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Cognitive-Affective and Somatic Side Effects of Morphine and Pentazocine: Side-Effect Profiles in Healthy Adults

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Abstract

Objective—The side effects of opioids have been widely investigated, but it is unknown whether the subjective effects of mu agonists and mixed action opioids produce similar symptom profiles. This study examined the structure and predictive validity of somatic and cognitive/affective side-effect profiles of morphine and pentazocine using the Somatic Side Effects Questionnaire and the Cognitive and Affective Side Effects Questionnaire.

Design—The subjects were 122 female and 90 male healthy volunteers that received an intravenous bolus administration of either 0.08 mg/kg of morphine or 0.5 mg/kg pentazocine. Pre- and post-drug experimental pain testing was also performed. Exploratory and confirmatory factor analysis resulted in similar factor structures for both drugs.

Results—The most frequently reported side effects across both drugs involved feeling relaxed, sedation, and feeling in control. At equianalgesic doses, pentazocine had greater aversive side effects than morphine, whereas morphine was more associated with feelings of control and euphoria. For both drugs, females reported greater frequency of negative side effects than males. Using cluster analysis, we identified similar symptom profiles for each drug. These drug-related side-effect profiles were linked with analgesic responses. Specifically, groups that had a more positive side-effect profile experienced the greatest analgesic effect based on changes in ischemic pain sensitivity.

Conclusions—These findings have implications for decisions regarding opioid management of acute, chronic, and malignant pain conditions.

Keywords

pain; opioid; side effects; sex differences; pain sensitivity; analgesia; cluster analysis

INTRODUCTION

Opioid analgesics represent the most commonly used class of drugs for the treatment of moderate to severe pain. Opioid effects are mediated by activation of three receptor subtypes, mu (μ), delta (δ) and kappa (κ). The two clinically available classes of opioids include μ-agonists (e.g. morphine, fentanyl, hydromorphone) and mixed action agonist-

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antagonists (e.g. pentazocine, nalbuphine, butorphanol), which produce agonist effects at the κ-opioid receptor (1). All opioid receptors are G-protein-coupled receptors whose activation inhibits neuronal activity; however, the effects of these two opioid classes can vary, based largely on differing distributions of receptor subtypes in the central nervous system. Morphine, the prototypical μ-opioid, can also activate δ and κ receptors, but has dramatically higher affinity to μ receptors (2). In addition to their analgesic properties, opioids are associated with a number of adverse side effects, the most common of which are nausea and vomiting, loss of balance, and drowsiness (3–5). Some evidence suggests that the pattern of side effects varies for μ agonists versus mixed agonist-antagonists. For example, 30 mg of intravenous pentazocine was found to produce greater dysphoric effects and psychomotor impairment compared to 10 mg of morphine (6). However, most clinical investigations of opioids primarily evaluate the analgesic efficacy of the drugs and when side effects are reported, standardized measures are seldom used. Rather, the spontaneous occurrence of these events is often documented by the investigators or staff (5).

In clinical practice, opioid analgesia requires finding a satisfactory balance between pain control and adverse side effects (3,6). Indeed, in clinical trials of oral opioids for chronic non-cancer pain, one-quarter of patients withdrew prematurely due to side effects (8). The lack of systematically obtained information on side effects precludes the evidence-based clinical management of opioid-induced symptoms. In their review, Cherny et al. (9) concluded that there is “very little reproducible evidence” that one opioid has a more favorable side-effect profile than another because of lack of systematic and standardized measurement of side effects. They further state that despite multiple clinical and scientific recommendations for side-effect management, there is a dearth of supporting evidence for symptom management in general and particularly for understanding inter-individual differences. Therefore, additional information on the incidence, severity, and mechanisms of side effects is needed to help clinicians make better decisions for an optimal pain management plan.

Some evidence indicates sex differences in adverse events associated with opioids. In experimental settings, greater morphine-induced respiratory depression among women than men has been found (10,11). Increased negative feelings as well as enhanced nausea and vomiting among women have also been reported (12,13). Our own investigation revealed comparable frequencies of side effects between sexes in response to pentazocine (14), while women reported significantly greater number of subjective side effects in response to morphine, and compared to men, more women experienced at least one side effect (15). Consequently, this current study extends that line of investigation by examining sex differences in side-effect profiles.

The overall purpose of this study was to examine the structural and predictive validity of the Somatic Side Effects Questionnaire (SSE) and the Cognitive and Affective Side-Effect Questionnaire (CASE), standardized instruments designed for assessing opioid side effects. We have used data from subjects that received intravenously administered morphine, a mu agonist, and pentazocine, a mixed action opioid agonist-antagonist. The data derive from a previous study designed to examine sex differences in the analgesic effects of opioids varying in their affinities for μ versus κ receptors. Morphine was chosen as the prototypical μ agonist, and pentazocine (i.e. Talwin) was chosen for its κ agonist properties, because at the time of study design, findings had been recently published demonstrating sex differences in analgesic responses to pentazocine (16,17). The analgesic findings have been previously reported (14,15). The specific aims of the present analysis were to: 1) determine the number of symptom dimensions (side-effect factors) for each measure and to test whether the symptom dimensions are similar for each drug; 2) test for differences in the magnitude of side effects as a function of drug, sex of the subject; 3) test whether there are subgroups of

persons with similar profiles of aversive symptoms; 4) test whether these subgroups differ across sex, drug, pre-drug pain sensitivity or analgesic effect.

METHODS

Subjects

The subjects were 122 female and 90 male healthy volunteers ages 18 to 42 (mean=24.4, SD=5.6) recruited via posted advertisements at our institution. The participants were non-smokers and were free of clinical pain, psychiatric disturbance, substance abuse, or use of centrally acting medications as assessed by self-report health history, and urine drug screen. All participants underwent a history and physical exam by the study physician prior to inclusion. Subjects refrained from any over-the-counter medication use for at least 48 hours prior to testing and had eaten a light breakfast. An additional 21 subjects began the protocol and failed to complete the protocol. The most common reasons for withdrawal were adverse effects or logistical issues (e.g. scheduling problems). There were no differences on age, sex, height, weight, or marital status between those who completed and those who dropped out. All subjects provided verbal and written informed consent. All procedures were approved by the University of Florida Institutional Review Board. Subjects were paid for their participation.

Experimental Procedures

The study was conducted at the General Clinical Research Center of the University of Florida. All subjects participated in two experimental sessions. One session involved a double-blind intravenous bolus administration of either 0.08 mg/kg of morphine or 0.5 mg/kg pentazocine (i.e. drug was a between subject variable), and saline placebo was administered in the other session, in randomly counterbalanced order. These doses were chosen to approximate a low-to-moderate clinical dose for each drug, with a goal of producing equianalgesia. Analysis of our previously published data indicated that there were no significant differences in the magnitude of analgesic responses for morphine versus pentazocine, suggesting that these doses were equianalgesic (14,15). Subjects remained in the supine position on hospital beds during all study procedures. Each experimental session started with insertion of an intravenous cannula for drug administration followed by a 10-minute rest period, during which blood pressure and heart rate were monitored. Next, pre-drug experimental pain testing was performed as described below. Following a 15-minute rest period, drug was administered. Fifteen minutes after drug administration, pain testing was repeated in a manner identical to the pre-drug testing, and this post-drug testing was completed within 60 min of drug administration. After post-drug pain sensitivity testing, subjects completed questionnaires assessing somatic and cognitive/affective side effects. For women, all sessions were conducted during the follicular phase of the menstrual cycle, between days 4 and 10 after the onset of menses. The sessions were spaced at similar intervals for men. This report involves side-effect data collected during the day of active drug administration.

Pain Testing Procedures

The following procedures were performed before and after drug administration to assess pain sensitivity and analgesic response. Pressure and thermal pain were delivered first in counterbalanced order, separated by a 5-min rest period. The tourniquet procedure always occurred last in order to reduce carryover effects. Before each pain testing procedure, standardized recorded instructions were played for the subject. Subjects were paid $300 for completing all study procedures. Pain testing procedures are described in greater detail in previous publications (15,18).

Pressure pain threshold—A handheld algometer (Pain Diagnostics and Therapeutics, Great Neck, NY) using a 1 cm^2 probe was used to assess pressure pain threshold. Pressure was increased at a rate of 1 kg/s. Pressure pain was assessed at the center of the right upper trapezius, the right masseter, and the right ulna in counterbalanced order. Subjects were instructed to report when the pressure first became painful. The average force to threshold for three trials across the three sites was used as the measure of pressure pain (PPTh).

Heat pain threshold and tolerance—The first thermal procedure assessed thermal pain threshold and tolerance using the ascending method of limits. Contact heat stimuli were delivered to the right ventral forearm using a computer-controlled Medoc Thermal Sensory Analyzer (TSA-2001, Ramat Yishai, Israel), which is a peltier-element-based stimulator using a 3 cm × 3 cm contact probe. 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 they first felt warmth, pain, and when they no longer felt able to tolerate the pain. The position of the thermode was altered slightly along the ventral forearm between trials in order to avoid either sensitization or response suppression of cutaneous heat nociceptors. Four trials of heat pain threshold (HPTh) and heat pain tolerance (HPTo) were recorded with the average temperature for the trials serving as measures of HPTh and HPTo.

Temporal summation of thermal pain—After a 5-min rest period following heat pain trials, the temporal summation procedure was conducted using 49°C and 52°C administered to the right dorsal forearm. Subjects rated thermal pain intensity of 10 repetitive heat pulses delivered for less than 1s, with a 2.5s interpulse interval during which the temperature of the contactor returned to a baseline of 40°C. Subjects rated the peak pain for each of the 10 heat pulses on a scale where 0 represented no sensation, 20 represented a barely painful sensation, and 100 represented the most intense pain imaginable (19). The average rating across all 10 trials at each temperature was computed, which we will refer to as the heat pain rating (HPR).

Ischemic pain threshold and tolerance—Following the first two pain procedures, a 5-min rest period was observed, after which subjects underwent the modified submaximal tourniquet procedure (20,21). First, the right arm was elevated above heart level for 30s, then the blood flow to the lower arm was slowed 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, USA). Subjects performed 20 handgrip exercises of 2s duration at 4s intervals at 50% of their maximum grip strength as determined by a maximal trial. 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), and these time points were recorded. An uninformed 15-min time limit was observed to prevent tissue damage.

Ischemic suprathreshold pain index—During the tourniquet procedure, the subjects rated the intensity and unpleasantness of their ischemic pain every 60s using joint numerical (0–20) and verbal descriptor box scales (22). A total pain score was created 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. This measure was labeled the ischemic pain rating (IPR).

Measures of Aversive Symptoms

The Somatic Side Effects questionnaire (SSE) is a 28-item questionnaire that assesses a range of common somatic side effects associated with the use of opioid pain medications. Items are rated on a 5-point force choice scale with the following response choices: 1=Not at

all, 2=A little bit, 3=Somewhat, 4=Quite a bit, 5=Extremely (23). The SSEQ has demonstrated a high correlation with observers rating of sedation, vomiting and itching and demonstrated an increase in side effects following morphine infusion (23).

The Cognitive and Affective Side-Effect questionnaire (CASE) is a 44-item questionnaire that asks about a range of common cognitive and affective side effects associated with the use of opioid pain medications. Items are rated on a 5-point force choice scale with the following response choices: 1=Not at all, 2=A little bit, 3=Somewhat, 4=Quite a bit, 5=Extremely (24).

Statistical Methods

To determine an initial factor model for each of the symptom measures (SSE and CASE) for both morphine and pentazocine, eight exploratory factor analyses for each measure were performed using two different factor extraction methods each paired with two different rotation algorithms to allow for replication of factor structures across different methodologies. One criticism of exploratory factor solutions has been that the final solution differs across factoring methodology. We chose Principle Axis (based on matrix factoring) and Maximum Likelihood methods (based on factor fitting by statistical functions) for factor extraction. As we expected the symptom factors to be correlated, Oblimin and Promax factor rotational techniques were used. Item-factor loading matrices were examined from the eight factor analyses for each measure. Items with factor primary or secondary loadings of ≥ 0.30 were included in a confirmatory model for each measure.

The factor models evidenced in the previous step were further tested using confirmatory factor analysis with bootstrap sampling to study the distribution of factor loadings and standard error for each factor using Prelis 2 (25). This technique involved sampling with replacement from the original sample to generate replicate samples of equal size (n=120). Factor analyses using LISREL were run on each of 100 bootstrap resamples (26). These repeated samples provide a sampling distribution for each factor loading, and based on the central limit theorem should have desirable distributional characteristics. Mean factor loadings of ≥ 0.40 for each drug were retained in a final model.

Differences between placebo and active drug for each factor were verified using repeated measures ANOVAs. Next, a series of one-way ANOVAs were performed to test for differences in each of the opioid side effects as a function of drug and then for sex within each drug. We used a critical value of $p<.01$ for each of these analyses because of the number of tests performed.

Before side-effect profiles could be determined, it was necessary to address the overlap between side-effect factors of the SSE and CASE by combining highly correlated factors within and across measures. The thirteen SSE and CASE factor scores were entered into a Principal Components Analysis followed by an Oblimin rotation. Since higher-order groupings of adverse side effects were expected to be correlated, the oblique rotation was used. To identify homogenous groups of subjects based on side effects, the three higher-order symptom factors were subjected to a hierarchical cluster analysis. This is a statistical technique that assigns entities into groups based on common properties, in this case, assigning subjects to groups with common opioid side effects. Clusters were formed separately for each drug as we were interested in testing whether similar side-effect profiles emerged for morphine and pentazocine. Sex and analgesic-related differences across side-effect profiles were tested using one-way ANOVAs. The analgesic response was calculated by subtracting the post-drug pain sensitivity from the pre-drug value, as previously described (14,15).

RESULTS

Data Screening and Group Statistics

The data were screened and missing values were imputed for questionnaire protocols using maximum likelihood estimation. This technique was used because it makes fewer demands of the data in terms of statistical assumptions and is generally considered superior to imputation by multiple regression (27). For morphine, the mean total score for the SSE was 45.2 (SD=12.1, range 28–90) and 103.6 for the CASE (SD=19.9, range 61–164) and for pentazocine, the mean total score for the SSE was 55.3 (SD=15.5, range 28–97) and 114.3 for the CASE (SD=21.5, range 52–158). Total scores for the SSE and CASE were significantly higher for pentazocine than morphine, both at $p < .001$.

Factor Structure of the SSE and CASE

Initial factor model—For the SSE, seven stable factors emerged: 1) Sedation, 2) Vasodilation, 3) Tingling, 4) Dry mouth, 5) Poor balance, 6) Nausea, 7) Tremors. Pentazocine also had an eighth factor (feeling bloated) that consisted of items 22, 25, and 28, but it was eliminated because of inconsistent loadings that fell below the cutoff of 0.30 for several of the extraction/rotation methods. Items 14, 16, 22, and 25 did not load consistently on any factor. For the CASE, six factors emerged: 1) Mental dulling, 2) Relaxed, 3) Unusual thoughts, 4) Feeling in control, 5) Confusion, 6) Euphoria. CASE items 5, 16, 22, and 25 did not load consistently on any factor.

Confirmatory factor model—Tables 1 and 2 present the mean bootstrap loadings by drug for the final factor model (as determined by the exploratory factor analyses in the previous step) for the SSE and the CASE, respectively. When eliminating all items with mean factor loadings of less than 0.40, the final models for each drug are identical. Items that were dropped were among those with the lowest mean scores, indicating that these symptoms were rarely experienced. Cronbach's alpha for each factor were as follows: SSE Sedation, .90; SSE Vasodilation, .81; SSE Tingling, .74; SSE Dry mouth, .74; SSE Poor balance, .86; SSE Nausea, .79; SSE Tremors, .78; CASE Mental dulling, .90; CASE Relaxed, .91; CASE Unusual thoughts, .78; CASE In control, .76; CASE Confusion, .88; CASE Euphoria, .90.

The final model for each questionnaire was tested using a confirmatory model with LISREL separately for each drug to assess goodness-of-fit. Goodness-of-fit indices were as follows: SSE Morphine, $\chi 2$ (324) = 1676, RMSEA = 0.070, GFI = 0.89; SSE Pentazocine, $\chi 2$ (324) = 1212, RMSEA = 0.064, GFI = 0.92; CASE Morphine, $\chi 2$ (892) = 1661, RMSEA = 0.054, GFI = 0.91, CASE Pentazocine, $\chi 2$ (892) = 1176, RMSEA = 0.042, GFI = 0.93.

Differences in Side Effects

Significantly higher scores were found for all SSE and CASE factors for morphine versus saline, with the exception of SSE tremors. For pentazocine versus saline, significantly higher scores were found for all SSE and CASE factors.

Administration of pentazocine was associated with greater severity of side effects than morphine across multiple SSE and CASE subscales (see Table 3). Pentazocine was also associated with lower scores on the CASE control scale than morphine.

For morphine, females reported greater severity of side effects than males for the SSE sedation, SSE dry mouth, SSE nausea (Table 4). For pentazocine, females reported greater severity of SSE sedation, SSE dry mouth, SSE nausea, SSE tremor, and CASE mental dullness.

Side Effect Profiles

Principal components for the composite factor scores for the SSE and CASE are presented in Table 5. Three higher-order factors emerged, which accounted for 68% of the total variance. We found an independent factor of Positive Feelings (relaxed - euphoria) and two correlated factors (r=.49) of Neurocognitive Effects (confusion - unusual thoughts) and Somatic Symptoms (tremors, dry mouth, and sedation).

Inspection of the agglomeration coefficients following the clustering procedure for both drugs indicated that the percentage change is large between the three and four-cluster solutions after relatively small changes across the previous steps. This suggests that dissimilar clusters would have been combined at the three-cluster solution; therefore we concluded that there were four unique groups of subjects based on common higher-order side-effect profiles. See Table 6 for the side-effect profiles for each drug using standardized scores for each cluster group. We used any score that had a 0.5 SD above the factor mean as a sufficient criterion for characterizing each cluster.

For morphine, the first cluster included nearly 50% of the subjects (n=51). This group experienced low levels of Positive Feelings and Confused Cognition but reported higher than average levels of Somatic Effects, therefore subjects in this cluster were labeled “Somatic.” The second cluster (n=22) was characterized by low levels of Positive Feelings and Somatic Symptoms but had the highest levels of Neurocognitive Effects. Subjects in this cluster were labeled “Confused.” The third cluster (n=17) consisted of a profile with the highest levels of Positive Feelings, therefore subjects in this cluster were labeled “Euphoric.” The fourth cluster (n=24) had high levels of both Positive Feelings and Neurocognitive Effects, so these subjects were labeled “Confused with euphoric.”

For pentazocine, subjects were more evenly distributed across the four clusters. Subjects in cluster 1 (n=21) experienced low levels of Positive Feelings and Neurocognitive Effects but Somatic Symptoms were at the mean; therefore subjects in this cluster were labeled “Mild Somatic.” The second cluster (n=19) was characterized by low levels of Positive Feelings and Somatic Symptoms but the highest levels of Neurocognitive Effects, therefore these subjects were labeled “Confused.” The third cluster (n=32) consisted of a profile with the highest levels of Positive Feelings. These subjects were labeled “Euphoric.” The fourth cluster (n=24) had high levels of Somatic Symptoms so they were labeled “Somatic.”

When sex was considered, there was a significantly greater frequency of females than males in the morphine Somatic group compared to the other 3 morphine groups ($p < .05$). There was a significantly greater frequency of females than males in the pentazocine Somatic group compared to the pentazocine Euphoric group ($p < .05$).

Cluster group differences in analgesic effects were observed only within the ischemic pain measures (Table 7). For morphine, the Euphoric group had greater analgesic effect than both the Neurocognitive and Neurocognitive with Euphoria groups on the ischemic measures. For pentazocine, the Euphoric group had greater analgesic effect than the Neurocognitive or Somatic groups. None of the groups differed on baseline sensory testing.

Discussion

The results of factor analysis support the use of the SSE and CASE as standardized measures of opioid-related side effects and suggest they measure relatively unique dimensions of these side effects. Using these questionnaires, we found that side effects occur together and form similar clusters of symptoms across both drugs. The most frequently reported side effects were Feeling relaxed, Sedation, and Feeling in control. Quantitatively,

pentazocine and female sex were associated with a higher frequency of side effects. To our knowledge, this is the first study to systematically examine and compare the somatic and cognitive/affective side-effect profiles of mu and mixed action opioids using standardized instruments for assessing opioid-related adverse symptoms.

From a qualitative perspective, what does this mean to a person experiencing these symptoms? Some side effects differed between men and women or between drugs by effect sizes of 0.6 to 0.9, which from a statistical point of view is large. From a clinical or practical perspective, this would be answered by interpreting the ordinal scaling. A 1.0 unit difference would be the difference between not at all and a little bit, a little bit and somewhat, or somewhat and quite a bit. Descriptively, this translates to the difference between not at all nauseous or a little bit nauseous, which seems important. Similarly so for somewhat sedated compared to a lot sedated. So for some of these symptoms we are seeing 50% to 70% of this descriptive difference.

Clusters of Side Effects

Using several different factor extraction and rotation techniques, we found small but inconsistent differences in the item-level factor profiles of morphine and pentazocine. However, the specific side effects that ultimately formed stable symptom dimensions were not different between the two drugs. This suggests a similar factor interpretation for SSE or CASE with morphine and pentazocine and that both measures are valid for use in between-drug comparisons. Whether this holds true for other opioid drugs is not yet known.

Although the instruments were designed to measure different domains (cognitive vs. somatic/affective), there was overlap between the two instruments. In particular, during our examination of higher-order factors, the poor balance factor (of which poor balance and dizziness were the highest-loading items) formed a secondary factor with several of the negative cognition factors from the CASE that we labeled “Neurocognitive Effects.” This factor was moderately correlated with a somatic factor, whereas a positive symptoms factor (euphoria and feeling relaxed) was independent of the other two.

Both questionnaires were sensitive to differences in the intensity of symptoms for morphine or pentazocine compared to saline placebo, supporting the sensitivity of both instruments to the dosages used. As roughly equianalgesic amounts of the two drugs were administered (14,15,18), any differences in side effects may be of practical significance. Pentazocine consistently had greater aversive side effects than morphine, with the most pronounced differences occurring for vasodilation, tremor, mental dullness, and poor balance. Also, morphine was associated with feeling less confused and more in control than pentazocine. Similarly, another study comparing morphine with pentazocine found several differences, with pentazocine also having a greater negative effect than morphine (6).

Despite weight-adjusted, equivalent dosages, females had more frequent side effects than males, with the largest differences emerging for dry mouth, sedation, and nausea. This finding is consistent with clinical studies that have shown greater nausea after opioid use in females following surgery (13, 28–30) and when given opioids for pain control in medical emergency clinics (12). Using data collapsed across several studies, Zacny (31) reported sex differences in morphine-induced side effects with females feeling more spaced out, feeling heavy or sluggish, and dry mouth than males; however, no sex differences were reported by Zacny and associates when they compared morphine with pentazocine (6). Our previous research with pentazocine demonstrated common occurrences of nausea, dizziness, diaphoresis, and emesis but with similar frequencies in men and women (14), while women reported greater side effects from morphine (15).

Persons with Similar Side Effect Profiles

While increased side effects may lead to opioid discontinuation (4,7,9), our data suggest that the profile of symptoms should be considered in cost-benefit considerations for reducing dosage or changing to a different analgesic drug. The use of cluster analysis, a statistical technique that identifies naturally occurring subgroups, is an important contribution to improving our understanding of this phenomenon. Both drugs resulted in three groups of subjects with similar side-effect profiles, each with predominantly somatic, euphoric, or neurocognitive symptoms. Each drug also had a fourth group that was unique to that opioid.

We found subjects to be evenly divided across side-effect profile groups for pentazocine; however, subjects receiving morphine were distributed disproportionately in the somatic side-effect group. Membership in the high somatic groups was predominantly female for both opioids and this supports the clinical observation that females have more somatic side effects (12,13). What we did not find is that certain people are opioid responders in that all side effects of opioid drugs were more potent.

Of particular interest was the group that appeared to experience high levels of positive symptoms (euphoric cluster) with considerably less aversive effects. Interestingly, this group showed significantly more drug-induced reduction in ischemic pain compared to the other groups, thus providing the strongest link between side effects and analgesia. This association of the subjectively rewarding effects and the analgesic properties of opioids is consistent with recent neuroimaging studies of cerebral responses to opioids. For example, low dose intravenous morphine, which produced mild euphoria and analgesia, was found to increase cerebral blood flow in several brain regions associated with dopaminergic reward circuitry, including the nucleus accumbens, putamen, substantia nigra, and amygdala (32). In addition, expectations of analgesia (i.e. placebo) have been shown to activate both dopamine and μ-opioid receptors in the nucleus accumbens (NAC), an important component of the mesolimbic reward circuitry, and NAC opioid and dopamine receptor activation was positively correlated with the magnitude of placebo analgesia (33). Thus, opioid-mediated experiences of reward (e.g. euphoria) and analgesia may be mediated by the same dopaminergic brain circuits, as has been recently suggested (34). Interestingly, euphoria was comparable for morphine and pentazocine, and the association of the euphoric cluster with analgesic responses was similar for both drugs. Thus, despite their differing receptor affinities, both morphine and pentazocine may produce analgesia and euphoria by activating similar neural circuitry. It seems plausible that this group would be most likely to report clinical benefit and to continue opioid consumption in the clinical setting; however, it is also tempting to speculate that potential for opioid abuse might also be elevated in this group. Other studies have also reported “positive” effects of pentazocine (35,36).

An issue of clinical relevance is the extent to which persons in the euphoric cluster would be at increased risk to use opioids to treat their mood. Certainly opioid misuse, mental health, and pain symptoms overlap (37,38); and a recent study has indentified patient subgroups including two with increased mental health issues and opioid problems (39). On the other hand, Ives et al (40) reported that depression was not associated with opioid misuse among patients treated for chronic non-cancer pain. Nevertheless, it would be interesting to know the side-effect profiles for the groups identified by Banta-Green (39). Literature in pharmacogenetics has shown the influence of certain polymorphisms on reducing efficacy of morphine as well as influencing adverse effects by decreasing binding affinity of specific morphine metabolites (41). Moreover, we have shown that both analgesia and side effects, in response to pentazocine, are influenced by pre-drug psychological variables (18). Future research is needed to consider the multiple biopsychosocial processes contributing to individual differences in opioid use, analgesic response, and side effects.

Proper matching of patient to opioid regimen is critical and requires a comprehensive benefit-to-harm evaluation. Recent recommendations for opioid use from the American Pain Society and the American Academy of Pain Medicine support the regular monitoring of opioid-associated adverse effects (42). We suggest that standardized instruments such as the CASE and SSE could be used in pain clinics to accurately quantify patient's side effects. For example, clinic norms for each of the three higher order factors (somatic, positive, neurocognitive) could be developed and used in clinical decisions such as drug escalation or change. This could be most helpful for opioid-naïve patients that lack experience with opioid side effects or with older persons who may be more sensitive to these adverse symptoms. In addition, our data suggest that consideration of all three together as a side-effect profile should be considered. However, this area of investigation needs additional attention.

Limitations and Conclusion

The limitations of this study include the use of healthy young adults which may not generalize to clinical populations. Similarly, relationships between side effects and analgesic responses based on experimental pain measures may not extend to changes in clinical pain, and side effect profiles associated with acute opioid administration may differ from profiles observed in the context of long-term opioid use. As only a single dose of morphine or pentazocine was administered, we are unable to determine whether drug or sex differences are dose-dependent or how these findings might change with repeated drug administration. Plasma concentrations were not assessed; consequently the contribution of pharmacokinetic factors to the variability of the measured side effects is unknown. Future studies should address these issues.

This study identified opioid-related somatic and cognitive side effects that occur together and formed similar clusters of adverse symptoms for both morphine and pentazocine, with moderate overlap between somatic and cognitive symptoms. Consistent with other opioid literature, the most frequently reported side effects were feeling relaxed and sedation. This study suggests that when discussing opioid side effects, both positive and negative events should be acknowledged. Quantitatively, there were sex differences in side effects of opioid drugs, with females reporting a higher frequency of adverse symptoms. We have also identified empirically derived drug-related side-effect profiles to link the effects of morphine and pentazocine with analgesic responses. Specifically, the group that had a more positive side-effect profile experienced the greatest analgesic effect on the ischemic pain task. Despite the limitations noted above, these findings could have implications for decisions regarding opioid management of chronic and malignant pain conditions. Certainly more research is needed with other drugs and in clinical samples before specific clinical recommendations such as how to identify more favorable side-effect profiles can be made. In the short-term, using this approach may prove useful in studies that document the efficacy of interventions designed to manage adverse events.

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Table 1

Mean and SD for SSE factor loadings using CFA with bootstrap sampling.

	Morphine Mean (SD)	Pentazocine Mean (SD)
Factor 1. Sedation		
SSE 2 - Dizzy	0.18 (0.11)	0.30 (0.07)
SSE 5 - Sleepy	0.84 (0.04)	0.78 (0.04)
SSE 9 - Hard to keep eyes open	0.96 (0.02)	0.95 (0.04)
SSE 15 - Poor balance	0.28 (0.09)	0.30 (0.07)
SSE 26 - Fatigue, lack of energy	0.51 (0.03)	0.76 (0.04)
Factor 2. Vasodilation		
SSE 1 - Warm or hot all over	0.55 (0.04)	0.87 (0.04)
SSE 3 - Flushed	0.91 (0.06)	0.95 (0.04)
SSE 19 - Sweats	0.56 (0.05)	0.53 (0.04)
Factor 3. Tingling		
SSE 12 - Tingling in parts of my body	0.77 (0.06)	0.90 (0.06)
SSE 13 - Numbness in parts of my body	0.89 (0.06)	0.76 (0.05)
SSE 28 - Stiffness or muscle tension	------	0.28 (0.12)
Factor 4. Dry mouth		
SSE 6 - Short of breath	0.88 (0.05)	0.72 (0.04)
SSE 7 - Dry mouth	0.63 (0.04)	0.77 (0.04)
SSE 8 - Difficulty swallowing	0.61 (0.04)	0.81 (0.04)
Factor 5. Poor balance		
SSE 2 - Dizzy	0.90 (0.03)	0.63 (0.03)
SSE 3 - Flushed	0.29 (0.09)	0.28 (0.08)
SSE 4 - Headache	------	0.31 (0.06)
SSE 5 - Sleepy	0.28 (0.09)	0.25 (0.08)
SSE 9 - Hard to keep eyes open	0.35 (0.08)	0.21 (0.12)
SSE 15 - Poor balance	0.91 (0.04)	0.85 (0.03)
SSE 18 - Difficulty concentrating	0.64 (0.03)	0.68 (0.03)
SSE 20 - Muscle twitches	------	0.32 (0.10)
Factor 6. Nausea		
SSE 10 - Loss of appetite	0.68 (0.03)	0.65 (0.03)
SSE 11 - Stomach ache	0.75 (0.03)	0.87 (0.03)
SSE 23 - Nausea	0.89 (0.03)	0.94 (0.03)
SSE 24 - Vomiting	0.41 (0.07)	0.48 (0.06)
Factor 7. Tremors		
SSE 15 - Poor balance	------	0.29 (0.09)
SSE 17 - Restless	0.51 (0.07)	0.72 (0.05)
SSE 20 - Muscle twitches	------	0.31 (0.08)
SSE 21 - Tremors	0.91 (0.06)	0.90 (0.06)
SSE 27 - Jittery	0.83 (0.05)	0.72 (0.04)

Note: Items with loadings of ≥ .40 included from the final model. Items without factor loadings were eliminated following the series of exploratory factor analyses using a cut-off of .30.

Table 2

Mean and SD for CASE factor loadings using CFA with bootstrap sampling.

	Morphine Mean (SD)	Pentazocine Mean (SD)
Factor 1. Mental dulling		
CASE 2 - Difficulty figuring things out	0.31 (0.14)	------
CASE 7 - In control of my thoughts	−0.33 (0.10)	------
CASE 12 - Heavy or sluggish	0.67 (0.08)	0.67 (0.08)
CASE 18 - Difficulty concentrating	0.37 (0.13)	0.21 (0.14)
CASE 23 - I have a detached, unreal feeling	0.78 (0.08)	0.78 (0.08)
CASE 28 - My thinking seems slowed down	0.85 (0.08)	0.76 (0.04)
CASE 31 - My hands feel clumsy	0.74 (0.08)	0.68 (0.08)
CASE 34 - My mind and body do not seem connected	0.71 (0.08)	0.75 (0.08)
CASE 36 - I have a weird feeling	0.81 (0.08)	0.81 (0.08)
CASE 38 - I feel less in control than usual	0.78 (0.08)	0.80 (0.08)
CASE 39 - I feel a mental effect of the pain medicine	0.72 (0.08)	0.69 (0.08)
CASE 41 - It seems harder than usual to do things	0.74 (0.08)	0.84 (0.08)
CASE 43 - I notice a change in the way I feel or the way I am thinking	0.83 (0.08)	0.62 (0.10)
Factor 2. Relaxed		
CASE 1 - Contented	0.75 (0.09)	0.84 (0.08)
CASE 3 - Laid back	0.72 (0.09)	0.87 (0.08)
CASE 6 - Carefree	0.75 (0.09)	0.76 (0.08)
CASE 14 - On top of the world	0.73 (0.09)	0.79 (0.08)
CASE 17 - Mellow	0.73 (0.09)	0.71 (0.08)
CASE 20 - At ease	0.81 (0.08)	0.82 (0.08)
CASE 27 - I would be happy to relax and do nothing	0.50 (0.09)	0.63 (0.08)
CASE 29 - I have a very pleasant feeling	0.34 (0.11)	0.37 (0.11)
CASE 35 - I like the mental effects of the pain medicine	------	0.34 (0.10)
CASE 44 - I feel great	0.30 (0.12)	0.39 (0.09)
Factor 3. Unusual thoughts		
CASE 8 - Vivid or strange dreams	0.86 (0.08)	0.69 (0.09)
CASE 15 - Seeing or hearing things that seem unusual or strange	0.91 (0.08)	0.72 (0.08)
CASE 32 - Everything seems unusually vivid	0.60 (0.09)	0.54 (0.09)
CASE 33 - I feel like avoiding people	0.72 (0.08)	0.70 (0.09)
CASE 37 - Other people might think my thoughts are strange or unusual	0.80 (0.08)	0.79 (0.09)
Factor 4. In control		
CASE 7 - In control of my thoughts	0.82 (0.08)	0.74 (0.09)
CASE 9 - Clearheaded	0.71 (0.09)	0.79 (0.09)
CASE 10 - In harmony with the world	0.40 (0.10)	0.53 (0.09)
CASE 13 - In control of my body	0.78 (0.05)	0.71 (0.09)
CASE 40 - I feel like my usual self	0.70 (0.09)	0.60 (0.09
Factor 5. Confusion		

	Morphine Mean (SD)	Pentazocine Mean (SD)
CASE 2 - Difficulty figuring things out	0.91 (0.08)	0.83 (0.08)
CASE 4 - My mind keeps wandering	0.70 (0.08)	0.60 (0.09)
CASE 11 - In harmony with the world	0.68 (0.08)	0.70 (0.09)
CASE 16 - Confused	0.89 (0.08)	0.78 (0.08)
CASE 18 - Difficulty concentrating	0.84 (0.08)	0.81 (0.08)
CASE 22 - I have difficulty expressing my thoughts	0.87 (0.08)	0.77 (0.08)
CASE 28 - My thinking seems slowed down	0.34 (0.10)	0.24 (0.14)
Factor 6. Euphoria		
CASE 1 - Contented	0.22 (0.14)	0.37 (0.12)
CASE 3 - Laid back	-------	0.28 (0.13)
CASE 6 - Carefree	0.30 (0.12)	0.31 (0.12)
CASE 14 - On top of the world	0.27 (0.13)	0.35 (0.11)
CASE 19 - High	0.30 (0.11)	0.32 (0.12)
CASE 20 - At ease	0.18 (0.16)	0.35 (0.12)
CASE 21 - I would like to feel like this all the time	0.77 (0.08)	0.82 (0.08)
CASE 24 - My speech is slurred	0.71 (0.09)	0.65 (0.08)
CASE 26 - Anytime I had a chance to feel like this again I would take it	0.81 (0.08)	0.85 (0.08)
CASE 29 - I have a very pleasant feeling	0.84 (0.08)	0.92 (0.08)
CASE 35 - I like the mental effects of the pain medicine	0.84 (0.08)	0.87 (0.08)
CASE 44 - I feel great	0.74 (0.09)	0.92 (0.08)

Note: Items with loadings of ≥ .40 included from the final model. Items without factor loadings were eliminated following the series of exploratory factor analyses using a cut-off of .30.

Table 3

Mean and SD for side-effect factor scores by drug.

	Morphine n=114	Pentazocine n=98	Effect size
SSE Sedation	2.8 (1.2)	3.5 (1.2)	0.6*
SSE Vasodilation	1.5 (0.6)	2.3 (1.2)	0.9*
SSE Tingling	1.8 (1.0)	2.1 (1.0)	0.3
SSE Dry mouth	1.6 (0.7)	1.7 (0.8)	0.1
SSE Poor balance	2.0 (0.9)	2.8 (1.0)	0.8*
SSE Nausea	1.4 (0.7)	1.7 (0.8)	0.4*
SSE Tremors	1.3 (0.5)	1.8 (0.8)	0.8*
CASE Mental dullness	2.2 (0.9)	3.0 (0.9)	0.9*
CASE Relaxed	3.4 (0.8)	3.6 (0.9)	0.2
CASE Unusual thoughts	1.4 (0.6)	1.7 (0.7)	0.5*
CASE Control	3.2 (0.8)	2.8 (0.8)	0.5*
CASE Confusion	1.8 (0.8)	2.1 (0.8)	0.5*
CASE Euphoria	2.5 (0.9)	2.5 (1.1)	0.0

Note: Factor composite scores are summed and divided by the number of items to return the total to the original scaling: 1= Not at all, 2 = A little bit, 3 = Somewhat, 4 = Quite a bit, 5 = Extremely. The 50 percentile value is also the median.

* $p < 0.01$

Table 4

Mean and SD for side-effect factor scores by sex.

	Male	Female	Effect size
Morphine (n=114)	n=46	n=68	
SSE Sedation	2.4 (1.0)	3.1 (1.2)	0.6*
SSE Vasodilation	1.4 (0.5)	1.6 (0.7)	0.3
SSE Tingling	1.7 (0.8)	1.9 (1.0)	0.2
SSE Dry mouth	1.4 (0.6)	1.8 (0.7)	0.6*
SSE Poor balance	1.9 (0.9)	2.0 (0.9)	0.1
SSE Nausea	1.2 (0.4)	1.6 (0.7)	0.7*
SSE Tremors	1.2 (0.4)	1.3 (0.6)	0.2
CASE Mental dullness	2.2 (0.9)	2.3 (0.9)	0.1
CASE Relaxed	3.4 (0.9)	3.3 (0.8)	−0.1
CASE Unusual thoughts	1.4 (0.5)	1.4 (0.6)	0.0
CASE Control	3.3 (0.8)	3.2 (0.8)	−0.1
CASE Confusion	1.9 (0.9)	1.9 (0.8)	0.0
CASE Euphoria	2.7 (0.8)	2.4 (0.9)	−0.4
Pentazocine (n=98)	n=44	n=54	
SSE Sedation	3.1 (1.1)	3.8 (1.1)	0.6*
SSE Vasodilation	2.2 (1.2)	2.3 (1.2)	0.1
SSE Tingling	1.9 (1.0)	2.2 (1.0)	0.3
SSE Dry mouth	1.5 (0.6)	1.9 (0.8)	0.6*
SSE Poor balance	2.6 (1.0)	2.9 (1.0)	0.3
SSE Nausea	1.4 (0.7)	1.9 (0.9)	0.6*
SSE Tremors	1.5 (0.8)	2.0 (0.9)	0.5*
CASE Mental dullness	2.7 (0.8)	3.1 (0.9)	0.5*
CASE Relaxed	3.5 (1.0)	3.5 (0.8)	0.0
CASE Unusual thoughts	1.7 (0.8)	1.6 (0.7)	0.1
CASE Control	2.8 (0.8)	2.8 (0.7)	0.0
CASE Confusion	2.1 (0.8)	2.3 (0.8)	0.3
CASE Euphoria	2.7 (1.0)	2.5 (0.9)	0.2

Note: Factor composite scores are summed and divided by the number of items to return the total to the original scaling: 1= Not at all, 2 = A little bit, 3 = Somewhat, 4 = Quite a bit, 5 = Extremely.

* $p < 0.01$

Table 5

Higher order factors

	Somatic effects	Positive feelings	Neurocognitive Effects
SSE Factor 1. Sedation	.77		
SSE Factor 7. Tremors	.75		
SSE Factor 2. Vasodilatation	.72		
SSE Factor 6. Aches/Nausea	.63	−.38	
SSE Factor 4. Dry mouth	.61		
CASE Factor 6. Euphoria		.91	
CASE Factor 2. Feeling relaxed		.90	
CASE Factor 5. Confusion			.89
CASE Factor 1. Mental dulling	.55		.83
SSE Factor 5. Poor balance	.50		.76
CASE Factor 3. Unusual thoughts	.40		.77
CASE Factor 4. Feeling in control	−.41	.40	−.74
SSE Factor 3. Tingling	.46		.48

Note: Values of less than + or −.35 are suppressed

Table 6

mean standardized score for by cluster for each drug.

	N	Female	Male	Somatic effects	Positive feelings	Confusion
Morphine (n=114)						
Somatic [a]	51	36 (53%)	15 (33%)	0.6	−0.5	−0.3
Confused	22	11 (16%)	11 (23%)	−0.8	−0.6	0.9
Euphoric	17	11 (16%)	6 (13%)	0.3	1.1	−1.1
Confused with euphoric	24	10 (15%)	14 (30%)	−0.4	0.5	0.8
Pentazocine (n=98)						
Mild somatic	21	9 (17%)	12 (27%)	0.0	−0.8	−0.3
Confused	19	10 (19%)	9 (21%)	−0.6	−0.9	0.9
Euphoric	32	16 (30%)	16 (36%)	−0.2	1.2	0.2
Somatic [b]	26	19 (35%)	7 (16%)	1.3	−0.8	−0.7

Standard scores are variables transformed so that the mean =0 and scores of ± 1.0 are one SD above or below the mean.

[a] There was a significantly greater frequency of females than males in the morphine somatic cluster compared to the other 3 morphine clusters ($p < .05$).

[b] There was a significantly greater frequency of females than males in the pentazocine somatic cluster compared to the euphoric clusters ($p < .05$).

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Table 7

Mean and SD for analgesic effect by cluster for each drug.

	ΔIPTh	ΔIPTo	ΔIPR
Morphine (n=114)			
Somatic	49.4 (104.8)	72.8 (104.2)	29.1 (42.4)
Confused	29.0 (70.4) [b]	50.7 (94.7) [b]	18.7 (21.8) [b]
Euphoric	95.5 (103.9) [a]	88.4 (74.3) [a]	38.1 (35.9) [a]
Euphoric and confused	25.1 (188.5) [b]	69.6 (92.4) [b]	21.3 (36.9) [b]
Pentazocine (n=98)			
Mild somatic	62.4 (93.6)	66.9 (102.1)	33.6 (40.3)
Confused	26.2 (98.4) [b]	55.7 (102.1) [b]	14.9 (54.0) [b]
Euphoric	109.4 (102.2) [a]	115.4 (101.4) [a]	44.9 (32.6) [a]
Somatic	21.9 (101.2) [b]	−19.5 (89.9) [b]	11.7 (48.4) [b]

Groups with differing superscripts are statistically different at $p < .05$.