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Original Research Article

Individual Differences in Morphine and Butorphanol Analgesia: A Laboratory Pain Study

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Abstract

Objective. Responses to opioid analgesics are highly variable, and the understanding of contributing factors is limited. This laboratory study was designed to examine the contributions of sex and race to inter-individual variability in response to opioids.

Design. A randomized, double-blind, mixed design was implemented in the evaluation of analgesic response to a μ-opioid agonist and mixed agonist–antagonist, using three well-validated experimental pain assays (thermal, pressure, and ischemic).

Subjects. Participants included a total of 142 healthy subjects (76 men/66 women), 119 non-Hispanic whites and 23 African Americans.

Intervention. Three sessions of pain testing were completed prior to and following an intravenous administration of morphine (0.08 mg/kg), butorphanol (0.016 mg/kg), and placebo (saline) in counterbalanced order.

Outcome Measures. A change score was calculated from the difference between the pre-drug and post-drug values. Three separate change scores (morphine, saline, and butorphanol) were computed for each experimental pain variable. Mixed-model analyses of covariance were performed on analgesic change scores.

Results. Significant sex differences emerged for predrug pain measures with minimal differences for race.

Sex differences in opioid analgesia were not demonstrated. However, significant race differences and race X drug interactions emerged for thermal, pressure, and ischemic pain measures. The pattern of results generally indicated that for pressure and ischemic pain, African American subjects showed greater analgesic responses to both medications compared with non-Hispanic whites. For thermal pain threshold, butorphanol but not morphine analgesia was greater for African American vs non-Hispanic whites.

Conclusions. Findings are among the first to demonstrate race differences in a laboratory study of opioid analgesia.

Key Words. Individual Differences; Experimental Pain; Opioid Analgesia; Race

Introduction

Pain and analgesic responses are characterized by robust inter-individual variability. While sex differences have been reported in experimental pain responses and in the prevalence and severity of clinical pain conditions, evidence

regarding sex differences in opioid analgesic responses has been more variable. Sex differences in preclinical studies indicate that male rodents demonstrate an increased μ-opioid analgesic response in comparison to their female counterparts [1–3]. However, evidence regarding sex differences in opioid analgesia among humans is less consistent [4,5]. Clinical studies have demonstrated greater analgesic responses to mixed-action opioid agonist–antagonists among women compared with men [6–8], while studies examining sex differences in μ-opioid analgesia have yielded mixed results [9,10].

Laboratory pain studies are even less conclusive with minimal sex differences indicated [9]. In contrast to clinical studies, a trend toward greater butorphanol analgesia was found among male compared with female volunteers tested against cold pressor pain [11]. Although sex differences in μ-opioid analgesia in laboratory studies have demonstrated limited support [12], pharmacodyamic differences have been revealed, indicating that women experience a slower onset of analgesia and increased side effects to μ-opioids [13–15]. Interestingly, conclusions from a recent meta-analysis of clinical and experimental pain studies indicated that overall, women demonstrated a greater analgesic response to morphine compared with men with insufficient evidence to support sex differences among other exogenous opioids [5].

In addition to sex differences, previous studies have demonstrated racial and ethnic group differences in clinical and experimental pain responses [10,16,17]. Compared with non-Hispanic white subjects, African Americans have been found to report greater pain and disability associated with several clinical pain conditions [18,19]. Also, laboratory pain studies consistently demonstrate greater pain sensitivity across multiple stimulus modalities among African American [10,17]. However, research regarding racial and ethnic group differences in opioid analgesia is limited. In a study of patients with cancer pain, Kaiko and colleagues reported that *Blacks* receiving 8 mg of morphine displayed analgesia that was comparable to *Whites* receiving 16 mg of morphine [20].* While a handful of clinical studies examining analgesic responses in other ethnic groups have been conducted, no study to date has compared analgesic responses in African American and non-Hispanic white subjects using laboratory pain methods [21–23].

The current study was designed to further delineate individual differences in opioid analgesia using laboratory pain models. The study included a large subject sample, multiple pain measures, the comparison of two opioid analgesic agents, and a control for nonspecific effects using a placebo condition. The choice of analgesic agents was based on previous literature suggesting that the pattern or magnitude of sex differences may vary across these two classes of opioids [5]. Moreover, given our interest in race group differences, the use of these two different opioids allowed us to determine whether the previous findings of greater analgesic responses among African Americans would be replicated in a laboratory setting and whether the findings would be specific to morphine or might extend to a mixed-action agonist–antagonist. For this study, a commonly prescribed μ-opioid, morphine, and a mixed-action agonist with a favorable side effect profile, butorphanol, were selected. The design of the study allowed for the evaluation of sex and race differences. Given the inconsistencies noted in the literature regarding sex differences and opioid analgesia, one goal of the study was to implement a within-subject laboratory design to help elucidate and clarify sex differences in opioid analgesia. A second goal of the study was to evaluate possible race differences. Based on previous studies [20,24], we hypothesized that African Americans would show greater morphine analgesia than non-Hispanic whites.

*When citing the work of other authors, the race and ethnic categories presented in the original publications are incorporated in the text to accurately represent the terms utilized (italicized with initial presentation).

Methods

Seventy-six men (eight African Americans, 68 non-Hispanic whites) and 66 females (15 AA, 51 NHW) were recruited through Institutional Review Board (IRB)-approved posted advertisements. The sample contained only healthy nonsmoking individuals between the ages of 18 and 45 without clinical pain, psychiatric disturbance, substance use disorder, or use of centrally acting medications assessed by a health history questionnaire. All the participants were screened by the study physician. Demographic information including age, sex, ethnicity, and race was collected by self-report. The terms African American and non-Hispanic whites are used to differentiate between participant race in the study. However, when citing the work of other authors, the terms specified in respective publications are incorporated in the text to accurately represent the group terms utilized. Fifty-six percent of women were taking oral contraceptives. Testing was scheduled between days 4 and 20 after the onset of menses to avoid result influenced by the perimenstrual time frame that has been associated with heightened pain sensitivity [9]. Prior to participation in each experimental session, subjects confirmed that they had refrained from taking over-the-counter medications within the past 24 hours and consuming caffeine in the past 2 hours, and reported no significant health changes. Participants were paid $25 an hour for their involvement in the study.

General Experimental Procedures

The research was conducted at the General Clinical Research Center at the University of Florida. The study involved four sessions, the first being an introduction to the study proto¹col and the following three involving the administration of morphine, butorphanol, and saline in a double-blind, randomized order. All the subjects provided verbal and written informed consent and completed a number of psychological and health-related questionnaires prior to

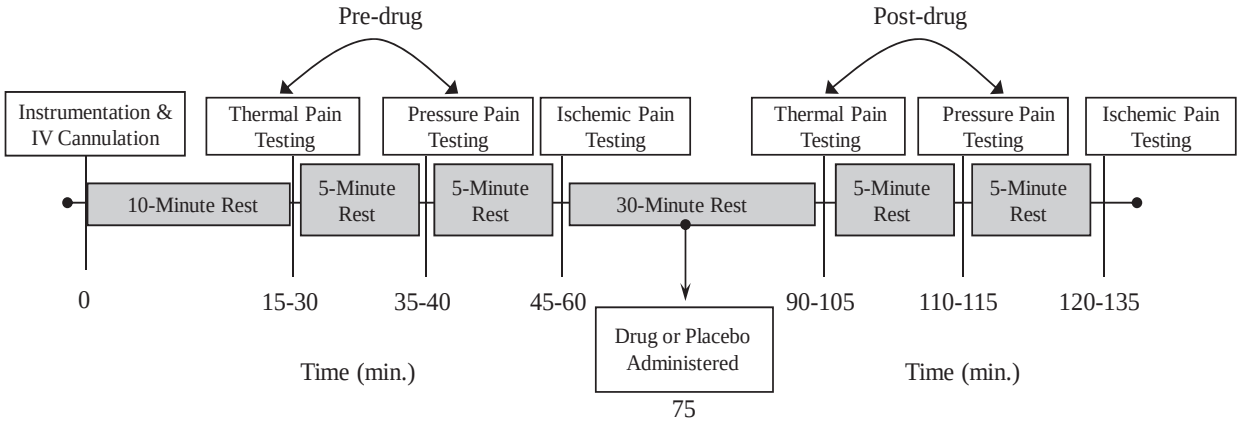

Figure 1 Time line representing the temporal structure of procedures during each experimental session. The boxed text represents the procedures (white) and rest breaks (gray) implemented during the experimental session. The numbers below the timeline reflect the approximate time in minutes at which experimental procedures were conducted. The bidirectional arrows between thermal pain and pressure pain indicate that these two procedures were conducted in counterbalanced order. Reprinted and adapted from Fillingim RB, Ness TJ, Glover TL, Campbell CM, Hastie BA, Price DD, Staud R [13], with permission from Elsevier.

participation in the research protocol. Following the introductory session, the three remaining experimental sessions were identical in procedure with the exception of drug administration (saline, morphine, or butorphanol), which was implemented in a counterbalanced order.

Experimental procedures used in this study followed the general protocol implemented successfully in our previous studies [13,25]. Specifically, two experimenters and a registered nurse conducted the testing sessions. One experimenter was responsible for the sensory testing component by the bedside and the other experimenter operated the equipment and recorded the data. The gender of the bedside experimenter remained consistent for each experimental session. The clinical research nurse was responsible for monitoring of vital signs, administering the placebo/analgesic drug, and completing blood draws. Subjects maintained a semirecumbent position in a hospital bed during all study procedures. An intravenous (IV) cannula was inserted at the beginning of each experimental session followed by a 10-minute rest period. Six minutes into the rest period, vital signs were taken including blood pressure, heart rate, respiratory rate, mean arterial pressure, end-tidal carbon dioxide level, and oxygen (O_2) saturation with a blood pressure monitor and capnograph coupled with a nasal cannula. Ten minutes following IV placement, the predrug sensory testing protocol was completed, including thermal pain, pressure pain, and ischemic pain measures (described later). The order of thermal and pressure pain was randomly determined for each subject and maintained for all sessions. The ischemic pain procedure was always completed last to reduce carry-over effects. Following pre-drug sensory testing, a 15-minute rest period was observed followed by the double-blind IV administration of 0.08 mg/kg of morphine, 0.016 mg/kg butorphanol, or saline over 5 minutes. These doses approximate a low–to-moderate clinical dose with estimated equianalgesia [26]. Fifteen minutes following drug administration postdrug sensory testing was repeated in a manner identical to the predrug testing. A time line of the experimental session is presented in Figure 1. All clinically significant adverse effects (either reported by the subjects or observed by the experimenters) were documented. The protocol and all procedures were approved by the University of Florida's IRB. Informed consent was obtained from each subject.

Pain Testing Procedures

Similar to our previous studies [13,25], experimental pain procedures were conducted during the introductory session to reduce novelty effects. Digitally recorded instructions were provided to the subjects during the introductory session for each of the experimental pain procedures. During the three experimental sessions, the same procedures were implemented prior to and following drug administration with verbal instructions reiterated before each procedure.

Pressure Pain Threshold

Pressure pain threshold (PPT) was assessed with a handheld algometer (Pain Diagnostics and Therapeutics, Great Neck, NY, USA). Mechanical pressure was applied with a 1-cm^2 probe with a constant rate of pressure of 1 kg/sec, which helps reduce artifact related to reaction time. Subjects were instructed to report (verbally or by raising their hand) their first feeling of pain as a result of the pressure. Three sites were used to assess PPTs on the right side of the body: the center of the upper trapezius (posterior to

the clavicle), the upper masseter (approximately midway between the ear opening and the corner of the mouth), and the ulna (dorsal forearm, approximately 8 cm distal to the elbow). The site order was randomly counterbalanced and a minimum of three trials (with readings within 1 kg) were recorded at each position. The average of the three assessments for each site was calculated and used in subsequent analysis.

Thermal Pain Procedures

Threshold and Tolerance

The first thermal procedure involved assessment of warmth threshold (WTh), heat pain threshold (HPTh), and heat pain tolerance (HPTo). Contact heat stimuli were delivered using a computer-controlled Medoc Thermal Sensory Analyzer (Pathway Pain & Sensory Evaluation System, Ramat Yishai, Israel), which includes 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/sec. The 3 cm × 3 cm contact probe was applied to the right ventral forearm. In separate series of trials, WTh, HPTh, and HPTo were assessed using an ascending method of limits. From a baseline of 32°C, probe temperature increased at a rate of 0.5°C/sec until the subject responded by pressing a button to indicate when they first felt warmth (WTh) and pain (HPTh) and when they were no longer able to tolerate the pain (HPTo). This slow rise time was selected as a test of pain evoked mainly by stimulation of C nociceptive afferents, as has been previously demonstrated [27,28]. Four trials of WTh, HPTh, and HPTo were presented to each subject. The position of the thermode was altered slightly between trials (remaining on the ventral forearm) in order 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

The second thermal procedure involved administration of brief, repetitive, suprathreshold heat pulses to assess temporal summation of heat pain [29]. Series of 10 repetitive pulses were applied to the right dorsal forearm using the Contact Heat Evoked Potential Stimulator (CHEPS), which combines heat-foil technology with a Peltier element, thereby achieving heating and cooling rates of at least 40°C/sec. Three series of 10 stimuli were applied at three different target temperatures set during the introductory session. The target temperatures were 46, 48, and 50°C. For each series, the baseline temperature was 35°C, the target temperature was delivered for 700 msec, and the interstimulus interval (at the baseline temperature) was 2.5 seconds. Subjects rated the peak pain for each of the 10 heat pulses using a numerical rating scale (0 represented no pain and 100 represented the most intense pain imaginable). The average rating across all 10 trials for each temperature was used in subsequent analyses.

Modified Submaximal Tourniquet Procedure

Following completion of the pressure and thermal pain procedures, a rest period of 5 minutes was implemented prior to beginning the tourniquet procedure [30,31]. The right arm was exsanguinated by elevating it above heart level for 30 seconds, after which, the blood flow to the arm was occluded with a standard blood pressure cuff positioned proximal to the elbow and inflated to 240 mm Hg using a Hokanson E20 Rapid Cuff Inflator (D.E. Hokanson, Bellevue, WA, USA). In response to recorded instructions, subjects performed 20 handgrip exercises of 2-second duration at 4-second intervals at 50% of their maximum grip strength. Subjects were instructed to report when they first felt pain (ischemic pain threshold [IPTh]), then to continue until the pain became intolerable (ischemic pain tolerance [IPTo]), at which point, the procedure was stopped. The IPTh and IPTo time points were recorded. Every 30 seconds during the procedure, subjects were prompted to alternately rate either the "intensity" or "unpleasantness" of pain using a combined numerical (0–20) and verbal descriptor box scales (e.g., intensity: 0—no pain sensation to >18—extremely intense; unpleasantness: 0—neutral to >17—very intolerable), which provides ratio-level scaling of both the sensory (intensity) and affective (unpleasantness) dimensions of pain. These scales have been used extensively in our laboratory with good results [12]. An overall ischemic pain intensity (IPInt) and ischemic pain unpleasantness (IPUnpl) summary score was created by summing all intensity ratings and all unpleasantness ratings obtained during the procedure, providing cumulative ischemic intensity and unpleasantness rating totals. Additionally, cardiovascular measures (systolic, diastolic, mean arterial blood pressure, and heart rate) were recorded every 60 seconds. An uninformed 15-minute time limit was observed. To replace missing values created by subjects terminating the procedure before the time limit, the last rating provided was carried forward.

Side Effects

Side effects were recorded by the clinical research nurse, observed by experimenters, or reported by the participant. Common side effects included: nausea, emesis, dizziness/light-headedness, pallor, diaphoresis, headache, pruritus, and fainting. Other less common side effects that occurred were recorded as "other." For analytic purposes, the total number of side effects experienced was computed for each drug administration.

Data Analysis

Each subject could participate in up to four separate testing sessions. Data from the introductory session were excluded from the analysis, as this session was intended solely to reduce novelty effects in the subsequent medication sessions. Predrug pain measures were defined as the average of up to three predrug sessions. For participants who discontinued the protocol before completion, predrug measures were computed based on the avail-

able predrug data. Ethnic group differences were analyzed by comparing non-Hispanic whites (N = 119) to African Americans (N = 23). The drug effect for each pain measure was determined by a change score calculated as the difference between the predrug value and the post-drug value. The difference scores were computed such that positive numbers represent a reduction in pain and negative numbers represent an increase in pain. Thus, subjects had three separate change scores (morphine, saline, and butorphanol) for each experimental pain variable. Analgesic analyses included only those participants who completed the entire study. Additionally, if subjects reached the cutoff on tolerance measures during predrug assessment, change scores were not computed (ceiling effect) for that specific measure. In this study, 17 subjects (14 non-Hispanic whites/3 African Americans) were excluded from the analysis of HPTo and 42 subjects (35 non-Hispanic whites/7 African Americans) were excluded from IPTo. However, these subjects were included in all other analyses. Data were analyzed with SAS (SAS Institute, Cary, NC, USA) software. Each pre-drug pain measure was analyzed using ANOVA with sex and race as between-subject variables. Analgesic measures were subjected to a mixed-model ANCOVA with sex and race as between-subject variables, drug condition (morphine and butorphanol) as the within-subjects variable, and saline response as the covariate. Significant effects from the omnibus tests were further explicated using follow-up comparisons. Significance level was set at $P < 0.05$. Due to the low number of subjects in the AA group, interpretations were limited to two-way interactions.

Results

Demographic Characteristics

Demographic characteristics are presented in Table 1. The average age for both groups of men and women participants was 23. A significantly greater proportion of African American participants were female compared with male participants ($P = 0.049$). A total of nine (two AA females, four NHW females, one AA male, two NHW males) participants discontinued the study before completion. Five subjects discontinued because of the side effects of the medications, including nausea and dysphoria, and the remainder dropped out for other reasons such as vasovagal response to the IV insertion or due to scheduling difficulties. Information regarding side effects is addressed in greater detail later.

Table 1 Demographic characteristics

Variable	Women (N = 66)	Men (N = 76)
Age (years)	23.1	23.1
Race (%)		
African American	22.7	10.5
Non-Hispanic White subjects	77.3	89.5
Weight (kg)	65.8	81.9
Body mass index	23.8	25.1
Morphine dose (mg)	5.3	6.6
Butorphanol dose (mg)	1.0	1.3

Table 2 Predrug response to pain measures by sex

Variable	Women (N = 66) Mean (SD)	Men (N = 76) Mean (SD)
WTh (°C)**	33.8 (0.6)	34.4 (1.2)
HPTh (°C)	41.4 (2.6)	42.2 (2.4)
HPTo (°C)**	46.1 (2.3)	47.7 (2.4)
Average rating at 46°C	37.5 (25.2)	34.6 (24.7)
Average rating at 48°C	56.2 (26.3)	50.3 (26.9)
Average rating at 50°C*	72.7 (22.8)	63.2 (26.6)
PPT masseter (kg)**	2.3 (0.7)	3.0 (0.8)
PPT trapezius (kg)**	3.8 (1.6)	4.7 (1.6)
PPT ulna (kg)**	3.8 (1.5)	4.8 (1.7)
IPTh (sec)	136.6 (109.9)	128.3 (80.2)
IPTo (sec)	484.0 (272.6)	530.5 (252.5)
IPInt	209.8 (57.4)	200.5 (64.6)
IPUnpl	212.2 (59.0)	206.5 (64.8)

* Sig. (two-tailed) $P < 0.05$, ** Sig. (two-tailed) $P < 0.001$.
HPTh = heat pain threshold; HPTo = heat pain tolerance; IPInt = ischemic pain intensity; IPTh = ischemic pain threshold; IPTo = ischemic pain tolerance; IPUnpl = ischemic pain unpleasantness; PPT = pressure pain threshold; SD = standard deviation; WTh = warmth threshold.

Predrug Pain Responses

Predrug data were analyzed for all participants on whom data were available. As noted in Table 2, significant sex differences were found for WTh ($P < 0.0001$), average rating of thermal pain at 50°C ($P = 0.035$), HPTo ($P = 0.0003$), and PPTs at the masseter ($P < 0.0001$), trapezius ($P = 0.0003$), and ulna ($P < 0.0001$). Women reported lower WTh and HPTo, higher heat pain intensity at 50°C, and lower PPTs. Sex differences for ischemic pain measures were not statistically significant ($P > 0.05$). Race differences were analyzed by comparing NHW with AA subjects; results are presented in Table 3. One significant difference emerged; AA reported higher IPTh ($P = 0.0015$).

Analgesic Responses to Morphine and Butorphanol Grouped by Sex and Race

No sex differences emerged for any analgesic measure (all $P > 0.10$). Analgesic responses for morphine and butorphanol for non-Hispanic whites and African Americans are presented in Table 4.

Heat Pain Measure

Drug effects on WTh did not differ by sex or race ($P > 0.10$). For HPTh, a significant race X drug interaction was found

Table 3 Predrug response to pain measures by non-Hispanic whites and African Americans

Variable	non-Hispanic whites (N = 119) Mean (SD)	African Americans (N = 23) Mean (SD)
WTh (°C)	34.1 (0.9)	34.2 (1.3)
HPTh (°C)	41.8 (2.4)	41.9 (2.8)
HPTo (°C)	47.2 (2.4)	45.9 (2.7)
Average rating at 46°C	36.3 (23.8)	34.3 (30.7)
Average rating at 48°C	53.2 (25.6)	52.1 (32.5)
Average rating at 50°C	67.0 (24.9)	69.7 (28.1)
PPT masseter (kg)	2.7 (0.8)	2.8 (0.8)
PPT trapezius (kg)	4.3 (1.6)	4.4 (1.7)
PPT ulna (kg)	4.3 (1.7)	4.4 (1.6)
IPTh (sec)*	121.0 (81.3)	189.9 (134.6)
IPTo (sec)	525.7 (259.1)	422.1 (266.0)
IPInt	204.9 (60.4)	204.5 (67.3)
IPUnpl	209.8 (60.8)	205.8 (69.7)

* Sig. (two-tailed) $P < 0.005$.
HPTh = heat pain threshold; HPTo = heat pain tolerance; IPTh = ischemic pain threshold; IPTo = ischemic pain tolerance; IPInt = ischemic pain intensity; IPUnpl = ischemic pain unpleasantness; PPT = pressure pain threshold; SD = standard deviation; WTh = warmth threshold.

($P = 0.02$). Analysis of simple effects for HPTh difference scores indicated that African Americans showed significantly greater butorphanol analgesia than non-Hispanic whites, while morphine responses did not differ across the two race groups. There were no other significant race differences in thermal analgesic responses ($P > 0.05$). A main effect of drug was found for heat pain ratings at 50 degrees ($P = 0.036$), indicating that the analgesic response was greater for butorphanol than for morphine for both non-Hispanic whites and African Americans.

Pressure Pain Measures

Main effects of race emerged for PPT analgesic scores at the trapezius ($P = 0.041$) and the ulna ($P = 0.013$), such that African Americans showed greater analgesia across both drugs compared with non-Hispanic whites. No significant differences were present for pressure pain analgesic scores at the masseter ($P > 0.05$).

Ischemic Pain Measures

Significant race differences were present for analgesic scores for IPTh ($P < 0.0001$), IPInt ($P = 0.022$), and IPUnpl ($P = 0.028$). In each case, across both drugs, African Americans showed more robust analgesic responses than non-Hispanic whites.

Side Effects

No significant race differences in side effects emerged ($P = 0.79$). The total number of side effects was

Table 4 Analgesic response to morphine, butorphanol, and saline for non-Hispanic whites and African Americans

	non-Hispanic whites (N = 84–113) Mean (SD)			African Americans (N = 14–20) Mean (SD)		
Variable	Morphine	Saline	Butorphanol	Morphine	Saline	Butorphanol
WTh (°C)	0.4 (0.8)	0.4 (0.7)	0.5 (0.9)	0.3 (0.6)	0.2 (0.9)	0.7 (1.2)
HPTh (°C)†	0.4 (1.7)	0.03 (1.4)	–0.003 (1.9)	0.4 (2.0)	0.4 (1.53)	1.3 (1.7)
HPTo (°C)	0.5 (1.0)	–0.2 (0.8)	0.3 (1.2)	0.5 (1.0)	0.3 (1.0)	0.7 (1.9)
Average rating at 46°C	1.8 (13.0)	–1.6 (12.6)	3.4 (11.7)	–2.0 (7.3)	–5.4 (14.2)	–1.8 (13.0)
Average rating at 48°C	3.1 (10.4)	–2.4 (11.5)	5.4 (12.2)	3.9 (16.5)	3.9 (21.3)	–1.4 (20.4)
Average rating at 50°C‡	2.7 (9.5)	–2.1 (9.7)	5.6 (9.4)	0.75 (18.0)	–0.9 (10.3)	5.6 (16.5)
PPT masseter (kg)	0.2 (0.5)	–0.1 (0.5)	0.3 (0.5)	0.3 (0.7)	–0.03 (0.4)	0.5 (0.8)
PPT trapezius(kg)*	0.3 (0.9)	–0.3 (0.8)	0.6 (1.2)	0.7 (1.1)	–0.4 (0.7)	1.1 (1.4)
PPT ulna (kg)*	0.4 (1.1)	–0.05 (0.8)	0.5 (1.1)	1.0 (1.3)	–0.2 (1.0)	0.7 (1.2)
IPTh (sec)**	24.0 (89.2)	13.4 (73.2)	30.6 (87.1)	108.1 (154.5)	30.5 (220.9)	136.6 (164.3)
IPTo (sec)	116.2 (103.9)	13.8 (100.2)	117.9 (175.1)	122.3 (154.3)	14.4 (173.4)	170.7 (201.7)
IPInt*	27.8 (27.8)	9.0 (28.6)	31.0 (50.6)	42.4 (48.1)	5.9 (62.6)	53.8 (64.3)
IPUnpl*‡	28.1 (28.6)	10.8 (32.8)	35.4 (45.8)	44.2 (52.4)	5.4 (65.5)	54.8 (55.7)

* Significant main effect for ethnic group with saline response as a covariate ($P < 0.05$), ** ($P < 0.0001$).
† Significant for ethnic group X drug interaction with saline response as a covariate ($P < 0.05$).
‡ Significant main effect for drug with saline response as a covariate ($P < 0.05$).
HPTh = heat pain threshold; HPTo = heat pain tolerance; IPTh = ischemic pain threshold; IPTo = ischemic pain tolerance; IPInt = ischemic pain intensity; IPUnpl = ischemic pain unpleasantness; PPT = pressure pain threshold; SD = standard deviation; WTh = warmth threshold.

Table 5 Side effects to morphine and butorphanol by sex and race

	% Women (N = 63)	% Men (N = 74)	% non-Hispanic White subjects (N = 115)	% African Americans (N = 22)
Morphine				
Nausea	30	14	20	27
Emesis	13	1	5	14
Dizziness	29	18	22	27
Butorphanol				
Nausea	30	23	24	38
Emesis	13	1	6	10
Dizziness	56	43	49	48

significantly greater for women than men across both morphine and butorphanol ($P = 0.02$). Also, butorphanol produced a greater number of side effects than morphine ($P = 0.0015$). The most common side effects experienced were nausea (reported by 21.2% of subjects after morphine and 26.3% after butorphanol) and light-headedness/dizziness (22.6% for morphine and 48.9% for butorphanol). The frequencies of common side effects by sex and race are presented in Table 5. There were no serious adverse events.

Discussion

The purpose of this study was to evaluate sex and race differences in analgesic responses to morphine (μ-agonist) and butorphanol (mixed agonist–antagonist) using three well-validated experimental pain models (thermal, pressure, and ischemic). One of the key features of this study was the opportunity to compare responses to analgesic agents within subjects. Consistent with the literature, results demonstrated significant sex differences in pre-drug pain measures. Minimal race differences in pre-drug measures were found. Unexpectedly, the study did not reveal sex differences in morphine analgesia. Less noteworthy, the absence of sex differences in butorphanol analgesia is consistent with previous laboratory findings [5]. In contrast to no sex differences, significant race differences emerged for several measures of opioid analgesia. Specifically, African Americans demonstrated greater analgesic responses to both morphine and butorphanol compared with non-Hispanic whites on measures of pressure and ischemic pain. For heat pain tolerance measures, African Americans demonstrated greater butorphanol (but not morphine) analgesia than non-Hispanic whites.

Group differences in basal pain responses generally aligned with patterns noted in the literature [9,32]. Previous findings indicate that women demonstrate increased sensitivity to pressure, electrical, temporal summation, and muscle pain measures. Women in the study reported lower WTh, HPTo, and PPTs and higher heat pain intensity ratings at 50°C. Ethnic/race group differences have also been consistently reported in experimental pain sensitivity with African Americans and Hispanics demonstrating lower tolerance for heat, cold pressor, and ischemic pain [10,17,33,34]. In the present study, significant findings for predrug measures were limited to African Americans reporting higher IPThs. Of note, increased IPThs in African Americans have been previously reported [10,17,34].

A primary goal of this study was to further investigate individual differences in opioid analgesia specific to sex and race. Notably, race demonstrated a more significant relationship to individual differences in opioid analgesia than sex-related influences. Interestingly, the greater analgesia among African Americans was not accompanied by increased side effects, suggesting a potentially larger therapeutic window for opioids in this population. In contrast, despite similar analgesic responses across sexes, women experienced significantly more side effects from both medications, consistent with previous findings [15,35,36]. While numerous clinical and laboratory studies have investigated sex differences in exogenous opioid analgesia, there is a dearth of information on ethnic and race differences in opioid analgesia.

Given the increasing ethnic and racial diversity in the United States, understanding the association of these variables with opioid analgesia is particularly important. By 2050, 47% of the U.S. population will be represented by minority groups with 88.6% of the population growth by 2100 attributable to non-Anglo individuals [37,38]. Ethnic/racial disparity in pharmacological management of pain is prevalent in the literature [39–43]. Unfortunately, many studies involve a retrospective review of medical records and do not allow for an evaluation of the effectiveness of the analgesic intervention, and it is difficult to determine if the discrepant dosage pattern represents overprescription to some populations or underprescription to others [41].

A few studies have attempted to address ethnic group/race differences in analgesic responses. Kaiko and colleagues evaluated pain relief scores from patients diagnosed with cancer and chronic pain in controlled trials of analgesia [20]. Results indicated that *Black* patients receiving 8 mg of intramuscular morphine reported pain relief comparable to that experienced by *Whites* receiving 16 mg of morphine. A second study demonstrated similar results with *Caucasian* subjects requiring higher doses of morphine to obtain pain relief postsurgically compared with *African* and *Asian* subjects [24]. The current laboratory findings indicating that African American reported greater opioid analgesic responses than non-Hispanic whites subjects provide additional evidence in support of these earlier clinical findings [20,24].

Results warrant speculation of possible underlying mechanisms contributing to ethnic group/race differences in analgesic response. Studies have indicated that opioid pharmacokinetic and pharmacodynamic properties are influenced by genetic and nongenetic factors [44]. Cepeda and colleagues assessed ventilation responses to morphine in *Caucasians, native Indians, and Latinos* [21].

Differences were found with native Indians demonstrating increased susceptibility to respiratory depression in contrast to Caucasians. In a second study, morphine clearance was analyzed in eight *Chinese* and eight *White* men [44]. The rate of morphine clearance and gastrointestinal side effects (nausea and emesis) was higher in the Chinese subjects. White subjects demonstrated greater ventilatory depression and blood pressure reduction. Although ethnic differences were apparent, analgesic efficacy was not included in the analysis of either study.

A number of different genetic polymorphisms have been identified that may contribute to individual differences in opioid analgesia. Allelic variations of CYP2D6 resulting in either poor or excessive metabolizers have been associated with altered opioid metabolism specifically in *African* populations [45]. Another potential candidate gene is the μ-opioid receptor gene (*OPRM1*). The rare allele of the A118G single nucleotide polymorphism of *OPRM1* occurs more frequently in *European* and *Asian* populations compared to *African American* populations [46]. Interestingly, though the findings are mixed, the rare 118G allele has been associated with attenuated μ-opioid analgesic responses [47–49], as well as reduced basal pain sensitivity [50]. Further research including the investigation of genetic contributions to ethnic and race differences in opioid analgesia is warranted.

In the present study, race differences in analgesic responses were more consistent for ischemic and mechanical pain than heat pain. One explanation for this is that heat pain was not particularly sensitive to the opioids administered, as postdrug changes in heat pain measures were quite modest in magnitude. Another potential consideration is whether race differences in baseline pain sensitivity may have contributed to differences in analgesic effects, as preclinical studies have demonstrated an inverse relationship between basal pain sensitivity and analgesic, antinociceptive response [51–53]. However, this seems unlikely to account for the present findings for several reasons. First, race group differences in analgesic responses emerged on most pain measures, while differences in basal pain sensitivity were limited. Second, extending preclinical findings to the present study, previous evidence of increased sensitivity to pain among African Americans [10,17] would predict poorer analgesia among African Americans compared with non-Hispanic whites, rather than the more robust analgesic responses that we observed [51]. Third, in a recent cluster analysis completed on data gathered from the present study, subgroups of individuals who differed in their analgesic response patterns did not differ in their baseline pain responses [54].

These findings should be interpreted in light of the limitations of the study. First, given that this is a laboratory study, the findings may not apply to clinical settings. However, one of the strengths of experimental pain models is the opportunity to investigate analgesic effects while controlling for a number of confounding factors that can influence results. Second, the participants in the study were healthy, young adults, and thus, the results obtained may not generalize to the population as a whole. Third, our group sizes were disproportionate with a significantly greater number of non-Hispanic white subjects contrasted to African American subjects. Replication with a larger number of African American subjects and other ethnic and race groups is warranted. Fourth, due to the sample size, we were not able to analyze the sex by drug by race interaction. Future studies with a larger sample size would help delineate the relationship among these contributing factors. Fifth, we conducted large number of statistical tests and did not apply a correction to control experimentwise error. Thus, some of our significant findings could have emerged due to chance alone. Finally, we administered only one dose of each opioid; therefore, whether race group differences in analgesic response are dose dependent cannot be determined.

Conclusions

Sex and race differences in clinical and experimental pain have been consistently reported. However, findings regarding opioid analgesia are less conclusive. Inconsistencies have been reported on sex differences in opioid analgesia in clinical and experimental studies, with some indication that, in general, women experience greater morphine analgesia than men. Few studies have explored ethnic and race differences in opioid analgesia. The design of the current laboratory study allowed a within-group analysis of two opioid analgesic agents and a placebo condition and the evaluation of sex and race differences. While no sex differences emerged, significant race differences in analgesia were observed across both drugs and for multiple pain measures. The findings from this study are novel and indicate that race-related factors significantly contribute to individual differences in laboratory measures of morphine and butorphanol analgesia.

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