to pain/analgesia. Many of the central regions implicated in pain and analgesia (i.e., periaqueductal gray, spinal cord, dorsal root ganglion) contain receptors for both estrogens and androgens and have the ability to synthesize steroids locally [18,56,146]. Binding of specific steroids to their receptors within these central and peripheral regions is likely involved in ligand-dependent transcriptional events, thereby influencing the expression of various neurotransmitters and receptors. Future studies are needed to further explore steroid-induced cellular consequences such as μ -opioid receptor internalization [55], uncoupling of the μ -opioid receptor from such downstream targets as ion channels [98] and regulators of gene expression, synthesis of endogenous neurosteroids that might modulate pain [155], and variables regulating the inflammatory response in chronic pain such as prostaglandins and cytokines [212]. Moving beyond steroids and steroid receptors may reveal new cellular pathways that mediate sex differences in sensitivity to pain and analgesia.

How do sex differences in pain/analgesia change over the lifespan?

The vast majority of animal and human studies have been conducted in relatively young, healthy adult subjects. A few studies suggest that sex differences in pain/analgesia develop by the early neonatal period in the rodent [37,110,192], although it is not clear whether sex differences are observed that early in humans [65,80,152]. In contrast, beginning around puberty, age-dependent sex differences occur for several types of pain in humans. Animal

models can be readily employed to determine sex differences in pain/analgesia over the lifespan, although pursuing this question will require continued development of age-appropriate and more comprehensive pain tests in animals. Additionally, a body of research exists on pain-related gender roles in college-aged men and women (at least in the United States), but we know very little about generational differences and change in pain-related gender roles over the lifespan. The importance of this issue is escalating as life expectancy increases world-wide.

Should diagnostic criteria for certain pain-related conditions differ by sex?

It is recommended that researchers use the same core instruments for measurement in both sexes, but investigate whether additional questions or tests need to be added for one sex or the other. Research is also needed on whether the form of specific diagnostic questions should differ for male and female patients.

Are there factors that lead to chronic pain resilience or chronic pain susceptibility?

Research is needed on sex/gender differences in factors that protect against developing a pain problem, or, when pain is present, prevent debilitating pain. Further research is also necessary to determine the impact of pain and trauma during the perinatal period on pain sensitivity and responsiveness to reinjury in adulthood. For example, a recent study in rats reports that long-term negative consequences of neonatal inflammatory pain are significantly exacerbated in females in comparison to males [115].

Can existing data be better exploited?

Existing clinical databases should be used to assess sex differences in the effectiveness of clinical treatments, including psychological, physical medicine, and medication treatments. For example, female–male comparisons of the analgesic effects of pain medications (measured in opioid equivalents), as well as of the effectiveness of SSRIs for pain, should be conducted.

8. Recommendations to governments and professional and research bodies

Clinical trial methods, analysis, and reporting should be modified such that subject flow through the study and reports of treatment effects (both positive effects and adverse events) is broken out by sex, e.g., through updated CONSORT guidelines.

Both sexes should be included in medication trials in sufficient numbers to detect sex or gender effects. Report of outcomes in each sex should also be mandated in medication trials. Governmental regulatory bodies are in a position to implement these recommendations.

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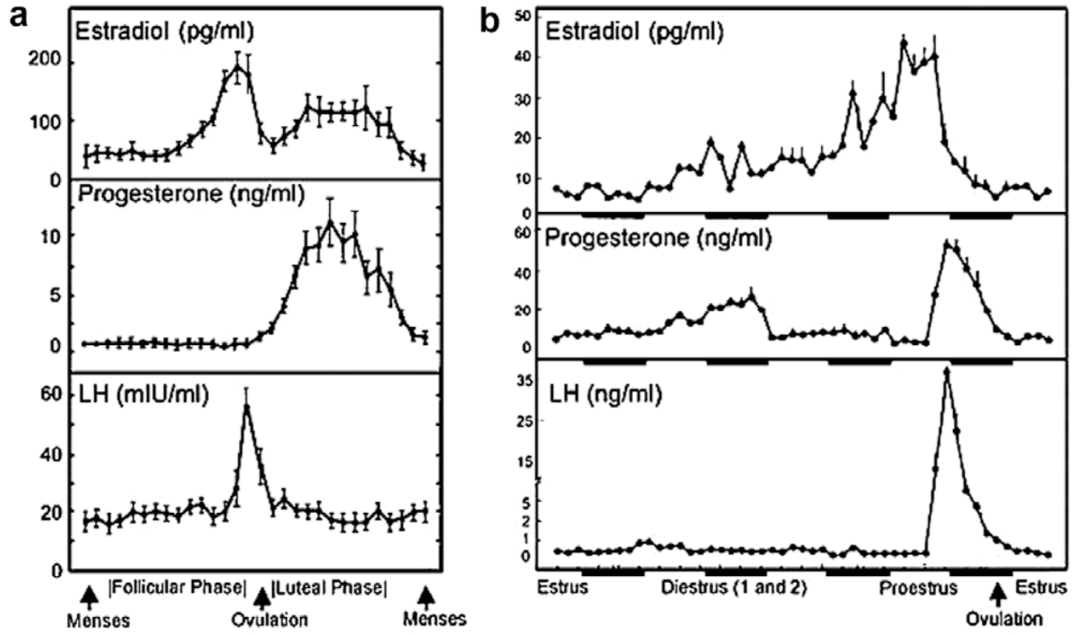


Fig. 1. Patterns of estradiol, progesterone, and leuteinizing hormone (LH) in humans (a) and rats (b) during the reproductive cycle. Time unit of the x-axis in (a) is days; in (b), it is hours. Dark bars in (b) indicate dark period of the day/night cycle. Note that during the follicular phase in humans and its analog in rats (diestrus 2), 17β -estradiol rises but progesterone secretion remains low. After the LH surge, progesterone is elevated in both rats and women. In humans, the corpus luteum also secretes some 17β -estradiol, whereas in rats, during the brief luteal phase, 17β -estradiol concentrations decline. Reproduced from [17], with permission.

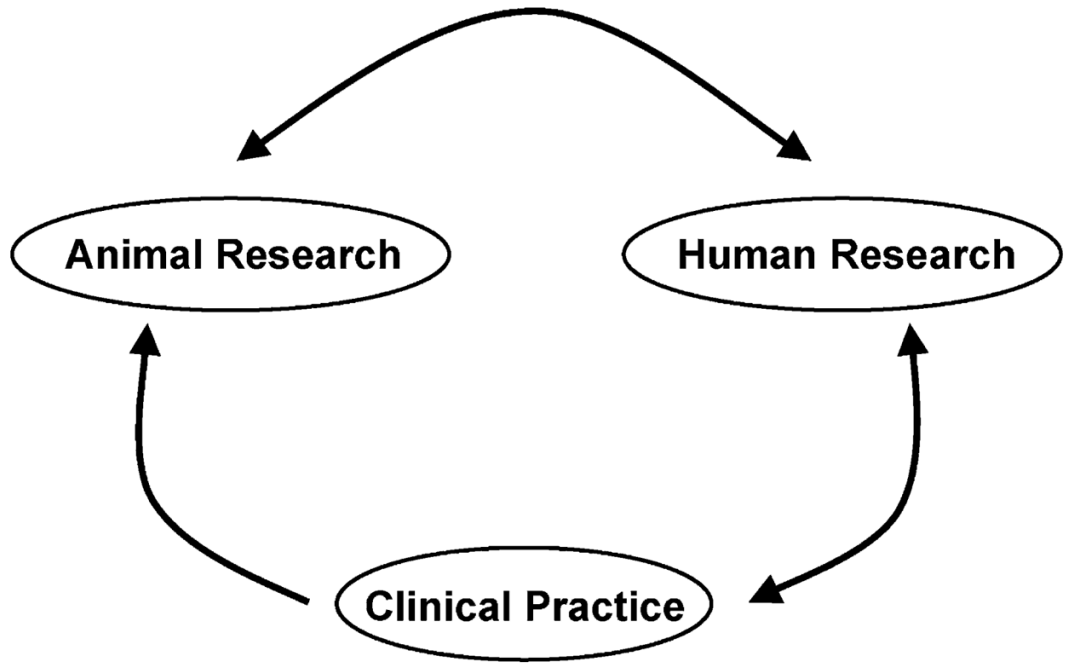


Fig. 2.
The full cycle of translational research.

Table 1

Factors decidedly or likely relevant to sex differences in experimental studies of human pain

Stimulus	Context	Individual	Response measures
Modality	Threat/safety	History	Threshold
Location	Stress	Age	Tolerance
Timing	Time of testing	Coping	Suprathreshold scaling
Tissue type	Experimenter gender	Genetic background	Stimulus discriminability
Phasic/tonic	Contingency	Race/ethnicity	Reflex
	Sleep history	Hormonal status	Imaging
	Co-stimulation (odor, sounds, etc.)	Anxiety (trait and state)	Cardiovascular system
		Reproductive status (females)	
	Social environment	Communication (extent and style)	
		Attention	
		Expectation	
		Mood state	

Table 2

Sex prevalence of various painful disorders

Female prevalence	Male prevalence	No sex prevalence
Migraine headache with aura	Migraine without aura	Acute tension headache
Chronic tension headache	Cluster headache	Clusertic syndrome
Post-dural puncture headache	Post-traumatic headache	“Jabs” and “jolts” syndrome
Hemicrania continua	SUNCT syndrome	Secondary trigeminal neuralgia
Cervicogenic headache	Raeder’s paratrigeminal syndrome	Neuralgia of nervus intermedius
Tic douloureux	Pancoast tumor	Painful ophthalmoplegia
Temporomandibular joint disorder	Thromboangiitis obliterans	Maxillary sinusitis
Occipital neuralgia	Brachial plexus avulsion	Toothache due to dentinoenamel defects
Periapical periodontitis & abscess	Pancreatic disease	Toothache due to pulpitis
Atypical odontalgia	Duodenal ulcer	Cracked tooth syndrome
Burning tongue	Abdominal migraine	Dry socket
Carotidynia	Lateral femoral cutaneous neuropathy	Vagus nerve neuralgia
Chronic paroxysmal hemicrania	Post-herpetic neuralgia	Stylohyoid process syndrome
Temporal arteritis	Hemophilic arthropathy	Thoracic outlet syndrome
Carpal tunnel syndrome	Ankylosing spondylitis	Brachial plexus tumors
Raynaud’s disease		Esophageal motility disorders
Chilblains		Chronic gastric ulcer
Causalgia		Chron’s disease
Reflex sympathetic dystrophy		Diverticular disease of colon
Hemicrania continua		Carcinoma of the colon
Chronic venous insufficiency		Familial Mediterranean fever
Fibromyalgia syndrome		Hereditary coproporphyrria
Esophagitis		Acute herpes zoster
Reflux esophagitis with peptic ulcer		Burns
Slipping rib syndrome		
Twelfth rib syndrome		
Gallbladder disease		
Post-cholecystectomy syndrome		
Irritable bowel syndrome		
Interstitial cystitis		
Acute intermittent porphyria		
Proctalgia fugax		
Chronic constipation		
Pyriformis syndrome		
Peroneal muscular atrophy		
Multiple sclerosis		
Rheumatoid arthritis		
Pain of psychological origin		
Age dependent sex differences		

Female prevalence	Male prevalence	No sex prevalence
Female prevalence	Male prevalence	
Gout (after age 60)	Gout (before age 60)	
Osteoarthritis (after age 45)	Osteoarthritis (before age 45)	
Livedo reticularis (after age 40)	Coronary artery disease (before age 65)	
	Erythromelalgia (over age 50)	

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