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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 2 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 (.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 higher) on the SOAPP-R exhibited significantly greater morphine liking, desire to take morphine again, and feeling sedated; less 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.**

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.***

Key words: *Opioid, analgesia, chronic pain, abuse risk, misuse, screening, personalized medicine.*

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.[18,35] In an effort to mitigate risks of opioid misuse, screening questionnaires have been developed to identify, 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.[9,26,32,36] For example, baseline SOAPP-R scores

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predicted subsequent aberrant drug behaviors in a clinical trial of opioid therapy in chronic pain patients.[36]

Although 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 regard 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 data set 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 2 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 opioids[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 2 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 2 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 and 55 years; daily low back pain of 3 months or more in duration with an average severity in the past month of 3 out of 10 or more on a numeric rating scale; 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 approximately 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 (eg, 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% vs 32.7% African American), and non-Hispanic (96.3%), with a mean age of 36.4 ($\pm$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 r = .27 in magnitude (ie, 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.[9,10,26,32,36] It is often used in clinical chronic pain management settings for purposes of opioid risk mitigation. Inspection of SOAPP-R item content indicates that 2 distinct content areas comprise the majority of the items (17 of 24 items). Similar to the item content approach of Jamison et al,[24] 2 subscales were created reflecting the SOAPP-R items tapping into negative affect–related issues (items 1, 3, 4, 5, 8, 10, 14, and 20) and the items tapping into medication-specific attitudes and behavior (items 2, 6, 7, 9, 11, 12, 15, 16, and 23) to evaluate whether these 2 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