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The Contribution of Differential Opioid Responsiveness to Identification of Opioid Risk in Chronic Pain Patients

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Abstract

The Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) predicts increased risk of opioid misuse in chronic pain patients. We evaluated whether higher SOAPP-R scores are associated with greater opioid reinforcing properties, potentially contributing to their predictive utility. Across two counterbalanced laboratory sessions, 55 chronic low back pain sufferers completed the SOAPP-R at baseline, and measures of back pain intensity, evoked pain responsiveness (thermal, ischemic), and subjective opioid effects after receiving intravenous morphine (0.08 mg/kg) or saline placebo. Morphine effect measures were derived for all outcomes reflecting the difference between morphine and placebo condition values. Higher SOAPP-R scores were significantly associated with greater desire to take morphine again, less feeling down and feeling bad, and greater reductions in sensory low back pain intensity following morphine administration. This latter effect was due primarily to SOAPP-R content assessing medication-specific attitudes and behavior. Individuals exceeding the clinical cutoff (18 or more) on the SOAPP-R exhibited significantly greater morphine liking, desire to take morphine again, and feeling sedated; lower feeling bad; and greater reductions in sensory low back pain following morphine. The SOAPP-R may predict elevated opioid risk in part by tapping into individual differences in opioid reinforcing effects.

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Keywords

Opioid; Analgesia; Chronic Pain; Abuse Risk; Misuse; Screening; Personalized Medicine

INTRODUCTION

The growing role of opioid analgesics in chronic pain management has been associated with increasing numbers of chronic pain patients experiencing problems with misuse of prescribed opioids[11,12,18,39]. Potential opioid misuse may be suggested by presence of behavioral indicators such as requests for early refills, lost or stolen prescriptions, unapproved dose escalations, obtaining opioids from multiple providers, and presence of unprescribed opioids on toxicology screens[18,36]. In an effort to mitigate risks of opioid misuse, screening questionnaires have been developed for the purpose of identifying prior to initiating opioid therapy those individuals more likely to misuse opioids. One of the most common is the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R), which is intended specifically for screening use in the chronic pain population[9,10]. There is evidence for the predictive validity of the SOAPP-R in the chronic pain management context[9,26,32,34]. For example, baseline SOAPP-R scores predicted subsequent aberrant drug behaviors in a clinical trial of opioid therapy in chronic pain patients[34].

While the SOAPP-R is empirically predictive of subsequent behavioral markers of elevated opioid risk, mechanisms contributing to these predictive effects have to our knowledge not been explored. Prior work by Edwards et al.[16] found that elevated SOAPP-R scores were associated with greater evoked pain responsiveness and greater chronic pain intensity, hinting that SOAPP-R scores might reflect individual differences in pain modulatory systems. Whether the SOAPP-R might predict risks of opioid misuse in part by tapping into individual differences in actual responses to opioids has not previously been investigated. Differential responsiveness to opioids with regards to their reinforcing effects is considered to be an important factor contributing to opioid abuse liability[15,22,27,40,46,49].

The current study capitalized on a dataset available from a larger study of predictors of opioid analgesic responses[5,6,23]. It sought to explore the general hypothesis that higher SOAPP-R scores predict subsequent risk of opioid misuse in part through differential reinforcing effects of opioid analgesics. Specifically, we hypothesized that when individuals were administered a weight-standardized dose of morphine under placebo-controlled conditions, those with higher SOAPP-R scores would report greater overall morphine effects, more morphine liking and desire to take morphine again, more positive and fewer negative subjective effects, and greater analgesia.

An additional issue addressed in this study related to the predictive contributions of specific content domains on the SOAPP-R. The 24 items on the SOAPP-R were selected empirically, based on their ability to predict objective aberrant drug behavior criteria, such as toxicology results[10]. As suggested by Jamison et al.[24], the SOAPP-R items tap into several distinct domains, with two broad domains most highly represented: negative affect-related issues and medication-specific attitudes and behavior. Prior work suggested that negative affect in particular is a predictor of both analgesic responses to[17,21,33,43]and abuse liability associated

with opioids[29,42], so differential mechanisms of predictive effects for different SOAPP-R content domains appeared plausible. A secondary aim of this study therefore was to evaluate the extent to which each of these two primary content areas of the SOAPP-R was associated with morphine responses relevant to opioid misuse.

METHODS

Design

This study used a double-blind, placebo-controlled crossover design with randomized, counterbalanced administration of morphine versus placebo. Identical data collection procedures were used at two sites (Vanderbilt University Medical Center and Rush University Medical Center). A third drug arm (with naloxone administration) was also carried out, but these data were not directly relevant to the current hypotheses (results detailed fully in Bruehl et al.[5]).

Participants

Participants included 55 individuals with chronic low back pain recruited through university e-mail recruitment systems, university pain management centers, print media advertisements, and posted flyers. Inclusion criteria were age between 18-55; daily low back pain of 3 months or more in duration with an average severity in the past month of 3/10 or more; no self-reported history of cardiovascular disease, hypertension, liver or kidney disorders, posttraumatic stress disorder, bipolar disorder, psychotic disorder, diabetes, seizure disorder, or alcohol or drug dependence; and no daily use of opioid analgesics (no opioid use within the prior ≈3 days was confirmed via urine opiate screen before each laboratory study session). Individuals experiencing chronic pain related to malignancy, fibromyalgia, or autoimmune diseases (e.g., lupus) were excluded, as were pregnant females. Eligibility regarding the latter criterion was determined based on urine pregnancy screens conducted prior to each laboratory session. Seven participants reported occasional as needed use of opioid analgesics and 3 reported use of antidepressant medications. The sample was predominately female (69.1%), white (61.8% versus 32.7% African-American), and non-Hispanic (96.3%), with a mean age of 36.4 (10.5) years. Median chronic pain duration was 94.1 months, and 52.7% showed a radicular pattern of back pain on examination. The study sample size had sufficient statistical power to detect an effect size as small as $\underline{r}$=0.27 in magnitude (i.e., a moderate or larger effect size[14]), an effect size likely necessary for clinically meaningful effects.

Primary Measures

The SOAPP-R is an empirically-developed measure designed to assess risk of opioid misuse in the chronic pain population[10]. It has demonstrated good reliability, as well as validity for prediction of subsequent objective markers of opioid misuse, such as toxicology results and aberrant drug behaviors[9,10,26,32,34]. It is often used in clinical chronic pain management settings for purposes of opioid risk mitigation. Inspection of SOAPP-R item content indicates that two distinct content areas comprise the majority of the items (17 of 24 items). Similar to the item content approach of Jamison et al.[24], two subscales were created reflecting the SOAPP-R items tapping into negative affect-related issues (items

1,3,4,5,8,10,14, 20) and the items tapping into medication-specific attitudes and behavior (items 2,6,7,9,11,12,15,16, 23) to evaluate whether these two components differentially predicted morphine response outcomes. Examples of negative affect-related items include "how often do you have mood swings?", "how often have you felt impatient with your doctors?", "how often have you been worried about being left alone?", and "how often have others told you that you had a bad temper?" Examples of medication-specific items are "how often have you felt you needed higher doses of medication to treat your pain?", "how often have you counted pain pills to see how many are remaining?", "how often have you taken more pain medication than you were supposed to?", and "how often have you felt consumed by the need to get pain medication?"

Non-analgesic subjective effects of morphine were assessed at the end of the acute pain protocol (see below) using the DELTA questionnaire and VAS opioid effects measures taken from Zacny[47,49]. The DELTA questionnaire asks participants to rate the magnitude of overall drug effects (Drug Effects; 0-5 scale), the degree of drug liking (Drug Liking; 0-100, with 50 indicating a neutral response), and the level of desire to take the drug again (Take Again; 0-100, with 50 indicating a neutral response). Non-analgesic morphine effects examined on the VAS opioid effects measure (0-100mm) for purposes of this study included: feeling high, feeling sedated, feeling elated, feeling down, feeling anxious, feeling good, and feeling bad. Both the DELTA and the VAS opioid effects measures appear to be sensitive to individual differences in opioid analgesic responses[48,50].

The McGill Pain Questionnaire - Short Form (MPQ[31]) is a standardized measure of the sensory (MPQ-Sensory) and affective (MPQ-Affective) dimensions of pain. It was used to assess both evoked pain responses and chronic back pain in the laboratory, with instructions slightly modified as appropriate. For chronic pain assessment, the MPQ was used to describe current back pain intensity during each laboratory session both before (baseline) and after administration of each study drug to evaluate acute morphine analgesic effects on clinical back pain intensity.

Study Drug

Morphine sulfate, the prototypic mu opioid receptor agonist, was given to all participants at a weight adjusted dosage of 0.08 mg/kg (in 20ml normal saline), which was infused over 10 minutes using an automated infusion pump through an indwelling venous cannula placed in the non-dominant arm. This dosage (approximately 6mg for a 165 lb individual) was selected because it was judged to be sufficient to produce analgesia, but low enough to avoid ceiling effects that might obscure key individual differences in morphine responding. Peak morphine activity is achieved within approximately 15 min[1]. The placebo control condition consisted of administration of an equal volume of saline in double-blinded fashion.

Laboratory Evoked Pain Tasks

After peak drug activity was achieved in each session, participants engaged in two laboratory evoked pain tasks. The first was a modified ischemic pain task based on that developed by Maurset and colleagues[30] which we have used in our past studies of opioid systems[3,4,7]. Participants first engaged in two minutes of dominant forearm muscle exercise

using a hand dynamometer at 50% of his or her maximal grip strength (determined prior to the laboratory procedures), followed by raising their dominant forearm over their head for 15 sec. A manual BP cuff was next inflated on the biceps to 200 mmHg SBP, the arm was lowered, and the cuff remained inflated until pain tolerance was reached, up to a maximum of 8 min. Participants were asked to rate the pain experienced during this task using the MPQ immediately after pain tolerance was reached.

The second laboratory pain task was a heat pain task using a Medoc TSAII NeuroSensory Analyzer (Medoc US., Minneapolis, MN) as in our prior work[8,13]. Four pain tolerance trials were carried out, with each trial conducted sequentially at one of four different non-overlapping sites on the non-dominant ventral forearm. An interval of 30 sec between successive stimuli was employed. For each trial, the probe started at an adaptation temperature of 40°C, with the temperature increasing at 0.5°C/sec until the participant indicated that maximum tolerance had been reached. MPQ ratings of pain for the last tolerance trial were obtained. Thermal pain tolerance values for analyses were derived as the mean of the four tolerance trials. Maximum possible tolerance temperature was set at 51°C due to an automated hardware cutoff in the TSAII unit. Participants underwent standardized training prior to starting the laboratory procedures in the first session to familiarize them with the thermal stimulus device and procedures.

Procedures

All procedures were conducted at the Vanderbilt General Clinical Research Center or a dedicated research room at the Rush University Pain Center. All procedures were approved by each university's Institutional Review Board. After providing informed consent, individuals participated in two identical experimental sessions (placebo versus morphine) at the same time of day to control for potential circadian rhythm effects.

Participants remained seated upright in a comfortable chair throughout all laboratory procedures. During each session, participants initially completed a 10-min seated rest period, after which an indwelling venous cannula was inserted into the non-dominant arm. After a 30-min resting adaptation period, subjects completed the MPQ to describe their current low back pain intensity. Subjects then received (via the cannula) either saline placebo or morphine, with order of drug administration across the two sessions randomly determined and counterbalanced. After a 15-min rest period to allow peak drug activity to be achieved, subjects again described their current level of low back pain using the MPQ. Participants next engaged in the ischemic task using procedures described above, after which the MPQ was immediately completed to describe responses to this evoked pain stimulus. Then, participants engaged in the thermal pain task, with the MPQ again immediately completed to describe the pain experienced during the heat pain tolerance trials. Upon termination of the final evoked pain trial in each drug condition, participants completed the DELTA and VAS opioid effects measures. All participants remained in the lab under observation for 2 hours after peak drug activity had been achieved to allow drug effects to remit. They were then released to a responsible adult.

Statistical Analyses

Analyses were conducted using SPSS for Windows version 22 (IBM Corporation; Chicago, IL). Prior to conducting analyses, indices of morphine analgesic responsiveness (morphine effects) were derived separately for the two evoked pain measures for both laboratory pain tasks, as well as for the low back pain intensity measures obtained during each laboratory session. For evoked pain measures (MPQ-Sensory, MPQ-Affective, Pain Tolerance), morphine effects were derived as the difference in evoked pain responses between the morphine and placebo conditions. Larger negative morphine effects for acute pain ratings indicated greater morphine-induced reductions in those ratings, whereas larger positive morphine effects for acute pain tolerance indicated greater morphine-induced increases in tolerance. For chronic pain outcomes (MPQ-Sensory, MPQ-Affective), morphine effects were derived as the difference between pre- to post-drug *changes* in the morphine condition relative to the placebo condition, such that larger negative morphine effect values indicated greater morphine-induced reductions in low back pain intensity in the laboratory. To control for possible placebo effects on non-analgesic morphine responses, a similar approach was used, with measures derived reflecting morphine condition subjective effects minus comparable placebo condition values, with higher scores indicating greater subjective effects with morphine.

Preliminary analyses were conducted using one-sample t-tests to determine whether degree of morphine analgesia for evoked and chronic pain outcomes was significantly different from zero. Given the continuous nature of the measures involved in testing the primary hypotheses, a correlational analytic approach was used (Pearson r). These primary analyses evaluated the extent to which SOAPP-R scores (total and content domain-specific subscales) were associated with subjective effects of morphine relevant to misuse and the analgesic effects of morphine on both evoked and chronic pain outcomes. To enhance clinical relevance of study findings, a categorical variable was also derived to indicate whether each participant exceeded the recommended clinical cutoff for identifying elevated opioid risk on the SOAPP-R (total score of 18 or greater[9,10]), with t-tests conducted to examine morphine effect outcomes as they related to this standard clinical opioid risk cutoff. Given the novel but hypothesis-driven nature of the study, an unadjusted probability value of $p<.05$ (two-tailed) was used as the criterion for significance in order to minimize the risk of Type II error.

The sample size was insufficient to formally examine gender interactions on the effects of interest. However, possible impact of gender on the results was considered. The primary correlational analyses were re-run using partial correlations controlling for gender. Results of these analyses did not substantively change the overall pattern of results and are therefore not presented.

RESULTS

Preliminary Analyses

Mean values (and standard deviations) for all study measures are summarized in Table 1. One sample t-tests revealed that morphine significantly reduced evoked pain responses on

the ischemic task for both the MPQ-Sensory [$t(54) = -2.12$, $p<.05$)] and MPQ-Affective subscales [$t(54) = -2.65$, $p<.05$)], as well as for ischemic pain tolerance [$t(54) = -2.30$, $p<.05$)]. Morphine did not significantly reduce evoked pain responses on the thermal pain task (p's>.10). Regarding morphine's impact on chronic back pain intensity in the laboratory, significant morphine-related pain reduction were observed for MPQ-Sensory ratings [$t(54) = -2.56$, $p<.05$)] but not for MPQ-Affective ratings ($p>.10$).

Examination of intercorrelations among the three classes of primary outcomes (i.e., morphine effects on the DELTA measure, VAS opioid effects, and pain-related outcomes) revealed several moderate correlations in the expected direction. Greater overall morphine effects on the DELTA measure were correlated with greater VAS ratings of feeling high ($r=0.46$, $p<.001$) and feeling sedated ($r=0.44$, $p<.001$). Greater VAS feeling good was associated with higher levels of morphine liking ($r=0.39$, $p<.005$) and desire to take morphine again ($r=0.44$, $p<.001$) on the DELTA. Larger morphine-related reductions in sensory low back pain intensity on the MPQ were associated with greater VAS ratings of feeling high ($r=-0.44$, $p<.001$), feeling sedated ($r=-0.44$, $p<.001$), feeling elated ($r=-0.44$, $p<.001$), and feeling good ($r=-0.43$, $p<.001$), as well as lower VAS ratings of feeling down ($r=0.49$, $p<.001$), feeling anxious ($r=0.46$, $p<.001$), and feeling bad ($r=0.35$, $p<.01$). All other associations were nonsignificant (p's>.10).

Mean scores on the medication-specific and negative affect-related SOAPP-R content subscales were 3.9 (5.60) and 7.5 (4.89), respectively. The correlation between these two content subscales was significant ($r=0.64$, $p<.001$), although represented only 41% shared variance. The clinical cutoff on the SOAPP-R (total score of 18 or more) for identifying elevated opioid risk was exceeded by 25.5% of the sample, similar to prior work[34].

SOAPP-R Scores and Pain Outcomes in the Absence of Morphine

Associations between SOAPP-R scores and both evoked pain responses and chronic pain intensity in the absence of morphine are summarized in Table 2. Significant positive correlations were observed across all three SOAPP-R indices for ischemic and thermal pain tasks for the measure of evoked sensory pain intensity (MPQ-Sensory), with comparable associations with the affective component of evoked pain (MPQ-Affective) found to be significant only for the thermal pain task. Associations with pain tolerance measures on both pain tasks were nonsignificant (p's>.10). Significant associations between SOAPP-R scores and baseline (i.e., mean pre-drug) chronic pain intensity were also observed, with the magnitude of these associations particularly large for the affective component of chronic back pain. Regarding SOAPP-R content domain subscales, it was notable that correlations for the medication-specific subscale were in all cases larger than for the negative affect-related subscale.

SOAPP-R Scores and Morphine Response Outcomes

Associations between morphine response outcomes and SOAPP-R scores are presented in Table 3. For the DELTA measure, both the total SOAPP-R and the negative affect-related subscale displayed significant positive correlations with desire to take morphine again as assessed shortly after actually receiving morphine. For the VAS opioid effects measures,

higher total SOAPP-R scores were associated with significantly less feeling down and feeling bad after receiving morphine (relative to placebo), with a nonsignificant trend towards greater feeling sedated ($p<.10$). SOAPP-R medication-specific subscale scores were also correlated with significantly less feeling down and feeling bad, as well as less feeling anxious after morphine, with a trend approaching significance for greater feeling good ($p<.10$). SOAPP-R negative affect-related subscale scores were also linked to significantly less feeling bad after morphine, as well as significantly greater feeling sedated. Associations with all other VAS opioid effects were nonsignificant ($p's>.10$). Consistent with the reinforcement hypothesis, the DELTA and VAS opioid effects findings suggest that heightened opioid risk (as indexed by the SOAPP-R and its key components) is associated with greater desire to take opioids again and lower negative subjective effects (feeling down, feeling bad, feeling anxious) after receiving morphine.

Table 3 also indicates that higher total scores on the SOAPP-R as well as higher scores on both content domain subscales were associated with significantly greater reductions in sensory low back pain intensity after receiving morphine (larger negative morphine effects). The effect size was largest for the medication-specific subscale. To determine whether these findings might have been confounded by the SOAPP-R related influences observed on placebo condition pain responses (Table 2), these analyses were repeated as partial correlations controlling for placebo condition sensory low back pain intensity. As in the primary analyses reported in Table 3, partial correlations between morphine effects on sensory low back pain intensity and SOAPP-R total scores (partial $r = -0.36$, $p<.01$), medication-specific subscale scores (partial $r = -0.40$, $p<.01$), and negative affect-specific subscale scores (partial $r = -0.36$, $p<.01$) remained moderate in magnitude and significant. Primary analyses of the affective component of chronic pain did not reveal significant effects ($p's>.10$). SOAPP-R scores were also not associated significantly with the effects of morphine on laboratory evoked pain responses ($p's>.10$).

To further explore the impact of SOAPP-R scores on individual differences in analgesic responses to morphine, follow-up regression analyses were conducted. Joint inclusion of both the SOAPP-R medication-specific and negative affect-related subscales accounted for 19.0% of the variance in morphine analgesic effects on sensory low back pain intensity, with most of this effect attributable to the medication-specific items (semi-partial $r = -0.30$ controlling for negative affect-related items) rather than the negative affect-related items (semi-partial $r = -0.05$ controlling for medication-specific items). In contrast, the total SOAPP-R score only predicted 16% of the variance in morphine analgesic effects on low back pain. In light of the findings above, results suggest that the medication-specific domain of the SOAPP-R might have somewhat more predictive utility in the clinical context.

Morphine Response Outcome Differences Using the Standard SOAPP-R Clinical Cutoff

For identifying heightened opioid risk in clinical chronic pain management, a clinical cutoff of 18 or more on the total SOAPP-R score is recommended[9,10]. To better translate the findings of the current study to clinical practice, morphine effect outcomes were examined to determine whether they differed as a function of patients exceeding this standard clinical cutoff. Table 4 summarizes results of these analyses. Chronic low back pain patients

exceeding the SOAPP-R clinical cutoff reported significantly higher morphine liking and desire to take morphine again, significantly more feeling sedated and less feeling bad after morphine, and experienced significantly larger morphine-induced reductions in the sensory component of their chronic back pain relative to patients below the SOAPP-R clinical cutoff. A nonsignificant trend ($p<.10$) for greater morphine-induced reductions in thermal evoked pain responsiveness (MPQ-Sensory) was also noted. To evaluate the likelihood that these clinically-relevant differences would replicate in a new sample, follow-up bootstrapped t-tests were conducted. Results of these analyses confirmed the findings above, with significant differences ($p's<.05$) observed for: morphine liking (95% CI = −26.956 – −2.061), desire to take morphine again (95% CI = −46.247 – −15.605), feeling sedated (95% CI = −39.178 – −4.149), feeling bad (95% CI = 4.077 – 39.761), and morphine-induced changes in sensory chronic pain intensity (95% CI = 0.449 – 8.434). When these five significant morphine effect outcomes were entered jointly as predictors of SOAPP-R clinical cutoff status in a logistic regression, only the effect for desire to take morphine again remained a significant predictor (B = 0.08, SE = 0.03, $p<.01$), suggesting that this subjective reinforcing response to morphine has a particularly dominant association with clinically-elevated SOAPP-R scores. The full model classified 84.9% of patients correctly in terms of SOAPP-R clinical cutoff status.

DISCUSSION

As the role of opioid analgesics in chronic pain management has increased, the number of pain patients affected by problems with opioid misuse has also grown[11,12,18,39]. In the clinical setting, opioid risk mitigation efforts often use the SOAPP-R and similar measures to target individuals at increased risk of opioid misuse[25]. While the SOAPP-R empirically predicts behavioral indicators of opioid misuse, mechanisms underlying its' predictive utility are unknown. Improved understanding of *why* instruments such as the SOAPP-R predict opioid risk may help enhance ability to predict and better mitigate this risk. The current study examined whether SOAPP-R scores are associated with differential responsiveness to opioids, specifically greater reinforcing effects of opioids, thus providing one potential pathway by which the SOAPP-R might be linked to elevated opioid risk. We hypothesized that chronic pain sufferers with higher SOAPP-R scores would report greater overall morphine effects, greater morphine liking and desire to take morphine again, more positive and fewer negative subjective morphine effects, and greater analgesia.

Results provided support for the hypothesized reinforcement model. Individuals with higher SOAPP-R scores reported greater desire to take morphine again, described less feeling down and feeling bad after receiving morphine, and experienced greater reductions in clinical back pain intensity with morphine than did individuals with lower SOAPP-R scores. Positive results across drug taking attitudes, subjective effects, and analgesia after receiving morphine are consistent with a reinforcement model in which the SOAPP-R may predict risk of opioid misuse in part via associations with individual differences in opioid responsiveness. Future SOAPP-R studies incorporating both objective opioid misuse markers (e.g., toxicology results, aberrant drug behaviors) and controlled assessment of subjective and pain-related opioid analgesic responses could permit direct testing of the reinforcement model (i.e., mediation tests). It may be relevant to consider the current results

within the allostatic model of addiction, which proposes that in chronic opioid users, dysregulation in affective homeostatic processes marked by decreased sensitivity to reward contributes to addiction[19,38]. The current results suggest that in individuals *not* chronically using opioids, those at greatest risk for opioid misuse may exhibit elevated sensitivity to positive reinforcement. Whether the current findings are informative regarding patterns of reward sensitivity with chronic opioid exposure remains to be evaluated.

Another issue addressed by this study was possible differences in results as a function of the two largest, and very different, content domains of the SOAPP-R: medication-specific and negative affect-related. Contrary to expectations based on past literature indicating that negative affect is a predictor of opioid analgesic responses[17, 21,33,43], analyses examining both content domains jointly suggested that the medication-specific items played a somewhat larger role in observed predictive effects regarding analgesic outcomes than did negative affect-related items. Interestingly, associations between the medication-specific subscale and both evoked and chronic pain intensity in the absence of morphine were larger in magnitude than for comparable associations with the negative affect-related subscale. Consistency of the observed associations between SOAPP-R scores and both acute and chronic pain responses in the absence of morphine with findings of Edwards and colleagues[16] supports the idea that the SOAPP-R may to some degree tap into individual differences in pain modulatory systems. Alternatively, results might be considered in the context of opioid pseudoaddiction, a concept which proposes that many behaviors commonly interpreted as indicating opioid misuse (e.g., unapproved dose escalations) are instead simply a reflection of poorly managed pain[35,45]. Findings that higher SOAPP-R scores are linked to greater chronic pain intensity are as would be expected if pseudoaddiction accounted for some of the presumed opioid risk assessed by the SOAPP-R . Whether SOAPP-R scores are a general marker for elevated pain responsiveness or a more specific marker for pain modulatory system differences with implications for opioid pharmacotherapy and its' associated risks remains to be elucidated.

In addition to analyses using the SOAPP-R as a continuous measure, we also examined morphine response differences across individuals scoring below versus above the recommended empirically-derived clinical cutoff for identifying opioid risk in chronic pain patients[9,10]. Individuals scoring 18 or higher on the SOAPP-R reported both greater desire to take morphine again and greater reductions in sensory chronic pain intensity relative to those scoring below the clinical cutoff. In addition, unlike findings with continuous SOAPP-R scores, individuals exceeding the clinical SOAPP-R cutoff also reported significantly greater drug liking with morphine. Of particular note was the fact that exceeding the SOAPP-R clinical cutoff was associated with a large effect size[14] (d=1.24 standard deviations) in terms of impact on desire to take morphine again as rated shortly after receiving the drug. The current findings provide additional support for the validity of this clinical cutoff. These findings are likely to replicate in a new sample given their confirmation in bootstrapped analyses.

The concept of personalized pain medicine has been proposed in which information known about individual patients prior to initiating opioid therapy might be used to predict and guide therapy to optimize opioid risks versus benefits[2]. In this context, the SOAPP-R is already

used clinically for prediction of opioid risks. The current findings indicate that it may also be useful for predicting negative subjective opioid effects (e.g., feeling bad) that could serve as a barrier to successful opioid treatment, as well as enhanced analgesia. However, results of the current study also suggest the clinically challenging, yet intuitively obvious idea that chronic pain patients for whom opioid analgesics provide the greatest pain relief may also be those at greatest risk of opioid misuse. Indeed both heightened analgesia and greater risk of opioid misuse may be driven in part by common underlying differences in opioid receptors that result in different opioid response phenotypes. For example, the A118G single nucleotide polymorphism of the mu opioid receptor gene (*OPRM1*) has been shown to be associated with differences in both opioid analgesic responsiveness[41] and opioid abuse risk[28,37].

It is interesting to note that two behavioral interventions designed to improve opioid compliance and reduce opioid misuse in chronic pain patients both successfully reduced desire for opioids[20,44]. Such findings suggest that even if elevated risk for opioid misuse is linked to biologically-driven differences in opioid responses, it may be possible nonetheless to modify these responses to reduce risk. In the setting of an effective intervention to reduce opioid misuse, the heightened opioid analgesia noted in individuals at increased risk of opioid misuse in the current study (i.e., clinically elevated SOAPP-R scores) may actually prove advantageous to successful pain management (e.g., permit lower opioid doses).

Several limitations of the current study should be noted. First, factor analytic support for the rationally-derived SOAPP-R subscales used in this study would be desirable. Next, despite several significant associations identified, some subjective reinforcing effects of opioids (feeling high, feeling elated) were not linked to SOAPP-R scores as expected. For these outcomes, effects sizes were $\underline{r} = 0.02 – 0.10$, suggesting that absence of these associations was not simply a reflection of inadequate statistical power. We also note that adjustment for inflated Type I error using the highly conservative Bonferroni correction would have resulted in only 5 of the 12 significant correlations in Table 3 remaining significant. The current findings should therefore be interpreted cautiously until replicated. Another potential limitation is the possible impact of current as-needed opioid use (versus no current opioid use) on results. Re-analyses excluding the 7 subjects who reported as-needed opioid use did not appreciably alter results, suggesting that test-taking response biases related to recent opioid use were not a significant confound. A final interpretive limitation relates to the nature of the sample, which was comprised largely of relatively high functioning individuals with moderate intensity daily low back pain, and which excluded individuals using daily opioids for safety reasons (related to use of naloxone in the larger study). Given these sample characteristics, it is unknown whether the current findings would be similar in patients using opioids daily or in a sample of individuals with greater chronic pain severity and dysfunction like those more common in tertiary care pain management centers,. Future work should seek to replicate the current findings in the context of chronic opioid dosing and its analgesic effects on daily chronic pain in a more typical pain management population.

In summary, the current study found evidence suggesting that patient responses on the SOAPP-R, a clinical screening instrument for opioid risk in chronic pain patients, tap into

individual differences in subjective and analgesic responses to opioids. These opioid response differences may result in opioid use being more reinforcing for high SOAPP-R scorers, thereby contributing to the elevated risk of opioid misuse noted in these individuals. These findings and indications that the medication-specific content on the SOAPP-R may be somewhat more important for predicting opioid responses could prove useful in optimizing future opioid risk mitigation and personalized pain medicine protocols.

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PERSPECTIVE

Based on placebo-controlled morphine responses, associations were observed between higher scores on a common opioid risk screener (SOAPP-R) and greater desire to take morphine again, fewer negative subjective morphine effects, and greater analgesia. Opioids may provide the best analgesia in those patients at greatest risk of opioid misuse.

Highlights

- Elevated risk for opioid misuse as indexed by a common opioid risk screening instrument (SOAPP-R) was associated with experience of greater positive and less negative subjective effects following morphine administration and greater morphine analgesic effects on low back pain.
- SOAPP-R content assessing medication-specific attitudes and behavior was somewhat more predictive of opioid responses than negative affect-related content.
- Opioids may provide the best analgesia for chronic pain in those at greatest risk of opioid misuse, a finding with implications for personalized pain medicine.

Table 1

Mean SOAPP-R scores, pain, and subjective morphine response outcomes.

Measure	Mean ± SD
SOAPP-R Total	13.7±11.49
DELTA Drug Effect	2.9±1.00
DELTA Drug Liking	57.7±21.82
DELTA Take Again	63.1±25.02
VAS Feeling High	41.2±29.16
VAS Feeling Sedated	48.3±31.20
VAS Feeling Elated	37.1±29.09
VAS Feeling Down	9.5±20.96
VAS Feeling Anxious	10.7±18.54
VAS Feeling Good	53.7±30.43
VAS Feeling Bad	15.0±27.63
Placebo Acute Ischemic Pain –	
MPQ-Sensory	10.9±7.81
MPQ-Affective	1.8±2.63
Tolerance (sec)	294.6±172.15
Placebo Acute Thermal Pain –	
MPQ-Sensory	8.1±6.45
MPQ-Affective	1.1±2.15
Tolerance (deg C)	47.5±1.69
Morphine Effect on Acute Ischemic Pain –	
MPQ-Sensory	−1.7±5.99
MPQ-Affective	−0.7±1.99
Tolerance (sec)	38.84±126.56
Morphine Effect on Acute Thermal Pain –	
MPQ-Sensory	−1.1±5.06
MPQ-Affective	−0.2±1.83
Tolerance (deg C)	0.2±0.95
Baseline Chronic Pain Intensity –	
MPQ-Sensory	6.3±6.06
MPQ-Affective	1.0±1.85
Morphine Effect on Chronic Pain –	
MPQ-Sensory	−1.7±5.05
MPQ-Affective	−0.1±1.70

Note: DELTA and VAS values are presented for the morphine condition. For DELTA Drug Liking and Take Again, a value of 50 indicates a neutral response, with values greater than 50 indicating a positive response and values under 50 indicating a negative response. Negative values for morphine effects on acute and chronic pain ratings indicate reductions in pain with morphine relative to comparable placebo condition values. Positive values for morphine effects on acute pain tolerance indicate increased pain tolerance with morphine relative to placebo. Baseline chronic pain intensity values reflect the mean of the pre-drug values across the placebo and morphine laboratory sessions.

Table 2

Pearson correlations (r) between SOAPP-R scores and both acute and chronic pain outcomes in the absence of morphine.

	SOAPP-R Score		
Acute and Chronic Pain Intensity Outcomes	**Total Score**	**Medication-Specific**	**Negative Affect-Related**
Placebo Acute Ischemic Pain –			
MPQ-Sensory	0.41**	0.41**	0.33*
MPQ-Affective	0.17	0.20	0.13
Tolerance	−0.06	−0.11	−0.03
Placebo Acute Thermal Pain –			
MPQ-Sensory	0.44**	0.43**	0.40**
MPQ-Affective	0.29*	0.32*	0.25
Tolerance	0.07	−0.01	0.09
Baseline Chronic Pain Intensity–			
MPQ-Sensory	0.44***	0.46***	0.41**
MPQ-Affective	0.57***	0.61***	0.52***

* p<.05

** p<.01

*** p<.001

Table 3

Correlations (r) between SOAPP-R scores and morphine response outcomes.

	SOAPP-R Score		
Morphine Response Outcomes	**Total Score**	**Medication-Specific**	**Negative Affect-Related**
DELTA Drug Effect	−0.19	−0.22	−0.08
DELTA Drug Liking	0.05	0.04	0.09
DELTA Take Again	0.29*	0.24†	0.37**
VAS Feeling High	−0.02	−0.01	−0.01
VAS Feeling Sedated	0.23†	0.14	0.29*
VAS Feeling Elated	0.10	0.13	0.11
VAS Feeling Down	−0.28*	−0.41**	−0.11
VAS Feeling Anxious	−0.20	−0.30*	−0.07
VAS Feeling Good	0.19	0.26†	0.15
VAS Feeling Bad	−0.40**	−0.45***	−0.31*
Morphine Effect on Acute Ischemic Pain -			
MPQ-Sensory	0.03	0.06	−0.02
MPQ-Affective	0.04	0.09	0.02
Tolerance	0.10	0.15	0.00
Morphine Effect on Acute Thermal Pain -			
MPQ-Sensory	0.11	0.18	0.01
MPQ-Affective	0.14	0.17	0.09
Tolerance	−0.10	−0.07	−0.13
Morphine Effect on Chronic Pain -			
MPQ-Sensory	−0.40**	−0.43***	−0.34*
MPQ-Affective	−0.13	−0.09	−0.22

Note: DELTA, VAS opioid effects, and pain morphine response outcomes all reflect differences between morphine and placebo condition responses.

† p<.10

* p<.05

** p<.01

*** p<.001

Table 4

Morphine response outcomes by SOAPP-R clinical cutoff status.

	Clinical Cutoff Status	
Morphine Response Outcomes	**SOAPP-R <18 (n=41)**	**SOAPP-R ≥ 18 (n=14)**
DELTA Drug Effect	1.4±1.10	1.4±1.34
DELTA Drug Liking	3.8±23.87	19.3±20.53*
DELTA Take Again	3.4±23.88	35.9±26.79***
VAS Feeling High	34.0±32.04	40.1±34.25
VAS Feeling Sedated	22.9±32.42	45.0±29.42*
VAS Feeling Elated	14.9±31.63	27.0±33.31
VAS Feeling Down	4.8±16.90	−5.2±27.80
VAS Feeling Anxious	7.1±19.72	1.0±29.32
VAS Feeling Good	7.0±31.79	23.1±32.16
VAS Feeling Bad	8.6±27.33	−11.4±32.07*
Morphine Effect on Acute Ischemic Pain -		
MPQ-Sensory	−1.4±6.00	−2.7±6.06
MPQ-Affective	−0.6±1.84	−1.1±2.38
Tolerance	27.3±111.97	70.3±160.17
Morphine Effect on Acute Thermal Pain -		
MPQ-Sensory	−0.4±4.69	−3.1±5.71†
MPQ-Affective	0.0±1.17	−0.9±3.01
Tolerance	0.3±1.00	0.0±0.76
Morphine Effect on Chronic Pain -		
MPQ-Sensory	−0.7±3.75	−4.8±7.05**
MPQ-Affective	0.2±1.75	−0.6±1.45

Note: Clinical cutoff of 18 or higher on the SOAPP-R for identifying increased opioid risk in chronic pain patients is based on recommendations of Butler et al.[9,10]. DELTA, VAS opioid effects, and pain morphine response outcomes all reflect differences between morphine and placebo condition responses.

† p<.10

* p<.05

** p<.01

*** p<.001