Pressure sensitivity and phenotypic changes in patients with suspected opioid-induced hyperalgesia being withdrawn from full mu agonists

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Objectives: To assess changes in phenotype and pressure sensitivity in patients with suspected opioid-induced-hyperalgesia (OIH) after transitioning to buprenorphine.

Methods: Twenty patients with suspected OIH were enrolled to transition to buprenorphine therapy. Patients completed validated self-report measures at baseline and at 1, 4, 8 weeks, and 6 months after initiation of buprenorphine along with quantitative sensory testing including measures of pressure pain threshold, pain tolerance and Pain 50 (a pain intensity rating).

Results: 20 patients were enrolled, 17 were treated with buprenorphine and 11 completed all assessment points. We found that after transitioning to buprenorphine, patients on higher opioid doses (>100mg oral morphine equivalents) had significant improvements for some measures including decreased pain severity and fibromyalgia survey scores, fewer neuropathic pain features, less catastrophizing, fewer depressive symptoms, and improved functioning 1-week after transitioning to buprenorphine with an eventual return back to baseline. Although not statistically significant, patients on high dose opioids (>100mg OME) also showed a trend of decreased pressure sensitivity 1-week after transitioning to buprenorphine with a gradual return back to baseline.

Conclusions: Our study is the first to look at pressure pain sensitivity in patients who were taking opioids and transitioned to buprenorphine. These results suggest that the patients most likely to benefit from buprenorphine therapy are those on higher doses. In addition, the eventual return back to baseline on measures of pain phenotype and pressure sensitivity suggests that buprenorphine may over time result in a return of the hyperalgesic effects of a full mu agonist.

INTRODUCTION

As many as 90% of the patients who present to pain centers for treatment are already taking opioids (1), yet few studies support a favorable risk: benefit ratio for their long-term use in patients with chronic nonmalignant pain (2–4). Our group previously demonstrated that patients on opioids with persistently high pain scores reported a phenotype consistent with having a more centralized pain state (fibromyalgia-like presentation), which suggests the potential presence of opioid-induced hyperalgesia (OIH) (5). OIH is defined in animal studies as a decrease in pain threshold from baseline after single or repeated administration of opioids (6, 7). Clinically, OIH is characterized by: (i) an increase in pain intensity over time, (ii) the spreading of pain to other locations beyond the initial painful site, and (iii) an increase in pain sensation to external stimuli (8).
Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria

- Between ages of 18-65
- Speak English
- Willing to cooperate with all study procedures

Exclusion Criteria

- BMI > 40
- Medical conditions capable of causing patient’s symptoms and/or make it unsafe for them to participate
- Untreated active addiction to illicit substance
- History of consistent alcohol consumption:
  - exceeding 7 drinks/week for females
  - exceeding 14 drinks/week for males
- Severe psychiatric illness
- Prior history of allergies or intolerance to buprenorphine

Pain Phenotyping

Demographics and current medications were recorded. The average daily dose of opioids was obtained and converted to oral morphine equivalents (OME) (15-17). Patients were phenotyped using validated self-report measures, including pain severity and interference (Brief Pain Inventory [BPI]) (18), neuropathic pain descriptors (PainDETECT [PDQ]) (19), depressive and anxiety symptoms (Hospital Anxiety and Depression Scale [HADS]) (20), pain catastrophizing (Catastrophizing subscale of the Coping Strategies Questionnaire) (21), sleep disturbance (PROMIS Sleep Disturbance ) (22, 23), fatigue (PROMIS Fatigue ) (22, 23), physical function (PROMIS Physical Function) (22, 23), 2011 Fibromyalgia Survey Criteria(24). As outlined in our prior studies (25, 26), our group proposes higher fibromyalgia survey scores represent pain that is more “centralized” in nature (e.g. altered central nervous system pain processing).

Quantitative Sensory Testing (QST)

The Multi-modal Automated Sensory Testing (MAST) System was used to assess pressure pain sensitivity. The MAST is a small, portable device designed for research and potential point-of-care applications (27-29). It applies pressure stimuli to the thumbnail bed. The use of this device has been described extensively elsewhere (15). The measures obtained were pain threshold, pain tolerance and Pain50 (pain intensity rating halfway between pain threshold and tolerance).

Follow-Up Assessment

At 1, 4, 8 weeks, and 6 months after the initiation of buprenorphine, participants returned for a medical evaluation and to complete the same questionnaires and experimental pressure pain testing protocol used at baseline.

Statistical Analysis

To examine the longitudinal trajectories of each phenotypic variable from baseline to 6 months, mean scores were plotted for the overall sample and for those with a baseline OME of less than 100mg or OME ≥100mg. Differences between baseline and 1 week scores were compared using within-samples t-tests for those with OME < 100mg or OME ≥100mg. All available data were included in the analyses.

RESULTS

See Figure 1 for recruitment. For 20 patients, baseline demographic and OME data are presented in Table 2. Although the doses of buprenorphine for each visit were not recorded for all patients the most common range clinically used was from 2-16mg/day. Follow up and attrition are outlined in Figure 2.

Table 2. Baseline Demographic and Oral Morphine Equivalent (OME)

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>44.5 (9.15)</td>
</tr>
<tr>
<td>Female</td>
<td>13 (65%)a</td>
</tr>
<tr>
<td>Caucasian</td>
<td>18 (90%)</td>
</tr>
<tr>
<td>Married</td>
<td>14 (70%)</td>
</tr>
<tr>
<td>College graduate</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>OME</td>
<td>77.5 [67]b</td>
</tr>
<tr>
<td>OME &lt; 100</td>
<td>13 (65%)</td>
</tr>
</tbody>
</table>

a. Count and percentage are presented for dichotomous data.
b. Median and interquartile range [IQR]

Pain and Affective Phenotype Trajectory

Means across every time point for each phenotypic scale are presented in Figures 3 and 4. When examining patients with baseline OME < 100mg (n = 13) and those with OME ≥100mg (n = 7) separately, those with OME of ≥100mg experience a greater change from baseline to 1 week than those with OME < 100mg. Within-subjects t-tests confirmed that those with OME of ≥100mg had statistically significant improvements from baseline to 1 week for FM survey score (p = 0.020), BPI pain severity (p = 0.012), Pain DETECT (p = 0.032), Catastrophizing (p = 0.007), HADS depression (p = 0.021), and PROMIS Fatigue (p = 0.003). There were no statistically significant differences from baseline to 1 week for those with baseline OME < 100mg. Those with OME < 100mg had significant negative linear trends for BPI pain severity (p = 0.004), BPI pain interference (p = 0.044), Pain Detect (p = 0.002), FM score (p = 0.019), HADS anxiety (p = 0.003), Catastrophizing (p < 0.001) and PROMIS Sleep (p = 0.021). Those with an OME of ≥100 mg did not have any significant linear trends in any variable.
Figure 1. Patient flow chart to display patients screened, eligible, consented and completed for study.
Figure 2. Of the 20 patients consented, 11 patients completed the 6 month follow up.

Figure 3. Line graphs show average values for 4 of the 10 outcome variables from baseline to 6 month follow-up for the whole group, and for those on OME < 100 mg or OME ≥ 100 mg. Stars (*) denote statistical significance of at least $p < 0.05$ for change in outcome from baseline to 1 week follow-up. For patients taking 100mg or more OME, there were statistically significant decreases in FM survey score, catastrophizing, pain severity and depression (all $ps < 0.05$ or less) from baseline to 1 week follow-up.
Figure 4. Line graphs show average values for 6 of the 10 outcome variables from baseline to 6 month follow-up for the whole group, and for those on OME < 100 mg or OME ≥ 100 mg. Stars (*) denote statistical significance of at least p < 0.05 for change in outcome from baseline to 1 week follow-up. For patients taking 100mg or more OME, there were statistically significant decreases in pain interference, neuropathic pain, and fatigue (all ps < 0.05 or less) from baseline to 1 week follow-up.

Quantitative Sensory Testing (QST) Trajectory
Plots of means across each time point for QST measures tolerance, threshold, and P50 are presented in Figure 5. Those with baseline OME < 100mg have initial decreases in tolerance, threshold, and P50. Those with baseline OME of ≥100mg have initial increases in tolerance, threshold, and P50. However, none of the baseline to 1-week differences for either group were statistically significant. There were no significant linear trends for any QST variable for those with OME < 100mg or those with OME ≥100mg.

DISCUSSION
We observed that patients on higher doses of opioids (≥100mg OME) had significant improvements for various measures of pain phenotyping associated with centralized pain after transitioning to buprenorphine. Our study is the first to look at pressure pain sensitivity in patients suspected of OIH being transitioned to buprenorphine. Although we were unable to detect a significant difference in pressure pain sensitivity, we did find a trend showing that patients on higher doses of opioids had improved pressure pain sensitivity at week 1. These results suggest that the patients with suspected OIH who are most likely to benefit from buprenorphine therapy are those on higher OME doses. Further, the eventual return back to baseline for measures of pain, mood, and function, as well as pressure pain sensitivity suggests that buprenorphine may over time result in a return to the hyperalgesic effects of a full mu agonist.

Buprenorphine has been used as an effective agent for detoxification of patients on high dose opioids (17). However, what is not known is that once patients have been detoxified...
from the high dose opioids whether there is a role for continuation of buprenorphine long term. Based on our results it seems that long-term use of buprenorphine results in a gradual return to baseline hyperalgesia. It has been shown in animals that buprenorphine can induce hyperalgesia, which helps account for our findings (30).

LIMITATIONS

There are a number of limitations to our study. First, our sample size was small with only 20 participants and there was significant attrition; this is a challenging patient population not only to recruit but also to retain for a study. Also, the lack of a gold standard for clinical OIH diagnosis limits interpretation of these findings. Further, we used self-report questionnaires; however, all were well-validated measures. Finally, we did not control for buprenorphine dose and lower doses could influence return to baseline hyperalgesia. Nonetheless, these preliminary results suggest that it may be best to wean patients off of opioids altogether rather than to continue them on buprenorphine long term. This study excluded patients with a history of addiction, which may benefit from continued buprenorphine therapy regardless of the pain effects. Further, studies using larger cohorts are still needed to replicate our findings.

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DISCLOSURES

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