Experimental Pain Models Reveal No Sex Differences in Pentazocine Analgesia in Humans

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Background: Accumulating evidence suggests that there are sex differences in analgesic responses to opioid agonists. Several studies using an oral surgery pain model have reported more robust analgesia to κ-agonist–antagonists (*e.g.*, pentazocine, nalbuphine, butorphanol) among women than among men. However, evidence of sex differences in κ-agonist–antagonist effects from studies of experimentally induced pain in humans is lacking.

Methods: Therefore, the analgesic effects of intravenous pentazocine (0.5 mg/kg) were determined in healthy women (n = 41) and men (n = 38) using three experimental pain models: heat pain, pressure pain, and ischemic pain. Each pain procedure was conducted before and after double-blind administration of both pentazocine and saline, which occurred on separate days in counterbalanced order.

Results: Compared with saline, pentazocine produced significant analgesic responses for all pain stimuli. However, no sex differences in pentazocine analgesia emerged. Effect sizes for the sex differences were computed; the magnitude of effects was small, and an equal number of measures showed greater analgesia in men than in women. Also, analgesic responses were not highly correlated across pain modalities, suggesting that different mechanisms may underlie analgesia for disparate types of pain.

Conclusions: These findings indicate significant analgesic responses to pentazocine in both men and women across multiple experimental pain assays, and the absence of sex differences contrasts with previous data from the oral surgery model. The most likely explanation for the discrepancy in results is that of differences in the pain assays. These findings are important because they suggest that sex differences in opioid analgesia may be specific to certain types of pain.

OPIOID analgesic responses are characterized by substantial individual differences, and an understanding of the factors contributing to this variability is of tremendous clinical and scientific importance. In this regard, sex-related influences on responses to opioids have received i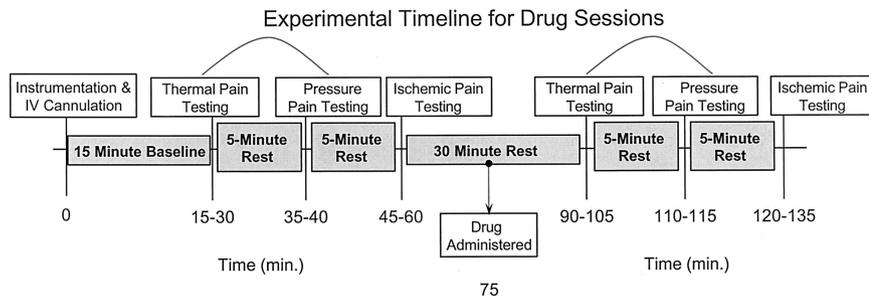ncreasing attention in recent years. A recent review indicated that women consume significantly less opioid medication postoperatively than men do.[1] However, because many of these studies failed to assess pain, it is difficult to determine whether the lower opioid consumption in women was due to enhanced analgesia or other factors (*e.g.*, side effects). A more recent investigation of nearly 2,300 patients found that female patients had similar or lower postsurgical pain ratings than male patients even though they consumed 23.5, 37.5, and 43% less opioid than the male patients on postoperative days 1, 2, and 3, respectively.[2] In addition to these findings from postoperative studies, which almost exclusively involve μ opioids, sex differences in μ-opioid analgesia have been demonstrated using experimental pain models. Sarton *et al.*[3] examined morphine analgesia among 10 healthy women and 10 healthy men using an electrical pain model. Women showed greater analgesic potency but slower onset and offset of analgesia. These authors had previously reported greater morphine-induced respiratory depression among women than among men.[4,5] Zacny[6] used two experimental pain models (pressure and cold pressor pain) to determine sex differences in analgesic responses to three μ-opioid agonists, morphine, meperidine, and hydromorphone, in a sample of 16 male and 15 female patients. No sex differences in analgesia emerged for pressure pain; however, analgesic responses for all three drugs were greater among female patients for cold pressor pain. Therefore, evidence from both laboratory and clinical studies suggests that women may experience greater μ-opioid analgesia than men.

A series of studies that have garnered considerable scientific and media attention has investigated sex differences in analgesic responses to κ-agonist–antagonist medications using an oral surgery model. These investigators first reported greater analgesic responses among female patients compared with male patients for pentazocine but not morphine.[7,8] Subsequently, they demonstrated more prolonged analgesia among female patients than among male patients with the κ-agonist–antagonists nalbuphine and butorphanol.[9] More recently, they have demonstrated that after low-dose nalbuphine (5 mg), pain ratings increased in men but showed no change in women, whereas higher doses (10 and 20 mg) produced analgesia of longer duration in women than in men.[10] These results indicate more robust analgesic responses to κ-agonist–antagonist medications among women but no differences in morphine analgesia. We recently demonstrated that the melanocortin-1 receptor gene (MC1R) moderated analgesic responses to pentazocine among

Experimental Timeline for Drug Sessions

Fig. 1. Timeline of the experimental session. The *boxed text* presents the components of the experimental session, and the *numbers* below the *timeline* indicate the approximate time in minutes at which experimental procedures were conducted. The *lines* linking thermal pain to pressure pain indicate that these two procedures were conducted in counterbalanced order.

women but not among men; however, there was no overall sex difference in pentazocine analgesia.[11] Therefore, sex differences in responses to κ-agonist–antagonists have yet to be replicated in other clinical assays or using experimental pain models.

The main purpose of the current study was to investigate sex differences in pentazocine analgesia using multiple, well-validated experimental pain models. Healthy women and men underwent three experimental pain procedures (heat pain, pressure pain, and ischemic pain) before and after double-blind administration of pentazocine and saline placebo. Laboratory pain models were used because they allow greater stimulus control and the effects of pentazocine could be tested in the absence of other medications that are administered in most postoperative pain models. Based on the previous findings of Gear *et al.*,[7,8] we hypothesized that women would show greater analgesic responses than men.

Materials and Methods

Subjects

Subjects included 41 women and 38 men recruited *via* posted advertisements. All participants were healthy nonsmokers and were free of clinical pain, psychiatric disturbance, substance abuse, or use of centrally acting medications. Subjects refrained from any over-the-counter medication use for at least 24 h before testing. Nineteen (46.3%) of the women were taking oral contraceptives. Based on our previous findings,[11] subjects (five women, nine men) with two variant alleles on the MC1R gene were excluded from the analyses. Subjects were paid $50 per experimental session for their participation.

General Experimental Procedures

All subjects participated in two experimental sessions, one involving administration of pentazocine and the other involving saline placebo, in randomly counterbalanced order. For women, all sessions were conducted during the follicular phase of the menstrual cycle, between days 4 and 10 after the onset of menses. Half of the women participated in the two experimental sessions within the a single menstrual cycle, separated by 2–7 days, and the other half participated across two

sequential menstrual cycles, in which case the sessions were separated by approximately 28 days. To maintain consistent intervals across sex, 19 men participated in the two sessions within 1 week, and 16 men participated with the longer interval (*i.e.*, 4 weeks).

Before the experimental sessions began, all subjects provided verbal and written informed consent and completed a series of health and psychological questionnaires to ensure that all subjects were free of any medical conditions, psychological conditions, or both. The two experimental sessions were identical, except that pentazocine was administered in one session and saline was administered in the other. All sessions were conducted by two experimenters, either two women or one woman and one man. Each experimental session started with insertion of an intravenous cannula for drug administration followed by a 15-min rest period, during which blood pressure and heart rate were monitored. Next, predrug experimental pain testing was performed, including assessment of thermal pain, pressure pain, and ischemic pain (described in detail in the next section, Pain Testing Procedures). After the predrug pain testing, a 15-min rest period was observed, followed by double-blind intravenous bolus administration of either pentazocine (0.5 mg/kg) or saline, in randomized order. Fifteen minutes after drug administration, pain testing was repeated in a manner identical to the predrug testing. A timeline depicting the experimental session is presented in figure 1. Adverse effects reported by subjects, observed by experimenters, or both were also recorded. All procedures were approved by the University of Florida Health Science Center's Institutional Review Board (Gainesville, Florida).

Pain Testing Procedures

The following experimental pain procedures were conducted before and after drug administration. Pressure and thermal pain were delivered first in counterbalanced order, separated by a 5-min rest period. Ischemic pain always occurred last to reduce the possibility of carryover effects. Before each pain procedure, digitally recorded instructions were played for the subject.

Pressure Pain Threshold. A handheld algometer (Pain Diagnostics and Therapeutics, Great Neck, NY) was used to assess pressure pain threshold (PPT). Me-

chanical pressure was applied using a 1-cm^2 probe. A relatively slow application rate of 1 kg/s was used to reduce artifact associated with reaction time. Subjects were instructed to report when the pressure first became painful. PPTs were assessed at three sites: the center of the right upper trapezius (posterior to the clavicle), the right masseter (approximately midway between the ear opening and the corner of the mouth), and the right ulna (on the dorsal forearm, approximately 8 cm distal to the elbow), with the order of site presentation counterbalanced. PPTs were assessed three times at each site, and the average of the three assessments was determined and used in subsequent analyses.

Thermal Pain Procedures

Threshold and Tolerance. The first thermal procedure involved assessment of heat pain threshold and tolerance. Contact heat stimuli were delivered using a computer-controlled Medoc Thermal Sensory Analyzer (TSA-2001; Ramat Yishai, Israel), which is a Peltier element–based stimulator. Temperature levels were monitored by a contactor-contained thermistor and returned to a preset baseline of 32°C by active cooling at a rate of 10°C/s. The 3 × 3-cm contact probe was applied to the right ventral forearm. In separate series of trials, warmth thresholds, heat pain thresholds, and heat pain tolerances were assessed using an ascending method of limits. From a baseline of 32°C, probe temperature increased at a rate of 0.5°C/s until the subject responded by pressing a button to indicate when he or she first felt pain and when he or she no longer felt able to tolerate the pain. This slow rise time was selected as a test of pain evoked mainly by stimulation of C-nociceptive afferents, as has been previously demonstrated.[12,13] Four trials of heat pain threshold (HPTh) and heat pain tolerance (HPTo) were presented to each subject. The position of the thermode was altered slightly between trials (although it remained on the ventral forearm) to avoid either sensitization or response suppression of cutaneous heat nociceptors. For each measure, the average of all four trials was computed for use in subsequent analyses.

Temporal Summation of Thermal Pain. After a 5-min rest period, the temporal summation procedure was conducted. This procedure involved administration of brief, repetitive, suprathreshold heat pulses to assess first and second pain and temporal summation of the latter.[14] Subjects rated thermal pain intensity of 10 repetitive heat pulses applied to the right dorsal forearm. The target temperatures were delivered for less than 1 s, with a 2.5-s interpulse interval during which the temperature of the contactor returned to a baseline of 40°C. Subjects were asked to rate the peak pain for each of the 10 heat pulses. Because subjects vary in their responses to heat pain, we examined temporal summation at two

different stimulus intensities. This increased the likelihood that at least one set of stimuli would be at least moderately painful but tolerable for the majority of subjects. Therefore, two sets of target temperatures, 49° and 52°C, were used. Subjects were instructed to verbally rate the intensity of each thermal pulse using a numerical rating scale as previously described,[15] on which 0 represented no sensation, 20 represented a barely painful sensation, and 100 represented the most intense pain imaginable. Subjects were told that the procedure would be terminated when they reported a rating of 100, when 10 trials had elapsed, or when they wished to stop. Two measures from the temporal summation procedure at each temperature were used in subsequent analyses. The rating of the first trial was selected to represent a measure of first pain, and the rating of the fourth trial was selected to reflect summated second pain. These ratings were chosen for two reasons. First, using similar methods, it has been established that the most intense pain from the first pulse is that of "first pain" and that the most intense pain from the third or fourth pulse is that of "second pain."[14,16] This pattern results from a progressive suppression of first pain and temporal summation of second pain throughout a train of four heat pulses. Second, inspection of the mean ratings for each trial indicated that the increase in ratings was most robust through trial 4, suggesting that trial 4 best reflected temporal summation.

Modified Submaximal Tourniquet Procedure

After the first two pain procedures, a 5-min rest period was observed, after which subjects underwent the modified submaximal tourniquet procedure.[17,18] Next, the right arm was exsanguinated by elevating it above heart level for 30 s, after which the arm was occluded with a standard blood pressure cuff positioned proximal to the elbow and inflated to 240 mmHg using a Hokanson E20 Rapid Cuff Inflator (D.E. Hokanson, Bellevue, WA). Subjects then performed 20 handgrip exercises of 2-s duration at 4-s intervals at 50% of their maximum grip strength. Subjects were instructed to report when they first felt pain (ischemic pain threshold [IPTh]) and then to continue until the pain became intolerable (ischemic pain tolerance [IPTo]), and these time points were recorded. Every 30 s, subjects were prompted to alternately rate either the intensity or the unpleasantness of their pain using joint numerical (0–20) and verbal descriptor box scales.[19] An uninformed 15-min time limit was observed. In addition to IPTh and IPTo, two total pain scores were created, one for pain intensity and one for pain unpleasantness, by summing all ratings obtained during the procedure. To replace missing values created by subjects terminating the procedure before the time limit, the last rating provided was carried forward.

Table 1. Demographic Characteristics and Predrug Pain Measures for Women and Men

	Women (n = 41)		Men (n = 38)	
Age, yr	23.9 (6.2)		26.4 (6.4)	
Ethnicity (% white)	79		78	
Weight, kg*	65.7 (11.3)		80.2 (10.8)	
Pentazocine dose, mg*	32.9 (5.7)		40.1 (5.4)	
	Pentazocine Day	Saline Day	Pentazocine Day	Saline Day
HPTh, °C*	40.8 (3.1)	40.5 (2.9)	41.9 (2.7)	42.4 (3.1)
HPTo, °C*	46.1 (2.7)	46.0 (2.8)	48.2 (2.0)	48.1 (2.3)
Trial 1 rating (at 49°C)	43.1 (25.1)	43.5 (24.7)	34.0 (18.9)	34.4 (18.8)
Trial 1 rating (at 52°C)	70.8 (26.5)	69.3 (26.7)	60.6 (25.9)	58.4 (23.7)
Trial 4 rating (at 49°C)	50.3 (25.8)	51.5 (27.2)	40.8 (22.8)	40.4 (22.3)
Trial 4 rating (at 52°C)*	78.4 (24.3)	79.3 (23.9)	67.5 (27.4)	64.9 (25.8)
PPT masseter, kg*	2.4 (0.8)	2.4 (0.8)	3.1 (1.1)	3.1 (1.2)
PPT trapezius, kg*	4.4 (1.5)	4.2 (1.4)	5.7 (2.0)	5.9 (2.2)
PPT ulna, kg*	4.5 (1.8)	4.6 (2.0)	6.3 (2.6)	6.3 (2.5)
IPTh, s	160.9 (132.0)	150.9 (103.9)	206.9 (218.6)	221.5 (227.8)
IPTo, s	604.0 (273.3)	578.6 (277.5)	598.4 (259.8)	610.8 (261.0)
Ischemic pain intensity	191.6 (67.5)	197.5 (70.6)	189.2 (89.4)	183.3 (89.4)
Ischemic pain unpleasantness	196.1 (65.5)	199.4 (71.6)	190.4 (85.0)	187.8 (86.9)

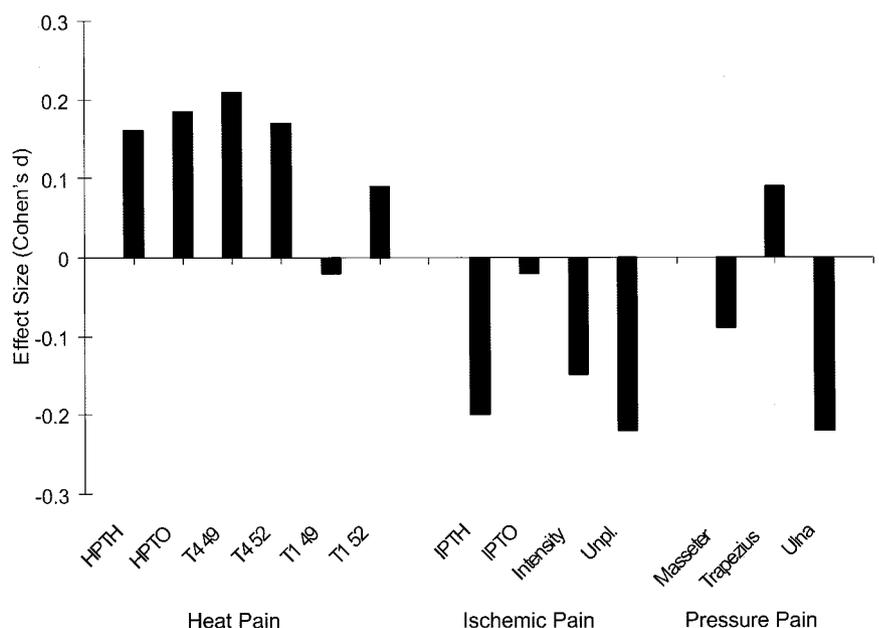Values represent mean (SD) unless otherwise indicated.

* Sex difference, $P < 0.05$.

HPTh = heat pain threshold; HPTo = heat pain tolerance; IPTh = ischemic pain threshold; IPTo = ischemic pain tolerance; PPT = pressure pain threshold.

Statistical Analysis

Because determination of analgesic responses requires reliability of pain measures, subjects' predrug pain values were analyzed for consistency. If the between-session change in any predrug pain measure was greater than 2 SDs above the average change for all subjects, then that observation was excluded as an outlier. This resulted in removal of 23 observations, 11 from women and 12 from men. Sex differences in predrug pain responses were evaluated using individual analyses of variance. To determine drug effects for each pain measure obtained, a change score was calculated by determining the difference between the predrug value and the postdrug value. These calculations were performed such that positive numbers always represented a reduction in pain. Thus, each subject had two change scores for each variable, one from the pentazocine day and the other from the saline day. For the two tolerance measures, change scores were not computed for subjects who reached the cutoff during predrug testing because this created a ceiling effect. This excluded 4 subjects for HPTo (all men) and 23 subjects for IPTo (13 women, 10 men). The statistical significance of drug effects was determined using separate mixed-model analyses of variance for each pain measure, in which sex was a between-subjects variable and drug was a within-subjects variable. Relations among analgesic indices from different pain modalities were determined using Pearson correlations. Significance was set at $P < 0.05$.

Results

Predrug Pain Responses

Characteristics of the sample and baseline pain data are presented in table 1. Men and women were of similar age and ethnicity, and equal numbers of men and women received pentazocine in session 1 and session 2. The majority of participants were white (78.5%), with 8.9% Hispanic, 6.3% African American, and 6.3% Asian. Predrug pain responses did not differ on the pentazocine day *versus* the saline day ($P > 0.05$). Men weighed more than women and received higher amounts of pentazocine ($P < 0.001$). Significant sex differences in HPTh and HPTo emerged, with women having lower values ($P < 0.05$). Women provided higher pain ratings for trial 1 and trial 4 during the temporal summation procedure, but the sex difference reached significance only for trial 4 at 52°C ($P < 0.05$). Also, PPT at all sites was significantly lower for women ($P < 0.001$). No sex differences emerged for any of the ischemic pain measures ($P > 0.05$).

Analgesic Responses to Pentazocine

Pre–post change scores for all pain responses are presented in table 2. Significant drug effects emerged for HPTh and HPTo, and both threshold and tolerance values increased after pentazocine but not after saline administration ($P < 0.05$). For temporal summation, no significant drug effects emerged for trial 1 ratings at either temperature ($P > 0.10$). However, pentazocine produced slightly lower pain ratings for trial 4 at 49°C ($P = 0.1$) and significantly lower ratings for trial 4 at 52°C ($P < 0.05$). PPT at all sites increased significantly after pentazocine relative to saline ($P < 0.001$ for all). Ischemic pain threshold and tolerance increased significantly after pentazocine compared with placebo, and summed pain intensity and unpleasantness decreased significantly after pentazocine compared with saline ($P < 0.005$ for all).

No sex differences emerged for drug effects on any of the pain responses ($P > 0.10$ for all). To determine the magnitude of any potential sex differences in analgesic

Table 2. Pre–Post Change Scores for All Pain Measures under Each Drug Condition (Pentazocine *vs.* Saline) for Women and Men

	Women (n = 41)		Men (n = 38)	
	Pentazocine	Saline	Pentazocine	Saline
HPTh, °C*	0.6 (2.3)	−0.1 (2.1)	0.8 (2.2)	−0.4 (2.0)
HTPo, °C*	0.7 (1.8)	−0.1 (0.8)	0.7 (1.3)	−0.5 (1.4)
Trial 1 rating (at 49°C)	−1.1 (12.8)	−2.3 (10.5)	0.1 (11.3)	−0.9 (9.5)
Trial 1 rating (at 52°C)	−0.6 (11.6)	−2.6 (9.1)	0.3 (10.2)	−2.9 (9.0)
Trial 4 rating (at 49°C)	0.3 (12.5)	−0.7 (12.5)	4.3 (11.5)	0.2 (11.2)
Trial 4 rating (at 52°C)*	2.4 (10.8)	−0.3 (8.7)	2.4 (11.0)	−2.4 (7.8)
PPT masseter, kg*	0.6 (0.5)	−0.1 (0.3)	0.5 (0.8)	−0.1 (0.7)
PPT trapezius, kg*	0.8 (1.1)	−0.2 (0.6)	0.8 (1.2)	−0.3 (1.0)
PPT ulna, kg*	0.6 (1.0)	−0.3 (0.8)	0.4 (1.1)	−0.3 (0.7)
IPTh, s*	65.3 (123.4)	0.4 (56.7)	59.9 (125.5)	19.1 (67.6)
IPTo, s*	120.1 (172.8)	31.9 (70.6)	97.8 (138.3)	36.0 (98.4)
Ischemic pain intensity*	43.2 (53.4)	11.2 (23.5)	39.6 (38.2)	15.0 (34.3)
Ischemic pain unpleasantness*	43.4 (59.3)	13.1 (26.5)	37.1 (45.7)	19.7 (37.5)

Values represent mean (SD) unless otherwise indicated.

* Drug effect significant, $P < 0.05$.

HPTh = heat pain threshold; HPTo = heat pain tolerance; IPTh = ischemic pain threshold; IPTo = ischemic pain tolerance; PPT = pressure pain threshold.

responses, effect sizes were computed as follows. First, an analgesic index was created for each pain measure by subtracting the pre–post saline change score from the pre–post pentazocine change score because this reflects the effect of pentazocine after removing the placebo response. Then, these analgesic indices were used to determine the Cohen D, by dividing the mean group difference (*i.e.*, men − women) by the pooled SD. Using this metric, 0.2 represents a small effect size, 0.5 represents a moderate effect size, and 0.8 represents a large effect size. These values are presented in figure 2, with positive values indicating that men showed greater analgesic responses than women and negative values indicating that women showed larger analgesic responses

relative to men. As can be seen, the effect sizes range from −0.22 to 0.21, and the average effect size is 0. Therefore, sex differences that occurred generally were small in magnitude and were equally divided between those showing greater analgesic responses among women and those showing greater responses among men. The pattern of effects suggests that men showed greater analgesia than women on thermal pain measures, whereas women showed greater analgesia than men on ischemic pain responses and perhaps for pressure pain.

Correlations among Measures of Analgesia. To examine associations among analgesic responses across pain modalities, an average analgesic index was computed for each pain modality. For example, the heat pain

Fig. 2. Effects sizes for sex differences in analgesic responses for each pain measure. *Bars* represent the effect size (Cohen D) reflecting the magnitude of the sex difference in the analgesic index. The analgesic index reflects the analgesic effect of pentazocine after accounting for any changes in pain produced by saline, which was computed by subtracting the saline change score from the pentazocine change score for each pain measure. The data presented in the figure reflect only the magnitude of the sex difference and do not provide information regarding the magnitude of the analgesic response. Positive values indicate that analgesic effects were larger in men than in women, and negative scores indicate that analgesic effects were larger in women than in men. A value near zero simply indicates no sex difference in analgesic response. The general rule of thumb for interpreting effect sizes is that 0.2 reflects a small effect, 0.5 reflects a medium effect, and 0.8 reflects a large effect. Therefore, all effects sizes presented in this figure are small. HPTH = heat pain threshold; HPTO = heat pain tolerance; IPTH = ischemic pain threshold; IPTO = ischemic pain tolerance; Unpl. = unpleasantness.

drug pain testing 15 min after drug administration, and it was completed within 60 min of drug administration. This timing is consistent with the period reported on in the University of California at San Francisco studies because they reported sex differences at 10 min and at 30 min in one study[7] and from 30 to 170 min in another.[8] However, Kobal *et al.*[25] reported that 30 mg intravenous pentazocine had a longer half-life among women than among men, although their fixed dosing resulted in women receiving a higher dose per unit body weight. Nonetheless, the longer residence time of pentazocine among women is interesting given that the only tendency toward greater analgesia for women in our data emerged for ischemic pain, the pain task that was conducted after the longest postdrug delay. In addition, previous research with morphine has shown more rapid onset of analgesia in men and longer duration of analgesia in women,[3] and nalbuphine, another κ-agonist–antagonist, produced more prolonged analgesia in women compared with men.[9] Therefore, future research exploring sex differences in opioid analgesia should evaluate sex differences in the onset and offset of drug effects.

In addition, sample selection may contribute to the different study outcomes. Participants in our protocol were recruited specifically for a study involving experimental pain testing and analgesics and may represent a different population than patients presenting for third molar extraction, who are then offered participation in a clinical protocol. These additional methodologic differences notwithstanding, variability in the pain assays seems most likely to account for the differences in findings. This could be an important finding because it indicates that sex differences in analgesic responses to pentazocine and perhaps other opioids may be limited to certain types of pain. Additional research is needed to determine the conditions under which sex differences in opioid analgesia are most likely to emerge.

The use of multiple pain assays in the current study yielded additional important results. First, consistent with studies of μ-opioid agonists on multiple pain tests,[16,36] pentazocine produced larger and more reliable effects on pain predominantly associated with C-nociceptor stimulation (HPTh, HPTo, ratings of the fourth heat pulse) than pain predominantly associated with A-δ nociceptor stimulation (ratings of the first heat pulse). Also, the largest analgesic effects emerged on measures of ischemic pain, a form of tonic muscle pain that reflects a combination of A and C nociceptors from deep tissue. This form of tonic pain may better simulate many types of clinical pain, as argued by Smith *et al.*[37] In addition, analgesic responses showed low correlations across pain modalities (table 3). For women, analgesic responses assessed using heat pain measures were significantly correlated with analgesia determined *via* ischemic and pressure pain assays; however, these correlations were low in magnitude and not significantly

different from the correlations in men, and no other significant correlations emerged. A similar pattern of results has been reported for baseline pain responses, in which measures based on different pain modalities are modestly correlated at best.[38,39] This suggests that despite significant analgesic responses across all pain modalities, analgesic sensitivity determined using one type of pain is a poor predictor of analgesic response to other types of pain and that different mechanisms underlie analgesic responses for different types of pain. An important practical implication of these findings is that multiple pain assays will be required to fully characterize the analgesic effects of many drugs.

Several limitations of the current study deserve mention. First, analgesic responses assessed using experimental pain models may not accurately reflect the analgesic responses that occur in the clinical setting. Experimental models offer several advantages, including control over stimulus parameters, the ability to test multiple pain modalities in the same sample, and freedom to examine analgesic responses in the absence of other medications or tissue pathology. However, the clinical relevance of analgesic responses measured against experimentally induced pain has yet to be empirically determined. As discussed in the third paragraph of the Discussion, sex differences in the analgesic effects of pentazocine may differ for inflammatory postoperative pain compared with nociceptive experimental pain. Therefore, these results do not refute the existence of sex differences in the analgesic effects of pentazocine for postoperative pain; rather, these findings suggest that sex differences in pentazocine analgesia may be specific to postoperative pain and do not represent a general phenomenon. To test this hypothesis, one would need to evaluate pentazocine analgesia against both experimental and postoperative pain in the same sample of women and men.

Second, our sample consisted of healthy young adults whose responses may not generalize to other populations that may differ in health status, age, or other relevant variables. Third, we only tested one dose of pentazocine over a limited time period and were unable to determine whether sex differences are present at other doses or whether time course influences sex differences. Similarly, we did not collect any pharmacokinetic or pharmacodynamic data; therefore, we were unable to determine whether there were sex differences in duration of action or plasma concentrations of the drug. As mentioned above, our doses and timing were similar to those reported previously in studies that demonstrated sex differences in pentazocine analgesia[7,8]; however, these investigators have also demonstrated that sex differences in responses to other κ-agonist–antagonists are dose dependent,[10] and others have reported sex differences in the kinetics of pentazocine.[25] Additional research to determine the importance of dose as well as

pharmacokinetic and pharmacodynamic factors to sex differences in opioid analgesia is needed.

These limitations notwithstanding, we tested a substantially larger sample than did previous studies, which provided sufficient power to detect a sex difference of moderate magnitude. In addition, we used multiple well-validated experimental pain procedures, each of which was sensitive to the analgesic effects of pentazocine. When combined with previous research, these findings suggest that sex differences in responses to κ-agonist–antagonists may emerge only under certain conditions, and further research is needed to better characterize sex differences in responses to opioid analgesics.

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