Facial Affect Processing in Patients Receiving Opioid Treatment in Palliative Care: Preferential Processing of Threat in Pain Catastrophizers

Erin M.A. Carroll, PhD, DClinPsy, Sunjeev K. Kamboj, DClinPsy, PhD, Laura Conroy, DClinPsy, Adrian Tookman, FRCP, Amanda C. de C. Williams, PhD, Louise Jones, FRCP, Celia J.A. Morgan, PhD, and H. Valerie Curran, PhD
Research Department of Clinical, Educational and Health Psychology (E.M.A.C., L.C., A.C.d.C.W.); Clinical Psychopharmacology Unit (S.K.K., C.J.A.M., H.V.C.); and Marie Curie Palliative Care Research Unit, Department of Mental Health Sciences (A.T., L.J.), University College London, London, United Kingdom

Abstract

Context. As a multidimensional phenomenon, pain is influenced by various psychological factors. One such factor is catastrophizing, which is associated with higher pain intensity and emotional distress in cancer and noncancer pain. One possibility is that catastrophizing represents a general cognitive style that preferentially supports the processing of negative affective stimuli. Such preferential processing of threat—toward negative facial expressions, for example—is seen in emotional disorders and is sensitive to pharmacological treatment. Whether pharmacological (analgesic) treatment might also influence the processing of threat in pain patients is currently unclear.

Objectives. This study investigates the effects catastrophizing on processing of facial affect in those receiving an acute opioid dose.

Methods. In a double-blind crossover design, the performance of 20 palliative care patients after their usual dose of immediate-release opioid was compared with their performance following matched-placebo administration on a facial affect recognition (i.e., speed and accuracy) and threat-pain estimation task (i.e., ratings of pain intensity). The influence of catastrophizing was examined by splitting the sample according to their score on the Pain Catastrophizing Scale (PCS).

Results. Opioid administration had no effect on facial affect processing compared with placebo. However, the main finding was that enhanced processing of fear, sadness, and disgust was found only in patients who scored highly on the PCS. There was no difference in performance between the two PCS groups on the other emotions (i.e., happiness, surprise, and anger).
Conclusion. These findings suggest that catastrophizing is associated with an affective information-processing bias in patients with severe pain conditions. J Pain Symptom Manage 2011;41:975–985. © 2011 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words
Catastrophizing, threat, emotion recognition, facial affect, opioid, pain, cancer

Introduction
The management of pain is a primary focus in palliative care settings, and opioids are widely used for this purpose. However, research into the pain experience has characterized pain as multidimensional and influenced by a number of psychological factors. Indeed, in cancer pain the cognitive and affective components of the pain experience may contribute to pain intensity ratings more strongly than sensory components1 and hence have an important bearing on adaptation.2 Given the high prevalence of psychological distress in cancer patients,3 it is important to gain further understanding of these psychological factors, and how they may interact with analgesic treatments.

Pain catastrophizing is a cognitive-affective style characterized by a preoccupation with pain, and a set of appraisals about the meaning of pain experiences.4 High levels of catastrophizing are associated with a number of adverse pain-related outcomes in noncancer pain.5,6 In cancer pain, catastrophizing is associated with higher negative affect,2,7 higher pain intensity,8,9 and increased expression of pain behaviors.10 One possible reason for this relationship is that catastrophizing may reflect primary appraisal of the level of threat when confronted with a stressor and secondary appraisal of one’s ability to manage the threat.2 Therefore, “pain catastrophizers” may appraise pain experiences as especially threatening, which in turn biases their attention toward these experiences. Negative emotions are generally considered to be generated as the result of this process.11

However, it remains possible that catastrophizing is associated with increased pain intensity and negative affect independently. For example, an aspect of catastrophizing, namely “magnification” (or “amplification”) may represent a general hypervigilance to external threat, as found in conditions such as fibromyalgia.12,13 irritable bowel syndrome,14 and functional gastrointestinal disorder.15 Hypervigilance to threat, including certain facial expressions (such as fear and disgust, which signal that an imminent “threat” has been perceived by the expresser) has been implicated in the onset and maintenance of emotional disorders.16 This “preferential processing” is expressed behaviorally as faster reaction times, greater accuracy, and enhanced memory and attention for threat-related stimuli.17–19 It is possible that such preferential processing could partly explain the association between chronic pain and psychological distress.20,21 However, there is a lack of evidence for a generalization of threat sensitivity beyond pain stimuli in life-threatening conditions such as cancer. If catastrophizing contributes to a general hypervigilance to external threat, then people with this cognitive-affective style may demonstrate preferential processing of various threat-related stimuli, including certain facial expressions (such as fear) but not others (such as expressions of happiness). Such a finding could, at least partially, explain the correlation between catastrophizing and trait anxiety,4,22 as preferential processing of threat is found in those high in trait anxiety.23

The preferential processing of threat in emotional disorders is modified by pharmacological treatments, such as antidepressants.24,25 However, the possibility that affective information processing might be modified pharmacologically in pain patients, particularly following opioid analgesia, has yet to be investigated. More generally, it is a striking fact that psychopharmacological studies of opioids have not tended to describe their behavioral effects on emotional processes in humans. This is despite the role of the opioid system in various emotional behaviors (especially affiliative- and reward-related behaviors) and its widespread neuromodulatory influence.26 Although acute
or “acute-on-chronic” opioid administration produces specific cognitive impairments in palliative care patients\textsuperscript{27} and healthy volunteers,\textsuperscript{28} no study has yet directly investigated the effects of opioids on emotional processing. Indirect evidence of opioid modulation of emotional information processing comes from studies of chronic methadone users, which suggest an effect on accuracy and reaction times in facial affect recognition tasks.\textsuperscript{29,30} Furthermore, drawing a parallel with the studies on depressed patients, whose performance on such tasks is modified by acute antidepressant treatment,\textsuperscript{25} pain patients with high levels of catastrophizing may be more susceptible to the effects of opioids in emotional processing tasks. Here, using a within-participant design to enhance power, we investigate affective information processing in patients receiving palliative care who score high and low on a measure of catastrophizing, focusing on the influence of commonly used acute-on-chronic opioid administration (i.e., the use of an acute opioid dose to manage breakthrough pain in the context of background long-acting opioid treatment). The design imitates a realistic clinical situation as closely as ethically possible, and, therefore, allows the interaction of multiple factors to be observed without the possible confound of individual differences in current pain levels.

**Methods**

**Design**

A placebo-controlled, double-blind, within-participants (crossover) design was used to compare the effects of a placebo to a single dose of immediate-release (IR) oral opioid. Patients were randomly allocated to receive either opioid or placebo on the first test day, and received the alternative substance no less than 48 hours later. Opioid/placebo administration was balanced, with half of the patients receiving an opioid dose on the first testing day. The IR opioid used here was individually tailored to each patient: It was the usual IR opioid used by the patient to control episodes of breakthrough pain (oral morphine or oxycodone in liquid form). The dose of liquid IR opioid used was identical to each patient’s usual IR dose for breakthrough pain. The placebo was the equivalent amount of inert liquid. Both placebo and opioid liquids were flavored with peppermint and prepared individually by the formulating pharmacist and the identity of the compound (placebo or opioid) was concealed from the experimenters (E. M. A. C. and L. C.) and the patient. Versions of tests were counterbalanced across participants and design.

**Participants**

This study was approved by the UCLH Ethics Committee and all participants provided informed written consent. The study was carried out in October 2008 to April 2009. The setting was a specialist palliative care unit in a major teaching hospital. To be included, patients were required to be clinically stable (no change in clinical condition in the two weeks preceding assessment as assessed by attending medical staff); be on a stable sustained-release (SR) dose of opioid; be receiving the same IR opioid doses for at least 48 hours prior to the study; have good spoken English and basic literacy; and have good vision. All participants had received daily opioid medication for more than three months. Participants were excluded if they required more than two IR opioid doses per day in addition to their SR opioid; had taken an IR dose of opioid in the eight hours preceding the assessment session; showed signs of dementia or gross cognitive impairment; had a known history of psychosis, substance misuse/alcoholism, or head injury; or had a moderate or higher clinical level of depression or anxiety as measured on the Hospital Anxiety and Depression Scale (HADS)\textsuperscript{31} (as this may affect facial affect processing independently). All assessments for suitability were determined from the clinical notes and consultation with medical staff. There was no further formal assessment of severity of illness.

Considering statistical power, our previous study on cognitive functioning following acute-on-chronic opioid administration\textsuperscript{27} showed that a sample size of 14 is sufficient to detect medium effects. Within the unit, 45 outpatients and 12 inpatients were screened for inclusion. Of these, 20 (9 male; mean age 58 years [standard deviation (SD) = 10]) were deemed suitable and consented and these patients constituted the sample described below. The SR opioid medications used by patients were
fentanyl patch (n = 2), controlled-release oxycodone (n = 9), oral morphine (n = 6), morphine via a syringe driver (n = 1), tramadol (n = 1), and codeine phosphate (n = 1). The mean equianalgesic IR morphine dose across both IR drug groups was 31.25 mg (range 5–200 mg, SD = 46.69), which typically represented one-sixth of the daily SR dose of opioid. Eighteen patients in the sample had a diagnosis of cancer and two had neuropathic pain linked to multiple physical conditions. At the time of the study, five participants were prescribed psychotropic medications (two each prescribed diazepam and citalopram, and one, venlafaxine). Three inpatients (admitted for respite or symptom management) and 17 outpatients participated.

Tasks

Self-Report Measures. The Pain Catastrophizing Scale (PCS) is a 13-item questionnaire (maximum score 52) that samples rumination, magnification, and helplessness in relation to pain. It was administered at the first testing session only. To determine stability of mood across testing occasions, the HADS was used to assess state anxiety and depression of the participants prior to opioid/placebo administration on each occasion. Each scale has seven items with several response options (maximum scores of 21 are possible for anxiety and depression each). Pain was assessed using numerical rating scales (NRSs) from 0 to 10 for pain intensity (“no pain” to “extreme pain”), distress (“not at all distressing” to “extremely distressing”), and interference (“does not interfere” to “interferes completely”) before and after placebo administration. Pain relief following opioid/placebo administration also was rated (0%–100%). Three NRSs (0–10) also assessed aspects of mood (calm-anxious; sad-happy; sleepy-alert) before and after opioid/placebo administration.

Facial Affect Recognition. This affective processing task has been used in several previous drug studies. The stimuli consist of gray-scale images formed using a computer program that morphs pairs of prototype expressions of each of the six basic emotions (anger, fear, disgust, surprise, happiness, and sadness, using the stimulus face JJ from the standard Ekman and Friesen series). The two emotions that were morphed were the ones most likely to be confused with one another (e.g., happiness and surprise) and the degree of morphing was systematically varied (e.g., 90% happiness to 10% surprise, 70% happiness to 30% surprise, 50% of each, etc.). The strategy of morphing easily-confused emotions was required to increase task difficulty, and hence reduce the risk of ceiling effects. However, only the responses to faces at 70% and 90% blend—the two highest intensities of a particular emotion—were recorded as “correct” (see Calder et al. for a full rationale for this method). There were six blocks, each formed by 30 images (a total of 180 images).

One image was displayed on each trial. Participants were required to decide which of the six emotional expression labels matched the image. They responded by clicking on a specially designed response hexagon displayed alongside each face, where all six emotion labels are equidistant from a central cursor “home” position. The task was completed on both testing occasions. The position of the emotion names on the response hexagon differed on each occasion. Each image was displayed for 2000 ms followed by a 1000 ms delay before the next stimulus. Accuracy and reaction times were recorded.

Threat Estimation. We piloted a task that involved estimating pain intensity in nonpain facial expressions, which used similar threat expressions to those used in the facial affect recognition task. Four actors displaying eight expressions (anger, fear, disgust, and neutral expression, with mouth open and closed for each; 32 picture stimuli in total) were used as stimuli on each occasion. The stimuli came from a published set of color photographs. To assess overestimation-interpretive bias (the tendency to attribute more severe pain ratings to nonpain threat expressions), participants were asked to rate the degree to which each expression displayed expressed pain on a numerical rating 1–10 (“no pain” to “extreme pain”). The decision to use nonpain stimuli was informed by the finding that facial actions involved in facial threat expressions and expressions of pain overlap to some extent. Different versions of the task were used for each testing occasion and were counterbalanced across occasion.
Procedure

Patients were tested on two separate occasions. They completed the PCS, HADS, and pain and mood NRSs immediately before a single oral IR dose of opioid or placebo. One hour following opioid/placebo administration, participants completed the experimental tasks. After opioid/placebo administration, testing took less than 45 minutes to avoid undue stress or discomfort. At the end of each test session, to assess the degree to which blinding was effective, participants were asked to guess whether they had received opioid or placebo. A concurrent replication study of previously found memory effects of opioid administration was simultaneously conducted with these patients. This served as a “positive control” for opioid effects as significant memory effects were found, suggesting an acute effect of opioids on at least one cognitive domain in the present study (unpublished data). Memory tasks were administered before and after the facial affect and threat estimation tasks.

Statistical Analysis

All data were analyzed using SPSS Version 14.0 for Windows (SPSS Inc., Chicago, IL). Repeated-measure ANOVAs were used for the main analyses of facial affect recognition and threat-pain estimation tasks, with “opioid/placebo administration” and “emotional expression” as within-subject factors and “PCS group” (high vs. low) as a between-subjects factor. Post hoc tests included Bonferroni correction. Nonparametric correlations (Spearman’s ρ) were calculated for HADS data, as they were not normally distributed.

Results

Self-Report Measures

Pain Catastrophizing. The mean PCS score for the sample was 19.80 (SD = 13.27; range 0–44). To further examine the relationship between catastrophizing and other measures and tasks, two groups were created based on PCS scores (median split): “high PCS scorers” (PCS scores ≥ 20; mean PCS score = 30.7 ± 7.32; n = 10) and “low PCS scorers” (PCS scores < 20; mean PCS score = 8.90 ± 7.36; n = 10). (Originally, a categorical distinction between high [≥22] and low [≥15] catastrophizers was made following Sullivan et al. but this excluded two cases. Furthermore, a median split method was used in Asmundson et al. when investigating the highly related construct of fear of pain.)

HADS Scores. Scores on the HADS did not change significantly from one testing occasion to the other [F(1, 17) = 2.93, P > 0.05]. (HADS data for two participants on Day 1 were incomplete so excluded.) Mean HADS anxiety scores were 7.30 (SD = 3.92) on the placebo occasion and 8.76 (SD = 4.6) on the opioid testing occasion, the former being in the nonclinical and the latter just within the mild clinical range (i.e., ≥8). Depression subscale scores were 6.55 (SD = 4.16; placebo occasion) and 6.83 (SD = 4.34; opioid occasion); both mean scores are below the clinical cut-off for mild symptoms (≥8). There was no significant interaction between HADS scores and opioid/placebo administration [F(1, 17) = 3.20, P > 0.05], suggesting a valid comparison between the conditions, unaffected by changes in mood over time. Importantly, the HADS depression scores for low PCS scorers (6.40 ± 4.12) and high PCS scorers were similar (6.70 ± 4.42; t(18) = 0.157; P > 0.05). Furthermore, although there was a small difference between the two catastrophizing groups in HADS anxiety scores, the differences were not statistically significant: low PCS scorers (5.80 ± 3.19); high PCS scorers (8.80 ± 4.16; t(18) = 1.81; P > 0.05).

Mood NRSs. Table 1 shows subjective effects of time (pre- vs. postadministration) and opioid/placebo administration. As can be seen, there were no significant interactions (all Ps > 0.1). There were no main effects (all Ps > 0.1). There was no significant difference between high and low PCS scorers on any of the mood NRS scales (all Ps > 0.1).

Pain Experience. In addition to an absence of opioid/placebo x time (pre- vs. postadministration) interactions for the three pain dimensions, there were no main effects of opioid/placebo on pain experience ratings (all Ps > 0.1). However, as shown in Table 1, all dimensions decreased with time [Intensity: F(1, 19) = 13.14, P = 0.01; Distress: F(1, 19) =
There was no significant difference between high and low PCS scorers on any of the pain NRS scales (all $P > 0.1$). As we were specifically examining the effects of catastrophizing and opioid modulation of affect recognition, it is important to note that patients were not experiencing breakthrough pain at the time of opioid administration, and did not experience pain relief following opioid/placebo administration (see Discussion).

### Facial Affect Recognition

#### Accuracy
Table 2 shows accuracy and reaction time for correct responses to facial expressions of happiness, surprise, fear, sadness, disgust, and anger. Opioid/placebo administration did not affect the number of correct responses overall [$F(1, 18) = 0.073, P > 0.05$], or any expression type [$F(5, 90) = 0.592, P > 0.05$].

Although there was neither an overall effect of catastrophizing level on accuracy [$F(1, 18) = 2.08, P > 0.1$] nor a catastrophizing $\times$ opioid/placebo interaction [$F(1, 18) = 0.001, P > 0.1$], there was a significant interaction between catastrophizing and emotional expression type [$F(5, 90) = 2.98, P = 0.02$] (Fig. 1). Post hoc comparisons revealed that when compared with low PCS scorers, high PCS scorers were significantly more accurate at recognizing fear ($P = 0.04$), but better recognition of sadness ($P = 0.07$) did not reach statistical significance. No three-way interaction emerged between opioid/placebo, expression, and catastrophizing [$F(5, 90) = 0.299, P > 0.1$].

### Reaction Times

Similar to accuracy, opioid/placebo administration did not affect reaction times across expression [$F(1, 18) = 0.447, P > 0.1$], and there was no interaction between opioid/placebo administration and expression [$F(5, 90) = 0.12, P > 0.1$]. However, as can be seen from Fig. 2, catastrophizing level had an effect on reaction times to correctly identifying emotion expression [$F(1, 18) = 4.907, P = 0.04$]. There was also an interaction between catastrophizing and expression [$F(5, 90) = 4.585, P = 0.01$]. Post hoc comparisons revealed that high PCS scorers were significantly faster at recognizing fear ($P = 0.04$), sadness ($P = 0.01$), and disgust ($P = 0.04$). Again, there was no three-way (opioid/placebo, emotion expression, catastrophizing group) interaction [$F(5, 90) = 0.281, P > 0.1$]. Given the faster reaction times for fear expressions in high PCS scorers,

### Table 1

Mean Mood and Pain Ratings Before and After Opioid/Placebo Administration

<table>
<thead>
<tr>
<th>Mood and Pain Subjective Ratings</th>
<th>Placebo Mean Score (SD)</th>
<th>Opioid Mean Score (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calm-anxious</td>
<td>2.78 (2.76)</td>
<td>2.58 (2.39)</td>
</tr>
<tr>
<td>Sad-happy</td>
<td>6.20 (1.85)</td>
<td>6.20 (2.28)</td>
</tr>
<tr>
<td>Alert-sleepy</td>
<td>4.98 (2.47)</td>
<td>5.33 (1.89)</td>
</tr>
<tr>
<td>Pain intensity</td>
<td>3.15 (2.62)</td>
<td>2.23 (2.44)</td>
</tr>
<tr>
<td>Pain distress</td>
<td>2.95 (2.74)</td>
<td>2.23 (2.47)</td>
</tr>
<tr>
<td>Pain interference</td>
<td>4.78 (3.10)</td>
<td>3.50 (2.88)</td>
</tr>
<tr>
<td>Pain relief</td>
<td>—</td>
<td>60 (35.36)</td>
</tr>
</tbody>
</table>

### Table 2

Mean Correct Responses and Reaction Time (msec) to Each Expression on the Facial Affect Recognition Task Following Opioid/Placebo Administration

<table>
<thead>
<tr>
<th>Expression</th>
<th>Placebo Mean Correct Responses (SD)</th>
<th>Opioid Mean Correct Responses (SD)</th>
<th>Placebo Mean RT (SD)</th>
<th>Opioid Mean RT (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Happy</td>
<td>21.30 (3.28)</td>
<td>20.80 (3.02)</td>
<td>2444.65 (803.89)</td>
<td>2372.67 (864.77)</td>
</tr>
<tr>
<td>Surprise</td>
<td>19.50 (3.38)</td>
<td>20.50 (3.25)</td>
<td>3147.52 (1048.47)</td>
<td>3047.71 (1011.88)</td>
</tr>
<tr>
<td>Fear</td>
<td>16.90 (4.13)</td>
<td>16.70 (5.08)</td>
<td>3091.48 (1184.21)</td>
<td>3015.07 (859.58)</td>
</tr>
<tr>
<td>Sad</td>
<td>18.70 (4)</td>
<td>17.85 (4.91)</td>
<td>3535.79 (1880.29)</td>
<td>3425.83 (1526.99)</td>
</tr>
<tr>
<td>Disgust</td>
<td>22.05 (2.11)</td>
<td>22.75 (1.80)</td>
<td>2886.19 (805.53)</td>
<td>2761.01 (712.48)</td>
</tr>
<tr>
<td>Anger</td>
<td>17.55 (5.31)</td>
<td>17.95 (4.32)</td>
<td>2819.71 (805.35)</td>
<td>2767.73 (767.86)</td>
</tr>
</tbody>
</table>
Threat-Pain Estimation

This experiment was piloted to examine the possible misattribution/overestimation of pain in affective, although nonpain stimuli. We found difference across expressions \(F(3, 54) = 144.21, P = 0.01\), with all threat expressions (anger, disgust, and fear) rated as displaying more pain than neutral expressions \((P = 0.01)\). Anger and disgust also were rated as displaying more pain than fear expressions \((P = 0.01)\). Table 3 shows that there was no difference in threat-pain face ratings between opioid/placebo administration conditions \([F(1, 18) = 0.33, P > 0.1]\). Pain ratings across emotion expressions varied according to catastrophizing level \([F(1, 18) = 5.361, P = 0.03]\); there also was a significant interaction between catastrophizing and emotion expression \([F(3, 54) = 3.924, P = 0.01]\). Post hoc comparisons revealed that high PCS scorers rated fear \((P = 0.03)\) and disgust \((P = 0.02)\) faces as expressing more pain than did low PCS scorers, suggesting overestimation/interpretative bias in the high PCS scorers group.

Correlations

Correlations revealed no relationship between HADS depression or anxiety scores and the affect processing tasks. The absence of correlations for these mood variables is significant as it suggests the association between catastrophizing and affect processing described above cannot more parsimoniously be explained by mood variables and also precludes covarying HADS scores in the main analyses.

Blinding

Twelve of the participants guessed opioid/placebo administration condition incorrectly on both occasions and eight correctly on both occasions. Taking into account chance-level guessing, treatment blindness appeared to be maintained \((\chi^2(1) = 1.98, P = 0.35)\). There was no difference in the performance of those who guessed correctly compared with those who did not on either of the experimental tasks (all \(P_s > 0.1\)) or post-treatment self-report mood or pain NRS (all \(P_s > 0.1\)).

Discussion

This is the first study that we are aware of that directly investigates the effects of pain catastrophizing and opioid administration on threat recognition. “Pain catastrophizers” showed preferential processing of threat: They were faster and more accurate in correctly identifying negative facial expressions, and they showed greater threat-pain overestimation. The present study did not support any relation between pain (intensity, distress, interference) and catastrophizing level. There was no effect of opioid administration compared with placebo on the tasks.
Our interest in determining whether pain catastrophizers showed greater preference for processing negative affective information, and the possibility that such a preference would be modulated by analgesic administration, originated from similar studies in mood disorders.24,25 Clearly, one possibility for a lack of modulation by opioid administration is that neuropsychopharmacological modulation of affective information processing in affective disorders and severe pain states is quite different. Other possible explanations for this null finding are discussed further below.

The finding that only high pain catastrophizers showed preferential processing of threat is novel; we are aware of no other study that shows this kind of generalization of threat sensitivity in pain catastrophizers. The finding is consistent with other research showing that preferential processing of somatic stimuli may be moderated by catastrophizing,41 but implies that, in addition, pain catastrophizers may display processing anomalies to "external" threat. The findings suggest that catastrophizing may contribute to increased emotional distress often found in those with cancer pain2,7 through heightened processing of negative affect. Our observation that preferential processing of affective information was restricted to pain catastrophizers has direct parallels with the established findings on cognitive biases in anxiety and depression,16,19 and perhaps of more direct relevance (given the low level of psychological disorder-related symptomatology in the sample as measured by the HADS), in trait anxiety.23 Indeed, the overlap between the current findings and those in psychological disorders is all the more striking, given the stimuli used here consisted of those associated with threat in facial expressions (i.e., the kinds of stimuli used in studies of psychological disorders) rather than illness or pain. The greater accuracy in processing fear in high catastrophizers compared with all other emotional expressions may highlight the relationship between catastrophizing and anxiety. Previous studies have demonstrated preferential processing of fear in both clinical and trait anxiety.16,23 It is important to note that there was a lack of correlation between processing of facial affect and HADS measures. Furthermore, pain catastrophizers and pain noncatastrophizers had similar total HADS scores, suggesting that the two groups did not differ substantially in neurotic symptoms or psychopathology. However, the specific strategy of emotional regulation used by an individual following "catastrophic" primary appraisal may determine whether such appraisals lead to higher emotional distress.42

Turning back to the lack of effect of opioid administration, we found that, despite an adequately powered within-participant design, we failed to observe an effect of acute opioid administration on the processing of facial affect. In previous studies, we and others have found acute drug effects on the facial affect processing tasks used here.34,35,43 Given that previous (albeit indirect) evidence suggests opioid modulation of facial affect processing29,30 and the neuromodulatory influence of the central endogenous opioid system in key "affective brain areas,"26 the absence of an effect of opioid administration may be because of experimental limitations. This absence is unlikely, however, to be explained by an insufficient dose of opioid (the dose used was individualized for each patient’s breakthrough pain), or by subpeak
concentrations of opioid (the tasks were conducted within the window of peak plasma opioid levels). Using an identical procedure, we previously have found moderate effects of acute-on-chronic opioids on memory. More importantly, simultaneous effects on memory were found in experiments run in parallel to those described here. In addition, it is possible that, unlike for memory tasks, acute effects of opioids on emotional processing may be susceptible to tolerance/habituation, and may not be detectable in the presence of long-acting background opioids. Furthermore, effects of opioids on affective processing may only be evident following remediation of pain states (the patients in the present study were not experiencing breakthrough pain at the time of treatment; see below).

**Limitations**

There are several limitations to our findings that may affect their interpretation. Although our study seems to imply a generalization of biased processing to a broader set of threat-related stimuli (beyond pain/illness stimuli) in pain catastrophizers, it is also possible that our findings with facial threat stimuli arise because of their resemblance to pain expressions. In other words, the generalization described actually arises because of a tendency to attribute pain meanings to threatening facial expressions. Indeed, this formed the basis of our piloting of a novel threat-pain estimation task. However, the task had a number of limitations that restrict the conclusions that can be drawn on this point. The overestimation of pain in pain catastrophizers may be largely attributable to the task demands, which require a judgment about the amount of pain perceived in nonpain (but threatening) faces. Therefore, the task instructions or type of stimuli used would need to be refined to provide more conclusive data in this respect.

Although the present study was specifically concerned with possible generalization of threat sensitivity in catastrophizing pain patients (reflected in our use of threat faces), it would be of interest to repeat such a study using pain faces as stimuli, particularly in relation to the effects of opioids. Furthermore, such effects may be more likely to be detected in opioid naïve subjects, as this would overcome any difficulty associated with tolerance. Furthermore, alternative experimental approaches might be used to examine preferential processing of threat. For example, attentional bias paradigms (e.g., dot probe or pain Stroop tasks) using pain/illness words previously have been used to examine cognitive biases among pain patients. Use of such stimuli also would help to disambiguate the contribution of general threat sensitivity, as word stimuli could be selected with limited semantic relatedness to pain (in contrast to the facial expression stimuli used in the present study).

It is important to note that the patients in the present study were not experiencing an acute exacerbation of pain at the time of opioid/placebo administration. To examine affective processing following breakthrough pain and subsequent administration of opioid or placebo in a randomized controlled design such as ours would be unethical (because of the 50% possibility of receiving placebo during a period of acute pain). In any case, the use of additional acute opioid in the absence of breakthrough pain may compromise the validity of the findings, at least in relation to how current pain experiences (breakthrough pain) might influence appraisal of threat and the modulation of this by catastrophizing and analgesia treatment. Finally, our participants were receiving specialist palliative care, which necessarily entails the issue of generalizability of our findings.

**Summary**

Results from this study indicate that pain catastrophizing is associated with preferential processing of negative facial affect in palliative care patients. Surprisingly, acute-on-chronic opioids did not influence this affective processing. It may be of further interest to determine whether this association is evident in noncancer chronic pain conditions, particularly in relation to fear and avoidance of activity. A rigorous and ethically sound methodology is a key strength of the present study, especially given that such data are sparse in palliative care settings.

**Disclosures and Acknowledgments**

Financial support for this project was provided by the Research Department of Clinical, Educational, and Health Psychology, University
College London Graduate School. The authors have no conflicts of interest to declare.

The authors thank the patients who participated in the study. The contributions of medical, nursing, and volunteer staff at the Palliative Center is also gratefully acknowledged. Paul Barry provided invaluable pharmacy support for the study. Professor Chris Brewin and Rachel Massey-Chase provided very valuable comments on the article.

References


