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Is the Pain Reducing Effects of Opioid Medication Reliable? A Psychophysical Study of Morphine and Pentazocine Analgesia

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Abstract

A number of laboratory studies have confirmed the efficacy of opioid medication in reducing pain generated by a number of psychophysical modalities. However, one implicit assumption of clinical and experimental pain testing of analgesics is that the analgesic response is stable and will be comparable across repeated administrations. In the current study, the repeatability of opioid analgesia was assessed in a randomized, double-blinded study using three psychophysical pain modalities (e.g., thermal, pressure, and ischemic) over four medication sessions (two with active drug, two with placebo). Psychophysical responses were evaluated before and after IV administration of either morphine (0.08 mg/kg; n=52) or pentazocine (0.5 mg/kg; n=49). To determine the ability of a drug to reduce pain, four analytic methods (i.e., absolute change, percent change, ratio, and residualized change scores) were calculated to generate separate analgesic index scores for each measure and drug condition. All analgesic index scores demonstrated a greater analgesic responses compared to saline for both medications, but stability (i.e. test-retest correlations) of the opioid analgesic indices depended on the pain measurement. Ischemic pain outcomes were moderately stable across sessions for both opioid medications; however, heat and pressure analgesic index scores were moderately stable for only morphine and pentazocine, respectively. Finally, within stimulus modalities analgesic index scores were highly correlated with each other, suggesting that the different methods for computing analgesic responses provided comparable results. These results suggest that analgesic measures are able distinguish between active drugs. In addition, analgesic responses to morphine and pentazocine demonstrate at least moderate reliability.

Keywords

Pain Psychophysics; Opioid Analgesia; Repeatability

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Conflict of interests

The authors of this study have no conflict of interests.

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1. Introduction

The management of pain in clinical settings continues to be a challenge. The cost of pain management is well established with a tremendous loss in productivity, decreased quality of life, and increasing costs to the health care system [33]. Currently, several strategies are used to manage acute pain including the utilization of opioid analgesics [48; 58], which exert their effects by activation of opioid receptors [63] in areas involved in pain processing [28; 64]. Analgesic efficacy, or the ability of an opioid analgesic to reduce pain, has been examined in experimental models of pain, which control confounding variables that can affect outcomes in clinical studies (e.g., inter-individual variability in disease severity and clinical symptoms). Experimental modalities also allow concurrent assessment of opioid effects on diverse pain modalities activating different mechanisms [56]. In these studies, two opioid analgesics have been shown to reduce experimental pain sensitivity across multiple stimulus modalities including morphine, a μ -agonist [21; 38; 49; 50], and pentazocine, a mixed action agonist-antagonist [18; 22; 49].

The most common analytical method for computing analgesic efficacy in experimental pain studies is the use of absolute change scores [14; 21; 22; 34; 52]. These scores are commonly derived by calculating the differences between the experimental pain outcomes collected during the pre-drug and post-drug. However, several questions have been raised about the reliability of these scores [4; 5; 9], particularly in studies designed for repeated assessment of pre-test/post-test paradigms. Despite being measured with the same methods (i.e., thresholds, ratings, etc.), difference scores can be considered a representation of two separate constructs [4] since the difference score incorporates properties from separate measures obtained before and after drug administration, and absolute difference scores do not take into consideration that changes in pain responses can be influenced by the initial value (e.g. regression to the mean, floor effects, ceiling effects). To address this problem, other methods can be used to calculate difference scores including percent change scores [15], ratio scores [31], and residualized change scores, which are derived from regressing the initial value onto the second value scores [4].

One implicit assumption, which is not commonly examined in experimental and clinical pain studies, is that subjects will respond consistently to an analgesic over repeated administrations. Subsequently, the expectation is that the analgesic response will be stable across repeated administration for a given individual. However, this assumption is not often tested due to the design of the study or issues related to tolerance [1; 13], common with opioids. The purpose of this study was to conduct secondary analysis of a previously study of opioid analgesia [21; 22; 47; 49] in order to examine the repeatability of experimental pain and analgesia produced by morphine and pentazocine. Thermal, pressure, and ischemic pain responses were evaluated before and after IV administration of the test drug. It is hypothesized that the analgesic efficacy of morphine and pentazocine, as determined by a reduction in experimental pain, will be highly comparable between two separate experimental testing sessions. Additionally, since it is unclear if one is a superior analgesic index a number of analytic methods were used to determine the ability of a drug to reduce pain.

2. Methods

2.1 Subjects

A convenience sample of 101 subjects was recruited through advertisements in the surrounding community and university. Demographics of the sample are listed in Table 1. Inclusion criteria for the study required that subjects be healthy non-smokers and free from clinical pain, psychiatric disturbance, substance abuse, or medication use. For each session,

subjects were required to abstain from over the counter medications and alcohol for at least 24 hours prior to testing. Subjects were compensated at the rate of \$25 per hour for their participation. The study was conducted at the General Clinical Research Center of the University of Florida, and all procedures were approved by the University of Florida's Institutional Review Board (Gainesville, Florida, USA). Prior to testing, subjects reviewed the study protocol and provided informed consent. Female subjects were tested at two different phases of the menstrual cycle, once during their follicular phase (days 4 to 10 after the onset of menses) and once during the late luteal phase (between 4 and 9 days prior to onset of menses). Whether the first session occurred during the follicular vs. luteal phase was randomly counterbalanced across women. Males were scheduled at comparable intervals. The study is a secondary analysis of a previously published dataset [21; 22; 47; 49].

2.2. General testing procedures

Subjects attended four psychophysical testing sessions, two sessions in which the active drug was administered and two sessions with placebo saline administered in a randomized, counterbalanced fashion. Placement into an active drug group was also randomized and counterbalanced. Each subject was randomly assigned to receive only one active drug, and this drug was administered during both of the testing sessions. Thus, the medication used was manipulated between subjects, and 52 subjects received an intravenous dose of morphine (0.08 mg/kg), while another cohort of 54 subjects received an intravenous dose of pentazocine (0.5 mg/kg). Sessions were scheduled with approximately 14 days between sessions to accommodate menstrual cycle schedules and to minimize carryover effects. The goal of this study is not to compare the analgesic effect between morphine and pentazocine, as these doses were chosen produce equianalgesic effects [18; 21].

Experimental pain responses were assessed before and after study drug administration (Figure 1) at the same time across sessions. For each session, subjects completed study related questionnaires, including assessment of general health. Then, an intravenous catheter was placed in the arm or hand for administration of the study medication, which was followed by a 15 minute rest period. Pre-drug psychophysical pain responses were measured including thermal, pressure and ischemic pain (see sections below). The order of testing was randomized, with thermal and pressure tests counterbalanced (i.e., some subjects underwent thermal followed by pressure; other subjects began with pressure then thermal). Ischemic pain was the last test before drug administration in order to prevent carryover effects and to account for inter-individual variability in the duration of ischemic pain. Five minute rest periods were observed between each series of tests. Fifteen minutes following the ischemic test, an intravenous bolus of study medication was provided. After an additional 15 minute rest period, post-drug psychophysical pain tests were repeated.

2.4. Psychophysical pain tests

The current study included three commonly used sensory testing modalities to evaluate the analgesic effects of opioid medication [18; 21; 49]. For each of the tests, recorded instructions were played prior to commencement of the procedure.

2.4.1. Pressure Procedure—Pressure pain threshold (PPT) was assessed using a handheld algometer (Pain Diagnostics and Therapeutics, Great Neck, NY, USA). With this device, mechanical pressure was applied at 1 kg/s until the subject first felt pain produced by a 1 cm³ probe, which was attached to the device. PPT was assessed at three sites in a counterbalanced order: the right upper trapezius (posterior to the clavicle), the right masseter (midway between the ear opening and the corner of the mouth), and, the right ulna (dorsal

forearm, 8 cm distal of the elbow). The PPT procedure was repeated three times for each testing site to create an average PPT for the site.

2.4.2. Thermal Procedures—For all of the thermal procedures, 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. *For heat pain threshold and tolerance*, stimuli were delivered to the right ventral forearm using an ascending method of limits with a 3 cm × 3 cm contact probe (baseline: 32 °C; rate of rise: 0.5 °C/s). Subjects were instructed to respond by pressing a button when they first felt pain (heat pain threshold, HPTH) and when they no longer felt able to tolerate the pain (heat pain tolerance, HPTO). Both HPTH and HPTO assessments consisted of four trials with the contact probe re-positioned to avoid sensitization or response suppression of cutaneous heat nociceptors. Average HPTH and HPTO were calculated across the four trials. *For temporal summation of thermal pain*, five minutes following the assessment of HPTH/HPTO, subjects underwent a second thermal procedure to assess temporal summation. Subjects were instructed to verbally rate the intensity of peak pain of 10 brief, repetitive, suprathreshold heat pulses applied to the right dorsal forearm. Verbal ratings were on scale of 0 (no pain sensation) to 100 (the most intense pain sensation imaginable). Two target temperatures (49°C, 52°C) were delivered for less than 1 second, with an approximately 2.5-second inter-pulse interval during which the temperature of the contactor returned to a baseline of 40°C. The procedure was terminated if the subject rated the thermal pain at 100. Last-observation-carried-forward (LOCF) methods were used to impute missing data during the temporal summation as previously reported [18; 21; 22; 47]. For statistical processing, heat pain ratings were averaged across 10 trials as in previous studies [18; 21; 22; 35; 47; 52], which provided an overall measure of suprathreshold heat pain sensitivity. Our group previously reported that average ratings during the temporal summation protocols loaded on the same factor with measures of heat pain threshold and tolerance [30]. Subsequently, a factor analysis of analgesic index scores showed morphine-induced changes in average heat pain ratings loaded with change scores for heat pain threshold and tolerance [35]. The average pain intensity can be considered a more representative of a general change in sensitivity rather than an index of temporal summation of heat pain.

2.4.3. Ischemic Pain Procedure—Following the thermal pain/pressure procedures, a modified submaximal tourniquet procedure was used to assess ischemic pain. For this procedure, the right arm was raised upright for 30 sec, and then the arm was occluded with a standard blood pressure cuff inflated to 240 mm Hg using a Hokanson E20 Rapid Cuff Inflator (D.E. Hokanson, Bellevue, WA, USA). 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) when the pain became intolerable (ischemic pain tolerance, IPTO), and these time points were recorded. Following reporting of first pain (IPTH), subjects rated the unpleasantness and intensity of their arm pain every 30 seconds using joint numerical (0–20) and verbal descriptor box scales [57]. Subjects continued until the perceived pain became intolerable or for 15-minutes.

2.5. Data analysis

Data are presented as mean ± SD, unless otherwise indicated. For PPT, HPTH, HPTO and verbal ratings for temporal summation, values for each trial were collapsed and averaged to yield single overall values. The analgesic index scores and their formulae are listed in Table 2. Previous studies have reported analgesic responsiveness by calculating a single index based on absolute difference between pre- and post-drug responses effect [18; 21; 22]. These calculations were arranged such that positive values indicated pain reduction. That is, for

threshold and tolerance measures, pre-drug values were subtracted from post-drug values, while for pain ratings, post-drug values were subtracted from pre-drug values. We computed three additional measures to determine analgesic efficacy. The percent change scores were derived by dividing the simple difference score by the pre-drug value, then multiplying by 100. We computed the ratios such that a score of 1.0 means no analgesic efficacy, while a score of 2.0 would indicate a two-fold reduction in pain after drug, and a score of 0.5 would indicate a two-fold increase in pain following drug. Specifically, for measures of threshold and tolerance, the post-drug value was divided by the pre-drug value, while for pain ratings, the pre-drug value was divided by the post-drug value. Ratio scores have also been used to determine the effect of opioids in humans [10]. Finally, residualized change scores were computed by regressing the post-drug score on the pre-drug score for each pain measure. This is statistically equivalent to using post-drug scores as the measure of analgesia and using pre-test scores as a covariate. An advantage of residualized scores is that they always have a Pearsonian correlation of zero with the corresponding pretest scores and have higher reliability coefficients compared to traditional change scores [62; 65].

In order to examine comparability of different analgesic indices, Pearson correlation coefficients were calculated across all analgesic indices for each of the two opioid medications. Index scores for the first and second sessions with active drug are indicated by the first (**DS₁**) and second (**DS₂**) drug sessions, respectively. With each of the calculated analgesic indexes, a series of 2 (Session: first and second session with medication) $\times$ 2 (Drug: Saline and Morphine or Saline and Pentazocine) Repeated Measures ANOVAs were used to determine differences between the active drug and saline as well as changes in analgesic responses across sessions with a Greenhouse-Geisser adjustment where appropriate. Analyses include the partial η^2 as a measure of effect size where appropriate. Following the conventions of Cohen [7], partial η^2 is considered a small effect, partial η^2 a medium-sized effect and partial η^2 a large effect. Relationships between active drug sessions (i.e., magnitudes of correlations) and analgesic index scores based on modalities were calculated with a Pearson correlation.

To limit the number of relationships and reduce the probability of type 1 error, z-scores were calculated for each analgesic index score. Then, an overall mean z-score for each pain modality was derived by averaging these z-scores. The modality z-scores were computed based on the following analgesic index scores: *heat z-score* = HPTh, HPTo, summed ratings at 49°C and 52°C; *pressure z-score* = masseter, trapezius, and ulna PPTH; *ischemic z-score* = IPTh, IPTO, summed intensity ratings, summed unpleasantness ratings [47]. For all z-scores, higher values indicate greater analgesia.

3. Results

3.1. Morphine

3.1.1. Analgesic effect of morphine as a function of analgesic index score—All four of the analgesic index scores reflecting the analgesic potency of morphine on ischemic, pressure, and thermal pain measures across DS₁ and DS₂ are presented in Table 3. For each of the analgesic index scores (see S1), neither the main effect of session (all p 's $> .05$; partial η^2 range: .00–.10) nor the drug $\times$ session interaction (most p 's $> .05$; partial η^2 range: .00–.06) was significant. The only exception was a drug $\times$ session interaction for ischemic pain unpleasantness based on difference scores ($p < .05$; partial η^2 : .08). However, the main effect of drug was significant, suggesting that morphine reduced pain in response to all experimental ischemic (p range: .05–.001; partial η^2 range: .10–.61), thermal (p range: .05–.001; partial η^2 range: .05–.21), and pressure (p range: .01–.001; partial η^2 range: .23–.39) pain more than saline across all four analgesic index scores. Overall, morphine increased the time to reach first pain and tolerance in the ischemic test in addition to reducing the overall

intensity and unpleasantness of the task. Likewise, PPT values were slightly but significantly higher following morphine. For the thermal pain procedures, a significant effect of morphine was observed for HPTH and HPTO in which the temperature to induce first pain and tolerance was higher after the drug treatment. Finally, verbal ratings of pain intensity were lower during the temporal summation trials at 49 and 52°C following morphine. However, the residualized scores of analgesia were not as consistent. The interaction of session and drug was not significant.

3.1.2. Correlations among morphine analgesic index scores—Analyses of the relationship among the four analgesic index scores for morphine for each drug session are presented in Table 4. Overall, the correlations among the four index scores are strong for ischemic, heat, and pressure pain z-scores, indicating that the different index scores are assessing similar aspects of the analgesic response. The magnitudes of these relationships were moderate to large (r range: 0.67 to 1.00, all $p < 0.001$). Overall, the data suggest that the analgesic index scores are highly related.

3.1.3. Correlations between repeated drug sessions with morphine—The magnitudes of the correlations of morphine z-scores between DS₁ and DS₂ are illustrated in Figure 2 across ischemic, pressure, and heat modalities. Overall, the stability of index scores across the two drug sessions with morphine was dependent on the pain modality. Ischemic pain (Figure 2, **Left Panel**) demonstrated a strong association between the two drug sessions across all of the analgesic indices (r range = 0.52 to 0.68, all p 's < 0.001). Heat pain (Figure 2, **middle panel**) demonstrated mild to moderate associations between sessions (r range = 0.31 to 0.48, all p 's < 0.05). However, pressure pain (Figure 2, **left panel**) did not reveal a significant relationship between the two sessions (all p 's > 0.10). Overall, the reliability of experimental pain indices of morphine analgesia was moderately consistent over repeated sessions, and seemed to produced more reliable responses on measures of ischemic ($r = 0.52$ – 0.68) and heat pain ($r = 0.31$ – 0.48), but not pressure pain ($r = 0.06$ – 0.17).

3.2. Pentazocine

Similar to morphine, across all four analgesic indexes pentazocine produced an analgesic effect by reducing experimental pain sensitivity across DS₁ and DS₂. Table 5 presents data derived from the calculation of the index scores. The results from the ANOVA are presented in Table S2. For each of the analgesic index scores, neither the main effect of session (all p 's $> .05$; partial η^2 range: .00–.08) nor the interaction (most p 's $> .05$; partial η^2 range: .00–.06) was significant. Several drug $\times$ session interactions were observed for ischemic pain threshold and intensity (all p 's $< .05$; partial η^2 's: .09). Drug $\times$ session interactions were also observed for temporal summation at 52°C (p range: .05–.01; partial η^2 range: .08–.13). However, the main effect of drug for ischemic (all p 's $< .001$; partial η^2 range: .30–.62) and pressure (all p 's $< .001$; partial η^2 range: .34–.62) pain was significant suggesting that compared to saline; pentazocine was able to reduce the sensitivity of experimental pain stimuli for all four analgesic index scores. With the exception of heat pain thresholds (all p 's $> .05$; partial η^2 range: .01–.02), the main effect was also observed the remaining thermal pain measures (p range: .01–.001; partial η^2 range: .07–.47).

3.2.1. Analgesic effect of pentazocine as a function of index score—Analyses of the relationship among the four analgesia index scores for pentazocine z-scores are presented in Table 6 for DS₁ and DS₂. Overall, the correlations were strong among the scores for ischemic pain intensity, heat pain thresholds, and pressure pain thresholds indicating that the index scores are assessing similar aspects of the analgesic response. The magnitudes of these relationships were moderate to large (r range: 0.61–0.99, all $p < 0.001$). Overall, the data suggest that any of the analgesic scores are sufficient to detect analgesic

effects with the percent change index scores exhibiting slightly lower inter-correlations with other scores.

3.2.2. Correlations between repeated drug sessions with pentazocine—The reliability of analgesic responses to pentazocine z-scores between DS₁ and DS₂ are presented in Figure 3. Ischemic pain (Figure 3, **left panel**) demonstrated a moderate to strong association between the two drug sessions (r range = 0.51 – 0.67, all p 's < 0.001). While the test-retest correlations for heat pain were weak in magnitude (Figure 3, **middle panel**; r range = 0.28 – 0.36, all p 's < 0.05), the magnitude ranged from moderate to strong for pressure pain (Figure 3, **right panel**; r range = 0.51 – 0.72, all p 's < 0.001). Overall, the reliability of experimental pain indices of pentazocine analgesia was moderately consistent over repeated sessions, and seemed to produced more reliable responses on measures of ischemic pain (r = 0.51–0.67) and pressure (r = 0.51–0.72) pain followed by heat pain (r = 0.28–0.36).

4. Discussion

The current study examined the stability of morphine and pentazocine analgesic responses across three experimental pain modalities. In order to accomplish this goal, analgesic index scores were used as indicators regarding the degree of change in pain sensitivity from pre to post drug administration. The results suggest that: 1) in general, analgesic responses showed moderate stability over a two week period, which varied somewhat across pain modalities and analgesic indices; 2) all analgesic indices were sensitive indicators of analgesia, able to distinguish between active drug and saline; and, 3) the consistently high inter-correlations among analgesic index scores suggest that they capture similar aspects of analgesic efficacy. Both opioids produced significant levels of analgesia, with ischemic pain exhibiting the greatest degree of analgesia, which is consistent with previous experimental studies of opioid medications [21; 22; 47; 52].

4.1. Comparison of analgesic measures

The current study evaluated four analgesic index scores. Each was selected to evaluate the ability of the opioid analgesic to reduce experimental pain that could be considered the drug's analgesic efficacy. The most common method has used simple difference scores (i.e., change scores [14; 21; 22; 34; 52]), but concern has been raised about the reliability of repeated scores [4; 5; 9]. However, evaluation of the different computational methods for determine analgesic indices using data from this repeated measures experimental design revealed comparable results across all methods. All of these measures demonstrated a significant drug effect compared to saline. Values reported for the difference scores were comparable to previous reports [21; 22]. Overall, morphine and pentazocine increased the time to reach first pain and tolerance in the ischemic test in addition to reducing the overall intensity and unpleasantness of the task. Likewise, PPT values were significantly higher following both medications. For the thermal pain procedures, with the exception of HPTH (morphine only), both medications produced a significant analgesic effect for HPTH and HPTO in which the temperature to induce first pain and tolerance was higher after the drug treatment. Finally, verbal ratings of pain intensity were lower during the temporal summation trials following morphine.

In addition, analysis of the data revealed that the strength of relationship between repeated drug sessions was dependent on the stimulus modality. For example, the most consistent analgesic responses to morphine and pentazocine were observed with ischemic pain, while heat pain demonstrated low to moderate repeatability. Repeated exposure to pentazocine produced consistent analgesic effects on pressure pain, while morphine analgesia for pressure pain showed poor reliability, perhaps due to the low magnitude of analgesic effects

on pressure pain. In general, the comparable sensitivity to analgesic efficacy was demonstrated by all four analgesic scores for both morphine and pentazocine. Scores were also highly correlated among each other, which suggest that the index scores are capturing similar information about analgesic efficacy.

4.2 Analgesic efficacy in experimental studies

The importance of opioid analgesics in the management of clinical pain is well understood [58; 63]. However, analgesic responses in clinical settings are often hard to assess since a number of psychological and physiological factors could impact the responsiveness to the opioid medication [56]. It is known that experimental models of pain provide a number of advantages to characterize analgesia [22; 56], including controlling the parameters of the experimental stimulus (e.g., frequency, duration, localization, intensity), evaluation a number of modalities in the same session, and assessment of psychophysical responses in the absence of confounding variables (e.g., impact of other medications or pathology). Furthermore, the use of different experimental modalities permits evaluation of different mechanisms within the nervous system that transmit [56] and process nociceptive input from a range of tissue sites, which is suggested in the full characterization of analgesia for a given drug [22].

Consequently, evaluation of analgesic efficacy has been examined in experimental models of pain. The present data support previous studies that demonstrate an analgesic effect of morphine and pentazocine across several experimental pain modalities [18; 21; 22; 38; 39]. Comparison of the analgesic effects reveals that both medications in general produce comparable levels of analgesia between the two testing session during testing modalities that engage C-nociceptors (e.g., heat pain tolerance, temporal summation [45; 59]). Reliability of both medications was the largest during measures of pain, which activates both A - and C-nociceptors in the muscle (e.g., ischemia), perhaps because this procedure presumably better replicates clinical pain due to the deep, tonic nature of the stimulus [55]. Again, this observation was consistently shown across the four analgesic index scores.

4.3. Repeatability of analgesic efficacy of opioids

Most drug studies, including studies evaluating the efficacy of analgesics, presume that a patient's response to medications will be consistent and stable [51]. However, the assumption that the analgesic response is stable and will be comparable across repeated administration is seldom tested, even in psychophysical studies of pain. Examining the reliability of analgesics across multiple sessions may provide further evidence of the drug's efficacy. In the current study, the analgesic efficacy demonstrated moderate stability across two drug sessions. For morphine, stability for analgesic efficacy was greatest for all of the ischemic pain measures while the stability for pressure pain was poor with the exception of the ulna. In general, the heat pain measures exhibited moderate levels of stability between the two drug sessions, though ratio scores showed the lowest reliability. The stability of pentazocine analgesic responses on ischemic measures was also strong. In contrast to the morphine condition, pressure pain measures showed modest stability, which was somewhat higher for difference and residualized scores. Stability of heat pain measures was lowest for pentazocine.

4.4. Factors influencing repeatability of analgesic efficacy of opioids

Considering that the analgesic responses were only moderately associated between the two medication sessions, a number of factors could be involved in attenuating this association and contribute to the remaining variance. While not measured in the study, a number of psychological factors could influence the stability of analgesic responses over repeated testing, which subjects develop pre-conceived thoughts about the study medication's actual

effect (i.e., opioid medications reduce pain and I believe that I will receive it today). For example, expectations are known to shape the perception and modulation of experimental pain [6; 24; 36]) including a neurologically based phenomenon known as placebo analgesia [8; 40; 44]. In addition, as subjects are tested over four separate sessions, mechanisms that underlie habituation are activated and could reduce the magnitude of associations among subsequent tests. Habituation (i.e., a progressive reduction in pain sensitivity over multiple trials) is a common observation with repeated testing of experimental pain [12; 27; 29; 53; 54]. Likewise, repeated testing is also associated with decreases in negative psychological states [2; 25; 26; 32; 40; 60; 61], which increases pain sensitivity and reduce the ability to internally modulate pain. Thus, over repeated sensory testing, negative psychological factors could be diminished. Finally, the average 14-day between-session time period allows the possibility that environmental exposures or changes in endogenous states (e.g. pain experiences or psychological changes) could attenuate reliability of analgesic responses.

4.5. Implications of drug repeatability in genetic studies of analgesia

Inter-individual variability in pain sensitivity and analgesic responsiveness has been well documented [16; 41–43] with a portion of individuals experience better analgesia [49]. A number of non-genetic [17; 18; 20–22; 46] and genetic [3; 11; 16; 19; 23; 43] factors may contribute to individual differences in opioid efficacy [37]. Subsequently, this variability should be repeatable (intra-individual repeatability) since the genetic predispositions are stable. Understanding this variability has important clinical and scientific implications for individual tailoring of pain treatments.

4.6 Limitations

Several limitations of our study should be considered when interpreting the findings. First, this study involved experimental pain testing in a young healthy population; therefore, the results may not be applicable to clinical pain. Only one dose of each medication was used, and we cannot comment on dose response relationships or the effects of repeated administration, as is often used in clinical settings. Finally, the two drug sessions among women occurred in different menstrual cycle phases, and we recently reported that morphine responses tested against ischemic pain were greater in the follicular versus the luteal phase [47]. No effects were observed for pentazocine nor for females taking oral contraceptives. The current analysis did not factor in the menstrual cycle since females were randomized to the order of menstrual cycle testing. While variability due to menstrual cycle phase may have attenuated reliability among women, this seems unlikely because the only measure that showed menstrual cycle variation was among the most reliable analgesic indices (ischemic morphine analgesia).

4.6. Conclusion

The current study tested the repeatability of two opioid analgesics (morphine, pentazocine) across three commonly used psychophysical pain modalities. Drug efficacy was also compared among analytic methods, which demonstrated consistent analgesic responses on the three pain modalities following both medications. In general, reliability of analgesia between the first and second medication sessions was moderate, which differed depending on the modality (i.e., greatest with ischemic). Stronger associations may have been hampered by a number of factors including expectations and habituation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Schematic representation of the experimental timeline for each drug session

Subjects underwent two identical psychophysical pain assessment periods before and after administration of study medication. The gray counterbalanced box indicates that thermal and pressure pain tests were alternated among subjects, which was followed by the ischemic test.

Figure 2. Magnitude of the relationship of analgesic responses based on z-scores between the first and second sessions with morphine (n = 53)

Scores converted to z-scores for each stimulus modality for analyses. Bars represent correlations between drug session 1 (DS1) and session 2 (DS2), which reflects the magnitude (i.e., strength) of the relationship between responses, for each analgesic index. Larger positive values indicate a stronger relationship between DS1 and DS2.

Abbreviations: *, p<0.05; **, p<0.01; ***, p<0.001.

Figure 3. Magnitude of the relationship of analgesic responses based on z-scores between the first and second sessions with pentazocine (n = 53)

Scores converted to z-scores for each stimulus modality for analyses. Bars represent correlations between drug session 1 (DS₁) and session 2 (DS₂), which reflects the magnitude (i.e., strength) of the relationship between responses, for each analgesic index. Larger positive values indicate a stronger relationship between DS₁ and DS₂. Abbreviations: *, $p < 0.05$; ***, $p < 0.001$.

Table 1Demographic characteristics (mean $\pm$ SD).

	Morphine	Pentazocine
Age (Years)	23.3 $\pm$ 4.2	24.6 $\pm$ 6.4
Height (cm)	168.23 $\pm$ 8.8	168.76 $\pm$ 7.8
Weight (kg)	69.82 $\pm$ 13.58	70.22 $\pm$ 13.2
Gender (Female/Male)	35/17	36/18
Race		
<i>Non-Hispanic White</i>	29	30
<i>Hispanic White</i>	14	10
<i>African American</i>	2	8
<i>Other</i>	7	6

Table 2

Description of analgesic index scores.

Score	Description	Calculation
Difference	<i>Post-drug values subtracted from pre-drug values</i>	$= b - a$
Percent Change	<i>Difference scores divided by pre-drug values $\times 100$</i>	$= \frac{b-a}{a} \times 100$
Ratio	<i>Post-drug values divided by pre-drug values</i>	$= b/a$
Residualized	<i>Covarying out pre-drug values from post-drug values</i>	Regression of post-drug values on pre-drug values

Abbreviations: a, pre-drug values; b, post-drug values; c, cut off value

Table 3
Comparison of analysis models regarding the analgesic effect of morphine on experimental pain modalities (n = 52)

Values represent changes from pre-drug administration (i.e., analgesic responses). Each score represents an analgesic effect of morphine after accounting for changes in pain following saline. Positive scores indicate a reduction in pain responsiveness.

	Difference Scores		Percent Difference Scores (%)		Ratio Scores		Residualized Difference Scores	
	DS ₁	DS ₂	DS ₁	DS ₂	DS ₁	DS ₂	DS ₁	DS ₂
Ischemic Pain								
IPTH (sec)	77.57 (153.25)	70.84 (121.13)	51.64 (105.88)	39.38 (67.92)	1.51 (1.05)	1.37 (0.68)	36.91 (152.60)	13.54 (125.84)
IPTO (sec)	150.90 (124.77)	134.97 (115.94)	39.85 (33.61)	36.69 (34.07)	1.31 (0.34)	1.25 (0.33)	58.01 (118.27)	32.95 (115.35)
Intensity	38.41 (49.74)	35.84 (36.31)	22.06 (27.88)	21.64 (21.93)	1.66 (1.42)	1.48 (0.86)	-16.19 (48.81)	-11.11 (37.31)
Unpleasantness	41.39 (48.76)	32.84 (41.30)	22.82 (27.25)	19.60 (24.21)	1.60 (1.18)	1.45 (0.81)	-18.95 (48.29)	-8.09 (41.98)
Pressure Pain								
Masseter PPT (kg)	0.20 (0.52)	0.33 (0.44)	8.89 (20.24)	20.60 (41.44)	1.09 (0.20)	1.21 (0.41)	0.03 (0.46)	0.06 (0.44)
Trapezius PPT (kg)	0.36 (1.22)	0.48 (0.89)	10.46 (34.63)	10.95 (20.11)	1.10 (0.35)	1.11 (0.20)	0.17 (1.21)	0.10 (0.91)
Ulna PPT (kg)	0.51 (0.85)	0.60 (0.99)	12.35 (21.78)	15.08 (22.52)	1.12 (0.22)	1.15 (0.23)	0.36 (0.83)	0.33 (0.98)
Thermal Pain								
HPTH (°C)	0.56 (1.64)	0.47 (1.41)	4.64 (20.26)	6.15 (17.94)	1.01 (0.04)	1.01 (0.04)	0.05 (1.61)	0.07 (1.13)
HPTO (°C)	0.42 (1.25)	0.31 (0.80)	3.43 (10.44)	2.61 (6.32)	1.01 (0.03)	1.01 (0.02)	0.12 (1.00)	0.15 (0.62)
Intensity @ 49.0°C	0.88 (7.48)	1.37 (9.30)	1.56 (23.45)	-0.68 (24.14)	1.14 (0.72)	1.04 (0.22)	-1.47 (7.39)	-0.24 (9.20)
Intensity @ 52.0°C	-0.84 (9.35)	0.87 (10.81)	-2.23 (22.20)	2.56 (12.10)	1.04 (0.36)	1.05 (0.16)	0.62 (9.23)	-1.49 (8.33)

Abbreviations: DS₁, 1st drug session with morphine; DS₂, 2nd drug session with morphine; IPTH, Ischemic pain threshold; IPTO, Ischemic pain tolerance; PPT, Pressure pain threshold; HPTH, Heat pain threshold; HPTO, Heat pain tolerance.

Table 4

Relationships among four analgesic index scores based on z-scores for three experimental pain modalities for the first and second sessions with morphine.

		Morphine Session (n = 53)					
		First Session			Second Session		
		DIFF	PTC	RTO	DIFF	PTC	RTO
Ischemic Pain							
<i>Percent change</i>		0.98	-	-	0.97	-	-
<i>Ratio</i>		0.95	0.94	-	0.89	0.93	-
<i>Residualized</i>		0.99	0.97	0.94	0.99	0.94	0.88
Heat Pain							
<i>Percent change</i>		0.92	-	-	0.96	-	-
<i>Ratio</i>		0.67	0.88	-	0.94	0.97	-
<i>Residualized</i>		0.90	0.84	0.67	0.90	0.84	0.85
Pressure Pain							
<i>Percent change</i>		0.92	-	-	0.82	-	-
<i>Ratio</i>		0.92	0.99	-	0.82	1.00	-
<i>Residualized</i>		0.95	0.86	0.86	0.98	0.78	0.78

Abbreviations: DS1, 1st drug session with morphine; DS2, 2nd drug session with morphine; DIFF, Difference; PTC, Percent Change, RTO, Ratio scores.

Table 5
Comparison of analysis models regarding the analgesic effect of pentazocine on experimental pain modalities (n = 54)

Values represent changes from pre-drug administration (i.e., analgesic responses). Each score represents an analgesic effect of pentazocine after accounting for changes in pain following saline. Positive scores indicate a reduction in pain responsiveness.

	Simple Difference Scores		Percent Difference Scores (%)		Ratio Scores		Residualized Difference Scores	
	DS ₁	DS ₂	DS ₁	DS ₂	DS ₁	DS ₂	DS ₁	DS ₂
Ischemic Pain								
IPTH (sec)	99.06 (130.83)	84.98 (152.40)	90.35 (150.43)	56.43 (89.19)	1.87 (1.48)	1.54 (0.88)	55.67 (130.35)	34.17 (147.06)
IPTO (sec)	136.38 (126.85)	132.43 (156.10)	29.14 (27.24)	28.34 (36.22)	1.19 (0.26)	1.20 (0.33)	37.56 (115.22)	44.66 (140.99)
Intensity	47.51 (40.73)	36.50 (42.55)	32.75 (29.09)	26.00 (37.33)	2.05 (1.94)	1.68 (1.34)	-24.92 (40.11)	-12.76 (42.56)
Unpleasantness	48.09 (45.96)	40.19 (45.74)	32.87 (31.26)	26.92 (39.27)	2.38 (3.08)	1.77 (1.47)	-25.06 (44.91)	-15.57 (46.10)
Pressure Pain								
Masseter PPT (kg)	0.63 (0.69)	0.59 (0.46)	25.11 (25.83)	21.44 (14.92)	1.25 (0.26)	1.21 (0.15)	0.43 (0.69)	0.35 (0.43)
Trapezius PPT (kg)	1.21 (1.67)	0.96 (1.05)	28.81 (41.70)	22.20 (23.33)	1.29 (0.42)	1.22 (0.23)	1.02 (1.61)	0.59 (1.03)
Ulna PPT (kg)	0.60 (1.23)	0.68 (0.98)	13.18 (29.17)	14.93 (21.21)	1.13 (0.29)	1.15 (0.21)	0.45 (1.21)	0.41 (0.99)
Thermal Pain								
HPTH (°C)	1.15 (2.79)	0.51 (1.83)	5.60 (29.63)	3.33 (19.78)	1.03 (0.07)	1.01 (0.05)	0.61 (2.61)	0.22 (1.71)
HPTO (°C)	0.87 (1.55)	0.65 (1.14)	5.42 (10.99)	3.02 (12.94)	1.02 (0.04)	1.01 (0.03)	0.59 (1.37)	0.53 (1.14)
Intensity @ 49.0°C	4.66 (11.25)	3.56 (11.38)	10.06 (26.31)	10.10 (25.71)	1.26 (0.62)	1.20 (0.37)	-5.33 (11.18)	-4.08 (11.31)
Intensity @ 52.0°C	1.91 (12.54)	4.83 (6.96)	0.53 (26.88)	7.94 (12.17)	1.07 (0.28)	1.11 (0.19)	-2.27 (12.22)	-4.75 (7.33)

Abbreviations: DS₁, 1st drug session with pentazocine; DS₂, 2nd drug session with pentazocine; IPTH, Ischemic pain threshold; IPTO, Ischemic pain tolerance; PPT, Pressure pain threshold; HPTH, Heat pain threshold; HPTO, Heat pain tolerance.

Relationships among four analgesic scores based on z-scores for three experimental pain modalities for the first and second sessions with pentazocine.

Table 6

Pentazocine session (n = 53)						
	First Session			Second Session		
	DIFF	PTC	RTO	DIFF	PTC	RTO
Ischemic Pain						
<i>Percent change</i>	0.84	-	-	0.84	-	-
<i>Ratio</i>	0.61	0.79	-	0.79	0.84	-
<i>Residualized</i>	0.99	0.84	0.63	0.99	0.83	0.77
Heat Pain						
<i>Percent change</i>	0.96	-	-	0.94	-	-
<i>Ratio</i>	0.91	0.95	-	0.86	0.97	-
<i>Residualized</i>	0.98	0.95	0.89	0.97	0.94	0.87
Pressure Pain						
<i>Percent change</i>	0.92	-	-	0.87	-	-
<i>Ratio</i>	0.92	0.99	-	0.87	0.99	-
<i>Residualized</i>	0.99	0.90	0.90	0.98	0.85	0.85

Abbreviations: DS1, 1st drug session with pentazocine; DS2, 2nd drug session with pentazocine; DIFF, Difference; PTC, Percent Change; RTO, Ratio scores.