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Changes in Pain During Buprenorphine Maintenance Treatment among Patients with Opioid Use Disorder and Chronic Pain

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Abstract

Objective: Opioid use disorder (OUD) and chronic pain frequently co-occur. Little is known about changes in pain during buprenorphine/naloxone (BUP/NX) maintenance and whether outcomes vary by pain levels. The current study examined changes in pain intensity and pain interference over 12 weeks of BUP/NX maintenance among participants with OUD and chronic pain (N=194). Differences in outcomes were assessed during BUP/NX maintenance (week 12) and two months following a BUP/NX taper (week 24). *Method*: Data from Phase 2 of the Prescription Opioid Addiction Treatment Study were used. Two latent transition models were conducted to characterize profiles and transitions between profiles of pain intensity or pain interference (estimated separately). *Results*: Each model identified a high and low profile. In the pain interference model, the majority were classified in the low profile at baseline. In the pain intensity model, the majority were classified in the high profile at baseline. In both models, patients were more likely to remain in or transition to the low profiles by week 12. Worse depression was associated with membership in the high profiles and transition to the high pain intensity profile. Those in the high pain intensity and high pain interference profile at week 12 reported worse mental health quality of life (MH-QOL) and depression at week 12. Those in the high pain intensity profile reported worse MH-QOL at week 24. *Conclusions*: For a subgroup of

patients, high pain intensity and high pain interference remains unchanged during BUP/NX maintenance treatment. Depression is related to changes in pain intensity.

Keywords: Chronic pain, opioid use disorder, buprenorphine, latent transition modeling.

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Introduction

Approximately 4.4% of the United States population uses opioids not as prescribed (i.e. misuse) and about 1% meet criteria for opioid use disorder (OUD; Centers for Disease Control and Prevention, 2018). Rates of opioid misuse and OUD among those with chronic pain are significantly higher: approximately 21-29% of patients and 8-12%, respectively (Vowles et al., 2015). Additionally, chronic pain is among the most frequently co-occurring diagnoses among those with OUD, ranging from 49 to 64% (Hser et al., 2017; Wollschlaeger et al., 2017). The current gold standard treatment is medication treatment for OUD (MOUD), of which the most frequently prescribed are methadone and buprenorphine (Volkow et al., 2018).

While previous work has suggested that MOUD alone may be effective for the treatment of chronic pain in people with OUD (Daitch et al., 2014), patients taking MOUD with chronic pain consistently exhibit worse health-related quality of life and distress, more disruptions in social and physical functioning, and poorer sleep quality in comparison to those without chronic pain (Dunn et al., 2015; Griffin et al., 2016; Mark A. Ilgen et al., 2006; Jamison et al., 2000). Those with chronic pain also benefit less from MOUD in comparison to those without chronic pain, suggesting there may be additional treatment needs (Ilgen et al., 2006). Finally, MOUD appears to have limited analgesic effects in those with OUD and chronic pain (Lazaridou et al., 2020). Therefore, MOUD alone may be insufficient for the management of co-occurring OUD and chronic pain.

Prior work has examined whether the presence of chronic pain at the time of MOUD induction predicts opioid relapse. While a meta-analysis found no evidence that chronic pain predicts illicit opioid use (Dennis et al., 2015), differences in relapse have emerged when proximal measurements of pain were examined. Thus, longitudinal differences may indicate

differences not evident in cross-sectional data. For example, the Prescription Opioid Addiction Treatment Study (POATS) clinical trial, which enrolled individuals with OUD seeking MOUD treatment, found no differences in rates of opioid relapse based on chronic pain status at baseline (Weiss et al., 2011). When these same trial data were used to examine weekly pain intensity in those with chronic pain, however, highly volatile pain was a risk for opioid relapse during both the active MOUD treatment phase and after MOUD taper (Worley et al., 2015, 2017). Further, higher current pain severity increased the probability of opioid use the following week (Griffin et al., 2016), which was mediated by opioid craving (Messina & Worley, 2019).

Overall, these findings suggest that there may be aspects of chronic pain, beyond a simple assessment of its presence or absence, that may influence rates of opioid relapse. For example, many studies indicate that pain's interference on functioning is an important consideration, perhaps moreso than pain's intensity. While chronic pain is likely to persist over the longer term (Andersson, 2004), reduction in pain intensity does not appear necessary for decreases in pain's interference on functioning (Vowles et al., 2017). Further, pain interference is significantly related to important chronic pain treatment targets, such as pain acceptance and pain catastrophizing, even after controlling for pain intensity among those with chronic pain and OUD (Mun et al., 2019). Hazardous substance use has also been found to be differentially related to pain interference and pain intensity (Jones et al., 2017; Ngo et al., 2021), suggesting that, although related, pain interference may involve a distinct underlying phenomenon separate from pain intensity. Therefore, it is important to examine pain interference independently. Prior work has often summed scores of pain intensity and pain interference together, which may be diluting important differences between the two mechanisms. Endorsement of severe pain interference is prevalent among those with chronic pain in MOUD treatment (Dunn et al., 2014), however more

work examining changes in pain interference and its unique relation to treatment outcomes, including relapse, is needed.

There is also a need for a nuanced assessment of treatment outcomes in those with MOUD. Prior work among those with chronic pain in MOUD treatment has almost exclusively focused on relapse as the sole outcome for treatment success. However, there are additional criteria that should be evaluated, including physical, psychological, and social functioning (Tiffany et al., 2012). Quality of life, in particular, is an important patient-centered outcome that assesses disease burden, and is sensitive to changes in opioid use and pain-related functioning (Bray et al., 2017; Dworkin et al., 2008).

Finally, patient characteristics should also be taken into consideration, as they may impact changes in pain interference, pain intensity, and subsequent treatment outcomes. Older age, being female, longer pain duration, and higher psychiatric distress have been related to worse pain severity and pain interference among those with chronic pain (Landmark et al., 2018). In particular, depression is one of the most common comorbidities in chronic pain and OUD populations and has been implicated in the development and maintenance of both conditions (Edwards et al., 2016; Volkow et al., 2019). Emotional functioning is also associated with pain sensitivity and pain tolerance, particularly in the context of opioid use (Wachholtz et al., 2015). Overall, broader inclusion of relevant variables in those with OUD and chronic pain is important to elucidate MOUD treatment responsiveness.

Taken together, there is a need to understand heterogeneity in MOUD response, particularly in those with chronic pain. Person-centered analyses are suitable as they help identify homogenous subgroups and model their developmental trajectories (Muthén & Muthén, 2000). For those on MOUD with chronic pain, person-centered analyses can highlight how

important pain mechanisms, such as pain intensity and pain interference, change over time and their differential relationships with key outcome domains, including opioid relapse, psychological functioning, and quality of life. These models can also assess how baseline patient characteristics are associated with pain intensity, pain interference, and their change over time.

The current study utilized data from the POATS clinical trial (Weiss et al., 2011). Prior work using these data has examined pain intensity in relation to relapse among those with chronic pain (Griffin et al., 2016; Messina & Worley, 2019; Worley et al., 2015, 2017), yet these studies lacked inclusion of outcomes outside of relapse. Baseline demographics, depression, quality of life, and opioid use has also been examined within the entire sample (Griffin et al., 2014, 2015; McHugh et al., 2013; Northrup et al., 2015; Peckham et al., 2020), yet have not been examined among those with chronic pain. To date, only one study has examined depression, pain intensity, and relapse together using person-centered analyses. Vest et al. (2020) used parallel process growth modelling to estimate how changes in depression and pain during treatment contributed to risk for relapse. High levels of depression or high levels of pain throughout treatment were a risk for relapse, particularly during the first three weeks of BUP/NX treatment. Not surprisingly, a substantial proportion of those who endorsed persistent high levels of depression or pain had a diagnosis of chronic pain, suggesting the need for further exploration of these symptoms specifically among this subsample. Pain intensity and pain interference scores were also summed to create a single pain score potentially erasing important nuances between the two domains. Lastly, inclusion of outcomes outside of relapse are necessary to capture overall patient functioning.

This study aimed to examine profiles of pain interference and pain intensity, and transitions between profiles, estimated in separate models, over the course of 12 weeks of the

buprenorphine/naloxone (BUP/NX) treatment using a person-centered statistical approach. Additionally, profiles were examined in relation to several treatment outcomes, including opioid use, depression severity, and mental health quality of life (MH-QOL) while still maintained on BUP/NX (week 12), and two months following a 4-week BUP/NX taper (week 24; see Figure 1 for trial design details). Baseline patient characteristics (age, sex, depression severity, and opioid use) were also examined in relation to profiles and transitions between profiles. Depression severity was examined as a predictor of pain intensity and pain interference profiles given that the indicators used were perceptions of pain in the last 24 hours. We included pain duration as a predictor of profile membership to help further elucidate durability of pain, given the high likelihood that individuals in this sample could be experiencing acute pain related to withdrawal or craving.

It was hypothesized that two profiles would fit these data for both the pain interference and pain intensity models at each time point (Phase 2 baseline and week 12). For the pain intensity model, a high pain intensity profile and a low pain intensity profile would emerge. For the pain interference model, a high pain interference profile and a low pain interference profile would emerge. It was also hypothesized that a majority of the sample would transition between the high and low pain interference profiles over the course of treatment, given that BUP/NX and the study treatment have been shown to promote opioid abstinence and lifestyle changes leading to improved quality of life (Volkow et al., 2019; Weiss et al., 2011). The high pain interference profile would exhibit worse depression and MH-QOL, and presence of opioid use at weeks 12 and 24 as compared to the low pain interference profile. Further, the pain intensity profiles would remain stable over the course of BUP/NX treatment, given that BUP/NX has a limited effect on pain intensity (Lazaridou et al., 2020) and the study treatment involved only one

session of pain coping skills. The high pain intensity profile would exhibit worse depression and MH-QOL, and presence of opioid use at weeks 12 and 24 as compared to the low pain intensity profile. Lastly, older age, being female, longer pain duration, worse baseline depression severity, and presence of opioid use were expected to predict membership in the high pain interference and high pain intensity profiles, as well as transitions to the high pain interference and high pain intensity profiles at week 12.

Method

Participants

The POATS study recruited participants (N = 653) from 10 substance use disorder (SUD) community treatment programs across the Northeast, Northwest, South, and Midwest United States (Weiss et al., 2011). The POATS study used a 2-phase adaptive research design. For the purposes of this study, we focus on Phase 2 (n = 353) during which participants received 12 weeks of BUP/NX maintenance. The sample for the present analysis included participants enrolled in Phase 2 of the study who had endorsed the presence of chronic pain per the Brief Pain Inventory (BPI; n = 194). Two participants dropped out of the study by week 12, and 74 missed the assessment leaving 118 participants with complete data at week 12. Another 20 participants missed the following assessment leaving 98 participants with complete data at week 24.

Inclusion criteria for the larger study required that participants were 18 years or older, met diagnostic criteria for current opioid dependence from prescription opioids based on the Diagnostic and Statistical Manual for Mental Disorders-IV (DSM-IV; APA, 1994), and were willing to be detoxified from opioids. Exclusion criteria included use of heroin for > 4 days in the past month preceding enrollment at Phase 1 baseline, a lifetime diagnosis of OUD due to heroin alone, had ever injected heroin, a requirement for ongoing pain management with opioids,

a prescription of >40 mg of methadone for pain, or experience of a major acutely painful event in the last 6 months. A major acutely painful event was characterized as a major injury, car accident, or surgery, and did not include pain flare-ups or worsening without a notable causal event.

Procedures

A full account and rationale of the procedures for the POATS clinical trial can be found in more detail (Weiss et al., 2011). In brief, this study employed a two-phase study design. Upon entering Phase 1 of the study, participants completed baseline assessment and were randomized to receive either Standard Medical Management (SMM) or Enhanced Medical Management (EMM). All participants received sublingual BUP/NX for two weeks and were then tapered off over a two-week period and followed for 8 weeks post taper. Doses ranged from 8 – 32 mg per day. As noted in the primary POATS outcome paper, participants who entered Phase 2 continued to have evidence of OUD. Upon entering Phase 2, participants completed a Phase 2 baseline assessment and were randomized to either SMM or EMM and maintained on BUP/NX for 12 weeks, followed by a taper over a 4-week period. Participants then completed follow up assessments at weeks 16, 20, and 24. The current study included participants in the Phase 2 trial, with a focus on assessments at Phase 1 baseline, and Phase 2 assessments at baseline, week 12, and week 24 (see Figure 1). There were no differences in outcomes based on treatment condition among those with chronic pain at baseline in the primary POATS outcome paper (Weiss et al., 2011), therefore, the data were collapsed across treatment condition in the current study.

Measures

Diagnosis of OUD, demographic information, chronic pain status, and pain duration were collected upon entering the trial, at the Phase 1 baseline assessment. Assessment of pain

interference, pain intensity, depression, and opioid use were collected at the Phase 2 baseline assessment, and monthly throughout Phase 2 of the trial. Assessments of quality of life were collected at the Phase 2 baseline assessment and at Phase 2 week 24.

Pain information. The Brief Pain Inventory (BPI) was used to assess for chronic pain, pain duration, pain interference, and pain intensity (Cleeland, 2009). Chronic pain was assessed by asking respondents if they currently had pain 'other than everyday kinds of pain', and if they selected yes, they were asked how long they have experienced this pain. Pain duration responses were categorical, ranging from <1 month to >4 years. Endorsement of pain, other than everyday kinds of pain, and duration of ≥3 months indicated the presence of chronic pain.

Pain interference was assessed using seven items evaluating the degree to which pain interfered with a number of areas over the last 24 hours on a scale from 0 (does not interfere) to 10 (completed interferes). Domains included general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. Pain intensity was assessed using four items asking respondents to rate worst, least, and average pain over the past 24 hours, and current pain on a scale from 0 (no pain) to 10 (pain as bad as you can imagine).

The indicators for the pain interference and pain intensity subscales were treated as continuous, as responses approximated a normal distribution. Internal consistency among the current chronic pain sample was deemed strong across timepoints for the pain interference (α = .944 - .955) and pain intensity (α = .923 - .949). Each subscale has evidence of adequate validity and reliability in chronic noncancer pain (Tan et al., 2004), and higher scores are robustly associated with poorer outcomes among those with chronic pain (Gerhart et al., 2017).

Mental health quality of life. The Medical Outcomes Study Short-Form 36 (SF-36) was used to assess MH-QOL over the past four weeks. There are 36 Likert-type items that yield two

quality of life subscale scores: physical and mental health. The current analyses only used the MH-QOL subscale. Scores range from 0 to 100, with higher scores indicating better quality of life. This measure has evidence of strong validity and reliability in a number of previous samples, including among those with chronic pain (Brazier et al., 1992). Internal consistency was strong across timepoints for the MH-QOL subscales (α = .920 - .938).

Depression severity. The Beck Depression Inventory-II (BDI-II) is a 21-item measure used to assess depressive symptoms over the past two weeks using a 4-point Likert-type scale. Scores are summed across all items and can range from 0 to 63, with higher scores indicating worse depression severity. Internal consistency was strong across timepoints (α = .956 - .961). The BDI-II has evidence of validity and reliability in chronic pain (Harris & D'Eon, 2008).

Opioid use. Opioid use was assessed using urine drug screens (UDS), which was analyzed for oxycodone, propoxyphene, illicit methadone, heroin, codeine, and morphine.

Demographic information. Demographic information included age, sex (male or female), race (American Indian/Alaska Native, Asian, Black/African American, Native Hawaiian/Pacific Islander, White, or Other), and ethnicity (of Spanish origin/Latino/Hispanic).

Analysis Plan

Descriptive statistics and attrition analyses were conducted using SPSS version 26 (IBM Corp., 2019). Attrition analyses assessed for differences among the study variables at the Phase 1 baseline, Phase 2 baseline, week 12, and week 24 assessments between those who had complete data and those who had missing data at each timepoint. Latent variable modeling analyses were conducted using the Mplus software program version 8.2 (Muthén & Muthén, 2018). The variance covariance matrix was estimated using all available data via the maximum likelihood estimator with robust standard errors.

Latent Profile and Transition Analysis. Latent profiles of pain intensity and interference were derived using confirmatory Latent Profile Analysis (LPA) models, which are a type of measurement model that derives profiles, or unobservable subgroups, from observable continuous indicators. Model constraints were applied in a confirmatory approach with two profiles at each time point, representing high and low pain interference and intensity. The pain interference LPA models used the seven items of the BPI pain interference subscale, and the pain intensity LPA models used the four items of the BPI pain intensity subscale. See Supplementary materials for model selection criteria and figures of proposed models. Latent transition analysis (LTA) models were used to examine how individuals transitioned between profiles of pain intensity and interference over time. We estimated separate latent profiles at each timepoint, and a transition probability, which is the probability of transitioning between latent profiles between timepoints (Collins & Lanza, 2009). Measurement invariance of each model was tested to ensure results could be compared across profiles and timepoints (see Supplementary materials for details).

Predictors of Profiles and Transitions. A manual three-step approach was used to test predictors of profile membership and transition between profiles (Asparouhov & Muthén, 2014). Age, gender, and pain duration, as well as Phase 2 baseline measurements of depression severity, and opioid UDS were examined as predictors of profile membership and transition between profiles.

Concurrent and Distal Outcomes. Lastly, profile membership at week 12 was examined in relation to several concurrent (week 12) and distal outcomes (week 24) using the manual BCH method (Bolck et al., 2004). Outcomes included mental health quality of life,

opioid use, and depression severity. Average pain interference and average pain intensity scores at week 24 were also examined (see Supplementary materials for details).

Results

Descriptive Statistics and Attrition Analyses

Overall, participants were primarily White (91%), male (55%), and ranged in age from 19 to 61 (see Table 1). Over half of the sample had chronic pain for ≥4 years and had a positive UDS for opioids at the Phase 2 baseline assessment. The sample consisted primarily of individuals who had never received treatment (pharmacological or behavioral) in the past for opioids, with less than 20% ever having received a medication for OUD. Descriptive statistics for the study variables can be found in Table 2. Pain intensity and pain interference at Phase 2 baseline [r (192) = .80, $p < .01$] and week 12 [r (119) = .72, $p < .01$] were significantly correlated. See Supplemental Table 1 for further correlational analyses. Attrition analyses indicated minimal differences between those with complete data and those with missing data at each timepoint. Only those with complete data at week 12 were more likely to endorse higher depressive symptoms [F (1, 194) = 5.52, p = .020] at Phase 2 baseline, and those with complete data at week 24 were more likely to be younger [F (1, 273) = 5.87, p = .016] at week 12.

Latent Profile and Transition Analyses

Overall, for the both pain interference and pain intensity models, a two-profile LPA solution consistently fit these data best across timepoints with high entropy indicating excellent profile separation. See Supplementary materials for justification of model selection and fit statistics of LPAs (Supplemental Table 2). Figures 2 and 3 present the indicator means for each profile at baseline. As hypothesized and consistent with confirmatory model constraints, the two pain interference profiles at Phase 2 baseline and week 12 represented a high pain interference

profile and a low pain interference profile. The same pattern emerged for the pain intensity model, such that a high pain intensity profile and a low pain intensity profile were identified at each timepoint.

Measurement invariance of the unconditional latent transition models were supported. Tests of measurement invariance and details about class proportion shifts across LPA and LTA models can be found in the Supplementary materials. Transition probabilities were based on the invariant unconditional models (Table 3). Results indicated individuals who were initially classified in the low pain interference profile at Phase 2 baseline had a low probability of transitioning to high pain interference profile at week 12 (Probability (P) = .158; N=11, 6%), and a high probability of remaining in the low pain interference profile at week 12 (P=.842; N=102, 53%). Those classified in the high pain interference profile at Phase 2 baseline had a low probability of remaining in the high pain interference profile at week 12 (P=.342; N=17, 9%) and a high probability of transitioning to the low pain interference profile at week 12 (P=.658; N=64, 32%). Similarly, for the pain intensity model, individuals who were initially classified in the low pain intensity profile at Phase 2 baseline had a high probability of remaining in the low pain intensity profile at week 12 (P= .872; N=77, 40%) and a low probability of transitioning to the high pain intensity profile at week 12 (P=.128; N=6, 3%). Those classified in the high pain intensity profile at Phase 2 baseline had a higher probability of transitioning to the low pain intensity profile at week 12 (P=.586; N=80, 41%), and a lower probability of remaining in the high pain intensity profile at week 12 (P=.414; N=31, 16%).

Predictors of Profiles and Transitions

Using the 3-step approach, predictors of profile membership (Table 4) and transitions between profiles (Table 5) were estimated.

Pain Interference Model. In the pain interference model, those with longer pain duration and higher depression severity at Phase 2 baseline had higher odds of being in the high pain interference profile at both timepoints. Those who were older had higher odds of being in the high pain interference profile at week 12. Sex and opioid use were not significant predictors of profile membership at Phase 2 baseline or week 12. There were no significant predictors of transitions between profiles.

Pain Intensity Model. In the pain intensity model, those who were female, had longer pain duration, higher depression severity, and a positive UDS for opioids at Phase 2 baseline had higher odds of being in the high pain intensity profile at Phase 2 baseline. There were no significant predictors of profile membership at week 12. Older age and worse depression severity at Phase 2 baseline significantly predicted transitions between profiles (i.e., high to low, low to high) as compared to stability in one profile over time.

Concurrent and Distal Outcomes

Using the BCH method, concurrent (week 12) and distal (week 24) outcomes were estimated by final profile membership at week 12. Outcomes included were MH-QOL, depression severity, opioid use, average pain intensity, and average pain interference. Mean comparisons in outcomes by pain interference profile and pain intensity profile at week 12 can be found in Table 5.

Pain Interference Model. Data at week 12 indicated that those in the high pain interference profile had significantly worse MH-QOL and depression severity as compared to those in the low pain interference profile. Those in the high pain interference profile at week 12 continued to have significantly higher pain interference and pain intensity at week 24 as compared to those in the low pain interference profile.

Pain Intensity Model. Those in the high pain intensity profile at week 12 had significantly worse MH-QOL and depression severity at week 12 as compared to those in the low pain intensity profile. Those in the high pain intensity profile at week 12 had significantly worse MH-QOL, higher pain intensity, and higher pain interference at week 24 as compared to those in the low pain intensity profile.

Discussion

This study aimed to characterize latent profiles of pain intensity and pain interference, and transitions between profiles, over the course of 12 weeks of BUP/NX maintenance treatment among those with prescription OUD and chronic pain. Concurrent and distal outcomes were analyzed in relation to profile membership at week 12, and several patient characteristics were examined as predictors of profile membership and transitions between profiles. As hypothesized, and consistent with prior research (Tan et al., 2004; Vowles et al., 2017), pain intensity and pain interference were significantly correlated but not entirely overlapping constructs. High and low profiles were identified in the pain interference and pain intensity models at both timepoints, and the majority of individuals were classified in the low pain interference or low pain intensity profile at baseline. Regardless of profile membership at baseline, all individuals had a higher probability of remaining in or transitioning to the low pain interference or low pain intensity profiles over the course of 12 weeks of BUP/NX maintenance treatment.

Overall, individuals in the current study demonstrated improvements in pain intensity and pain interference during BUP/NX maintenance treatment, a finding consistent with prior work from the POATS data (Vest et al., 2020; Worley et al., 2017) and other BUP/NX clinical trials (Chakrabarti et al., 2010; Latif et al., 2019). There are, however, at least four findings that shed new light on this area. First, there was a small subgroup of individuals (15-20%) whose pain

intensity and pain interference remained high or worsened over the course of BUP/NX maintenance treatment. This finding highlights the utility of person-centered analyses in identifying heterogeneous subgroups of patients. It also suggests that, for the majority of patients with prescription OUD and chronic pain, BUP/NX maintenance treatment may be sufficient to improve pain-related functioning. However, there remains a minority of patients who continue to demonstrate high pain intensity and pain interference after three months of BUP/NX maintenance treatment. This subgroup also has a more severe clinical profile characterized by worse depressive symptoms and poorer quality of life, and possible continuation of high pain intensity and pain interference following a taper. Continual and frequent assessment of both pain domains are warranted to aid in identifying these individuals during BUP/NX maintenance treatment for whom additional treatment may be needed.

Second, while prior work using the POATS data has indicated that previous pain ratings, high baseline pain, and the experience of highly volatile pain to be associated with relapse (Griffin et al., 2016; Vest et al., 2020; Worley et al., 2015, 2017), the current results add to these findings by indicating that rates of relapse among those with chronic pain did not differ based on high or low pain intensity or pain interference. Taken together, these findings suggest that the negative impacts of pain on relapse may be mitigated following BUP/NX maintenance treatment and medical management.

Third, the analysis of baseline patient characteristics and their relation to pain intensity and pain interference profiles was a unique aspect of this study, in comparison to other studies utilizing this data. Most notably, worse baseline depressive symptoms were predictive of transitions between pain intensity profiles, as well as membership in the high pain intensity profile at baseline and the high pain interference profile at both time points. Depressive

symptoms are clearly relevant in the treatment of OUD in those with chronic pain and remain an important and modifiable treatment target. Women, those with longer pain duration, and those with a positive opioid UDS at baseline were more likely to be in the high pain intensity profile at baseline, however none of the patient characteristics in the current study were predictive of profile membership at week 12. This suggests that BUP/NX treatment responsiveness in relation to pain intensity may be equivalent across these patient characteristics. Lastly, those who were older were more likely to transition between pain intensity profiles, and had higher odds of being in high pain interference profile at week 12. Additionally, those with worse baseline depression and longer pain duration were more likely to be in the high pain interference profile at both timepoints. These findings suggest that patients who are older, have longer pain duration, and have worse baseline depression may experience higher impact pain that is less responsive to BUP/NX treatment.

Finally, a higher proportion of the sample endorsed high pain intensity as compared to high pain interference at both timepoints suggesting that some did not perceive their pain as significantly interfering with important areas of life. Given that POATS recruited from SUD community treatment programs, it is possible that they may have perceived other problems, such as substance use, as interfering in these domains rather than pain. This supposition may also explain the minimal differences between pain interference profiles in the outcome and transition analyses. It is possible that pain interference may not be an important mechanism among those presenting to SUD clinics and early in MOUD treatment where substance use is more likely to be perceived as the primary barrier to functioning. It remains possible that pain interference is a barrier to functioning later in BUP/NX maintenance treatment, at which point, it may become a more robust indicator of relapse or overall functioning.

Limitations

There are several limitations that should be taken into consideration when interpreting these results. First, there is no gold standard model fit index, therefore, model selection is based to some degree on existing guidelines and judgement of investigators. Second, the sample size was relatively small for the current analyses which may have impacted our ability to detect additional, smaller classes. Further work with larger sample sizes is needed. Third, all models are probabilistic and there is always the chance of misclassification. Entropy, a measure of misclassification, ranged from .767 to .960 suggesting that anywhere from 4-23% of participants may have been misclassified in the models. Fourth, while attrition analyses indicated minimal differences between those with missing and complete data at each timepoint, we are not able to describe the extent to which attrition had an impact on the study results. Fifth, the generalizability of findings is limited by characteristics of the sample, who were primarily White and of younger age, and further examination in more diverse samples is needed. Additionally, all participants received BUP/NX prior to Phase 2 of POATS, thus findings may not generalize to those who are completely treatment naïve.

Finally, average pain intensity and pain interference scores were typically in the mild to moderate range (i.e., 3-4 out of 10) at baseline and decreased over time. These scores are descriptively lower than more traditional chronic pain samples (i.e. 6-7 out of 10; Nicholas et al., 2019). This difference may be due to two reasons. First, it is possible that the first question of the BPI, which was used to categorize individuals as having chronic pain in these data, may be overly sensitive (Dennis et al., 2016). Second, there may be selection bias, as those endorsing more severe chronic pain may have received treatment in specialty pain clinics rather than SUD clinics or may have had limited access to treatment more broadly due to limited physical

capabilities or inadequate resources. Given these limitations, it should be noted that the findings depicted in the current study are not definitive in nature. While the current study may offer a more precise characterization of associations between latent pain profiles, patient characteristics, and psychopathology, there will likely be a number of deviations from the current findings in future research and real-world clinical practice.

Future Directions

There are several important implications. First, while BUP/NX maintenance and medical management may be effective for the treatment of prescription OUD and chronic pain (Daitch et al., 2014), there remains a small subgroup who continue to exhibit high pain intensity and high pain interference three months following treatment. These individuals are likely to experience worse mood, quality of life, and persistently high pain intensity and interference following a BUP/NX taper. Further medical and psychological treatment, particularly focused on pain coping, craving, and depression, may be warranted for these individuals.

Second, further integration of behavioral treatments and their potential role in co-morbid OUD and chronic pain is deserving of additional study. While one of the POATS study arms included pain coping skills training, this was only a small component of the behavioral therapy (Opioid Drug Counseling) and the efficacy of such integration is unclear across studies, including the original POATS outcome study (Ilgen et al., 2020; Messina & Worley, 2019; Weiss et al., 2011). One avenue of additional study may be an explicit focus on two mechanisms. First, reducing pain interference, given its importance to overall functioning and quality of life, and second, altering responses to craving, given its important role in mediating between pain intensity and relapse (Northrup et al., 2015; Tsui et al., 2016). In particular, mindfulness-based interventions and Acceptance and Commitment Therapy (ACT) may be particularly well suited

to address several presenting issues given their transdiagnostic framework (Hayes et al., 2012; Witkiewitz et al., 2014). A recent pilot study of an integrated mindfulness and ACT treatment successfully reduced pain interference and opioid misuse in veterans with chronic pain (Vowles et al., 2020). Further, two studies of mindfulness indicated positive treatment outcomes in these same two domains, using an approach called Mindfulness Oriented Recovery Enhancement (Garland et al., 2014, 2019), as did a recent pilot study of Cognitive-Behavioral Therapy (CBT) in opioid use (Barry et al., 2019). Further work is needed, particularly in relation to integrated treatments of OUD and chronic pain.

Third, observational studies of chronic pain among patients maintained on MOUD are needed to determine if patients experience changes to their chronic pain status and severity over a longer period of time. For example, a previous POATS study found 53% of patients reported variability in their chronic pain status over a 3.5-year period (McDermott et al., 2019), which suggests the reduction in chronic pain severity in the present results may not persist. Given this, it is important to continually monitor pain intensity and pain interference even if patients have experienced improvements in pain-related functioning during BUP/NX treatment. If chronic pain severity does worsen, interventions targeting pain coping, craving, and depression, may help prevent relapse and improve overall functioning and quality of life.

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Tables

Table 1. Sample demographic characteristics.

Measure	N	Mean (SD) or %
Age	194	35.3 (10.4)
Sex		
Male	107	55%
Female	87	44%
Ethnicity/Race*		
White	177	91%
Hispanic/Latinx	9	5%
Black/African American	5	3%
Asian/Native Hawaiian/Pacific Islander	2	1%
American Indian/Alaska Native	8	4%
Other	6	3%
Pain Duration		
3 mo to < 2 years	35	18%
2 to < 4 years	54	28%
≥ 4 years	105	54%
Ever been in treatment for opiates		
No	132	68%
Yes	62	32%
Received Methadone	21	11%
Received Buprenorphine	11	6%

*Does not add to 194 as participants were able to select all that apply.

Table 2. Descriptive statistics of all study variables at all study timepoints.

Variable	Phase 2 Baseline N = 194	Week 12 N = 118	Week 24 N = 98
	Mean (SD) or N (%)	Mean (SD) or N (%)	Mean (SD) or N (%)
BPI Pain Interference Subscale	3.93 (2.88)	2.48 (2.24)	2.57 (2.33)
General Activity	4.40 (3.28)	2.97 (2.77)	2.88 (2.76)
Mood	4.36 (3.35)	2.69 (2.59)	2.54 (2.55)
Walking Ability	3.20 (2.94)	2.33 (2.47)	2.18 (2.51)
Normal Work	3.79 (3.12)	2.51 (2.48)	2.52 (2.54)
Relations with Others	3.26 (3.21)	1.68 (2.11)	1.95 (2.43)
Sleep	4.55 (3.48)	2.92 (3.02)	3.35 (2.90)
Enjoyment of Life	3.98 (3.39)	2.24 (2.59)	2.54 (2.69)
BPI Pain Intensity Subscale	4.21 (2.55)	2.93 (1.98)	2.90 (2.05)
Worst pain	5.73 (3.04)	4.28 (2.66)	4.16 (2.60)
Least pain	3.01 (2.51)	2.09 (1.97)	2.00 (1.84)
Average pain	4.09 (2.39)	2.86 (1.91)	2.97 (2.09)
Pain now	4.01 (2.99)	2.49 (2.18)	2.46 (2.18)
Covariates[a] and Distal Outcomes			
Depression Severity	18.30 (13.08)	8.97 (10.54)	9.76 (10.77)
Opioid Use[b,c]	131 (69%)	24 (21%)	37 (40%)
Mental Health QOL	57.29 (20.43)	67.00 (19.22)	64.04 (18.79)

Note. BPI = Brief Pain Inventory; QOL = Quality of life. [a] = Age and sex were also used as covariates and are described in Table 1. [b] = Number of positive urine drug screen. [c] = Includes oxycodone, propoxyphene, illicit methadone, heroin, codeine, and morphine.

Table 3. Transition probabilities from Phase 2 baseline to week 12 for the unconditional pain interference and pain intensity models.

Phase 2 Baseline Profile	Week 12 Profile	
Pain Interference	Low interference	High interference
	(N =166; 86%)	(N= 28; 14%)
Low interference (N = 113; 58%)	.842	.158
High interference (N = 81; 42%)	.658	.342
Pain Intensity	Low intensity	High intensity
	(N =157; 81%)	(N= 37; 19%)
Low intensity (N=83; 43%)	.872	.128
High intensity (N=111; 57%)	.586	.414

Note. Entropy was .806 and .767 for the unconditional pain interference model and pain intensity model, respectively. Final profile counts and proportions are based on the most likely latent profile membership.

Table 4. Predictors of profile membership at Phase 2 baseline and week 12 for the pain interference and pain intensity models.

Predictor[a]	Phase 2 Baseline		Week 12	
	OR	95% CI	OR	95% CI
High pain interference				
Age	1.01	.99, 1.04	1.05*	1.01, 1.09
Sex[d]	1.84	.98, 3.47	2.01	.75, 5.41
Pain Duration	1.61*	1.02, 2.53	1.70*	1.02, 2.85
Depression severity	1.09*	1.06, 1.13	1.06*	1.02, 1.09
Opioid use[e]	.99	.53, 1.84	4.18	.95, 2.85
High pain intensity				
Age	1.00	.97, 1.03	.99	.94, 1.03
Sex[d]	2.73*	1.45, 5.14	.95	.37, 2.45
Pain Duration	1.41*	1.01, 1.96	1.48	.94, 2.34
Depression severity	1.03*	1.01, 1.06	1.01	.98, 1.04
Opioid use[e]	2.00*	1.07, 3.71	2.44	.87, 6.83

Note. * = $p < .05$. Reference group is the low pain interference/intensity profile. [a] = Age, sex, and pain duration were assessed at Phase 1 baseline, and depression and opioid/opiate use were assessed at Phase 2 baseline. OR = Odds ratio. 95% CI = 95% confidence interval; lower bound, upper bound. [d] = Male = 0, female = 1. [e] = No use = 0, use = 1. Entropy for the full conditional model was .85 and .80 for the pain interference model for the pain intensity model, respectively.

Table 5. Predictors of transitions between profiles at Phase 2 baseline and week 12 for the pain interference and pain intensity models.

Transition Pattern	Predictor[a]	OR[b]	95% CI[c]
Pain interference			
High – High[1]	Age	.99	.91, 1.08
	Sex[d]	.77	.10, 6.69
	Depression severity	1.02	.95, 1.10
Low – High[2]	Age	1.01	.92, 1.10
	Sex[d]	1.30	.15, 11.27
	Depression severity	.98	.91, 1.05
Pain intensity			
High – High[1]	Age	.90*	.82, .98
	Sex[d]	1.17	.05, 28.81
	Depression severity	.91*	.83, .98
Low – High[2]	Age	1.11*	1.02, 1.22
	Sex[d]	.85	.04, 21.01
	Depression severity	1.11*	1.02, 1.20

Note. * = $p < .05$. [a] = Age and sex were assessed at Phase 1 baseline, and depression was assessed at Phase 2 baseline. [b] = Odds ratio. [c] = 95% confidence interval; lower bound, upper bound. [d] = Male = 0, female = 1. [1] = Reference group is High – Low. [2] = Reference group is Low – Low. Opioid use was not examined in relation to transitions in either model due to convergence errors, likely due to the small sample size.

Table 6. Differences in outcome variables by profile membership at week 12 for the pain interference and pain intensity models.

	Week 12		Week 24	
Outcome	*t*	95% CI	*t*	95% CI
High pain interference vs. low pain interference profile				
Mental Health QOL	-19.44*	-24.74, -14.64	-7.04	-15.58, 1.50
Depression	7.38*	3.29, 11.47	2.22	-3.12, 7.57
Opioid use	-.72	-1.78, .34	-1.19	-2.46, .08
Average pain interference			3.07*	2.11, 4.04
Average pain intensity			1.55*	.74, 2.36
High pain intensity profile vs. low pain intensity profile				
Mental Health QOL	-13.69*	-18.94, -8.43	-10.16*	-16.36, -3.96
Depression	5.50*	1.75, 8.66	2.98	-1.14, 7.10
Opioid use	-.70	-1.66, .28	-.66	-1.63, .31
Average pain interference			2.23*	1.44, 3.02
Average pain intensity			2.41*	1.64, 3.18

Note. * = $p < .05$. Paired-sample *t* – test. 95% confidence interval; lower bound, upper bound.

Figures

Figure 1. Flow chart of the Prescription Opioid Addiction Treatment Study (POATS) clinical trial assessment timepoints, and timepoints (in **bold text**) used for the current study.

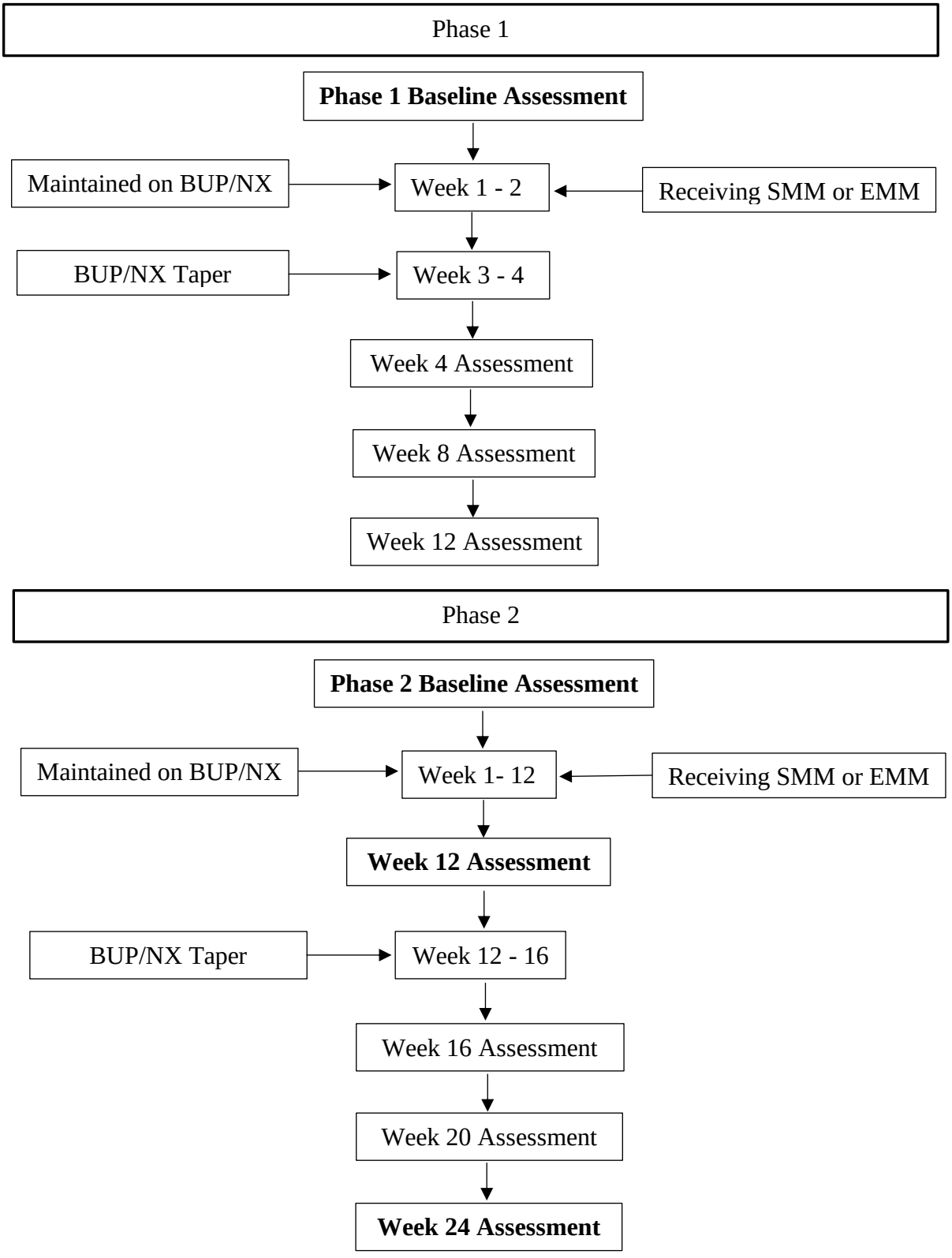


Figure 2. Mean indicator responses for the pain interference profiles at Phase 2 baseline.

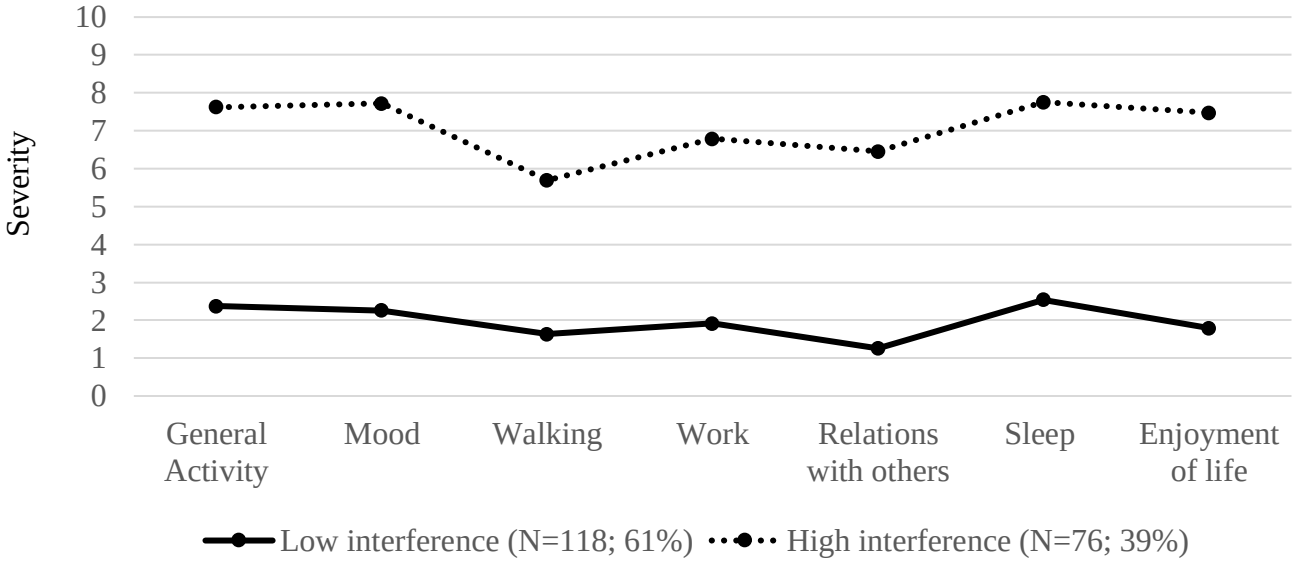
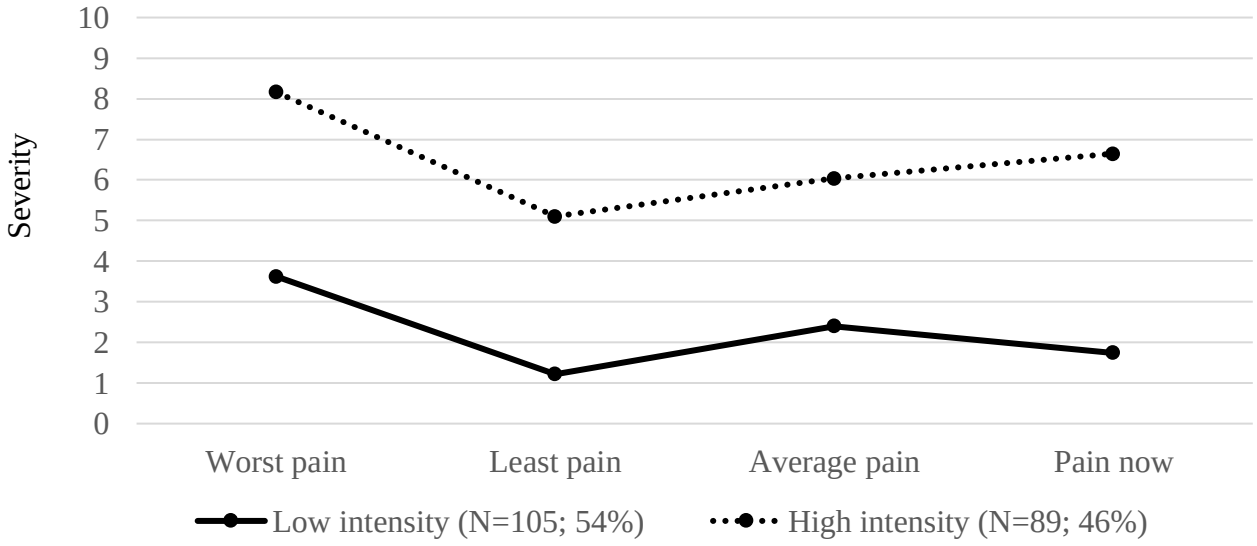


Figure 3. Mean indicator responses for the pain intensity profiles at Phase 2 baseline.



Supplemental Materials

Data Analysis Plan

We hypothesized a two-profile model a priori and conducted all analyses using a confirmatory approach. For full transparency and for the sake of future research that might use these data to examine pain interference and intensity, we also provide the results for 3- through 5- profile models in this supplement. At each timepoint, 2-, 3-, 4-, and 5-profile solutions were tested and number of profiles were determined by several model fit indices appropriate for LPA analyses, which included the Lo–Mendell–Rubin likelihood ratio test (LRT), bootstrapped likelihood ratio test (BLRT; Lo, Mendell, & Rubin, 2001), Bayesian Information Criterion (BIC; Schwarz, 1978), sample size adjusted Bayesian Information Criterion (aBIC; Hensen, Reise, & Kim, 2007), and entropy (Kline, 2015). Model selection for the latent profile models was based on the BIC and aBIC (where lower BIC and aBIC estimates indicate better fit), entropy ≥ 0.8, and a significant LRT and BLRT, which tests whether a *k*-profile model fits significantly better than a model with one fewer profile (e.g., a *k*-1 profile model; Nylund, Asparouhov, & Muthén, 2007). Sample size of the smallest extracted profile was also considered to guard against overextraction of profiles and selection of an unstable and poorly generalized model (Nylund-Gibson & Choi, 2018). Covariates were not included when selecting the number of profiles given misspecified covariate effects can lead to overextraction of profiles (Nylund-Gibson & Masyn, 2016).

As stated, two unconditional LTA models were estimated to test measurement invariance. This ensures the profiles measure the same construct over time and that transitions between latent profiles can be meaningfully compared. An unconditional LTA model with freely estimated means was compared to the same model in which the mean parameters for each profile

were constrained to equality at each timepoint. A maximum likelihood robust (MLR) scaled difference chi-square test was used to test whether the constrained LTA model fit significantly better than the freely estimated LTA model. The full set of calculations for this test are reviewed in more detail by Satorra & Bentler (2001). In brief, the loglikelihood, scaling correction factor, and number of free parameters for each model are used to estimate a scaled difference chi-square statistic (TRd), which is then compared to a typical chi-square distribution to attain a *p* value. If the constrained model fit significantly better (i.e. the chi-square test is significant at $p < .05$), than it would be concluded that the profiles are invariant over time. This test was done for both the pain intensity and pain interference model.

Next, to examine the relation of each predictor with profile membership and transition between profiles, a manual three-step approach was used. A three-step approach has been shown to produce more stable and unbiased estimates, even when entropy is low (i.e. 0.6 - 0.8) and sample sizes are small (N = 100-200; No & Hong, 2018; Nylund-Gibson, Grimm, Quirk, & Furlong, 2014). This approach ensures that the latent profile variable parameter estimates are not affected by the inclusion of predictors and therefore, preserves the meaning of the latent profile variable across time and when estimating each predictor. Generally, in this approach, the modal profile assignment becomes the indicator for the LPA models, although profile parameters are constrained to specific logit values to account for misclassification. This approach can be done while preserving measurement invariance and can account for missing data across timepoints [for detailed reviews of this procedure see Di Mari, Oberski, & Vermunt (2016), Nylund-Gibson et al. (2014), and Asparouhov & Muthén, (2014)].

As the name suggests, there are three steps to estimate indicator. The first step requires estimating the unconditional invariant LPA model at each timepoint, which ensures

independence across individual responses and provides the independent error structure at each timepoint. With each model run, profile probabilities and modal profile membership at each timepoint are saved into a single and separate datafile. The second step requires calculating the misclassification logit values, which represent the most likely profile misclassification error. The Mplus software automatically calculates these values which can be found in the output from the previous step. In the third and final step, the conditional LTA model is specified using the datafile generated in the first step, however the indicators of each latent profile variable becomes the modal profile assignment variable. The parameter of each modal profile assignment is then fixed based on the misclassification logits that were estimated in the first step. To account for missing data between Phase 2 baseline and week 12, the steps must be carried out a second time. The difference is that, in the first step, an arbitrary variable is specified in the model that is held equal across profiles and has no missing data (such as an ID variable). At each timepoint, modal profile assignment and profile probabilities are, again, saved into another separate datafile. This step is primarily used for data management as the arbitrary variable acts as a placeholder so that observations with missing data are also saved into the datafile. The third step is specified in the same way, however, the parameters of this model are fixed to the misclassification logits that were estimated from the first run that did not account for missing data. Missing data in the final model is accounted for using the maximum likelihood estimator with robust standard errors, which uses the standard covariance matrix to estimate covariate effects.

Lastly, profile membership at the final timepoint was examined in relation to several concurrent (week 12) and distal outcomes (week 24) using the manual BCH method (Bolck et al., 2004). This approach can be used with both categorical and continuous outcome variables (Bakk et al., 2013), and has been shown to produce robust estimates of distal outcomes when

using LPA analyses as compared to other distal outcome approaches (Dziak et al., 2016). The BCH method is similar to the manual three step approach described above. Instead of calculating the misclassification logits in the second step, however, classification errors for each individual are computed and the inverse logits of these error probabilities are used as weights in the third step. By using weights, the third step no longer requires the modal profile assignment variable to be specified as the latent profile indicators. In brief, the first step requires the specification of an unconditional LPA model with all covariates and outcomes listed in the "auxiliary" variable option, and saving BCH weights into a separate datafile. This datafile is then used in the third step, where the model is estimated with covariate and outcome variables using the BCH weights [for a detailed review of distal outcome analyses see Nylund-Gibson, Grimm, & Masyn (2019)].

Results

Correlation Analyses

Overall, pain intensity and pain interference demonstrated good test-retest reliability as demonstrated by significant correlations at each timepoint. In addition, pain intensity and pain interference were significantly correlated with each other at each timepoint (Supplemental Table 1).

Latent Profile and Transition Analyses

Model Selection. We hypothesized a two-profile model a priori and we conducted all analyses using a confirmatory approach. A two profile-solution was hypothesized given the small sample size of the current study and the likelihood that a two-profile solution would be most stable across timepoints. For full transparency we also estimated 3- through 5- profile models (Supplemental Table 2). For the pain interference model, the BIC, aBIC, and BLRT indicated progressively better fit as more profiles were extracted, and entropy changed only

marginally across profile solutions. However, the 4 and 5-profile solution for the week 12 data indicated possible model nonconvergence and the smallest sample size (n = 4) was suggestive of overextraction and an unstable model solution. The 3-profile solution did not fit significantly better than a 2-profile solution at week 12 (LRT =150.67, p = .150), therefore the 2-profile solution was selected given our confirmatory approach and because it demonstrated good class separation and fit significantly better than a one class model at both Phase 2 baseline and week 12.

Similarly, for the pain intensity model, the BIC, aBIC, and BLRT indicated progressively better fit as more profiles were extracted, and entropy shifted only marginally across profile solutions. However, the 4 and 5-profile solution for the week 12 data yielded small sample sizes (>10% of the sample) in the smallest profile suggestive of overextraction and an unstable model solution. The 3-profile solution did not fit significantly better than a 2-profile solution at Phase 2 baseline (LRT = 259.62, p = .063), therefore the 2-profile solution was selected given our confirmatory approach and because it demonstrated good class separation and fit significantly better than a one class model at both Phase 2 baseline and week 12.

Shift in Class Proportions. Shifts in class proportions can occur between LPA, unconditional LTA, and conditional LTA models, despite methods to counteract this phenomenon. In the current study, there were no significant shifts in class proportions between the unconditional and conditional LTA models for either the pain intensity or pain interference models (see Supplemental Table 3). There is evidence of mild proportional shifts in the week 12 profiles between the LPA and the unconditional LTA models, however this is most likely because LTA models can account for missing data between timepoints. Additionally, in the pain intensity model at Phase 2 baseline there was evidence of proportional shifts between the LPA

and unconditional LTA model, such that 11% more individuals were classified in the high pain intensity profile in the LTA model (n=111) as compared to the LPA model (n=89). There was no evidence of significant proportional shifts in the pain interference model at Phase 2 baseline.

Tests of Measurement Invariance. Four unconditional LTA models were estimated to test for measurement invariance across time (Phase 2 baseline to week 12) and profiles. The LTA model with means constrained to equality over time was tested against a model with means that were freely estimated using a Chi-square maximum likelihood difference test. For both the pain interference [$\chi 2$ (56) = 263.76, $p < .001$] and pain intensity model [$\chi 2$ (48) = 93.22, $p < .001$], the LTA model with means constrained to equality fit significantly better than the model with freely estimated means supporting score comparisons between profiles and across timepoints.

Figure 1. Proposed pain interference model with covariates predicting profile membership and transition between profiles at Phase 2 baseline and week 12, and profiles at week 12 predicting concurrent and distal treatment outcomes.

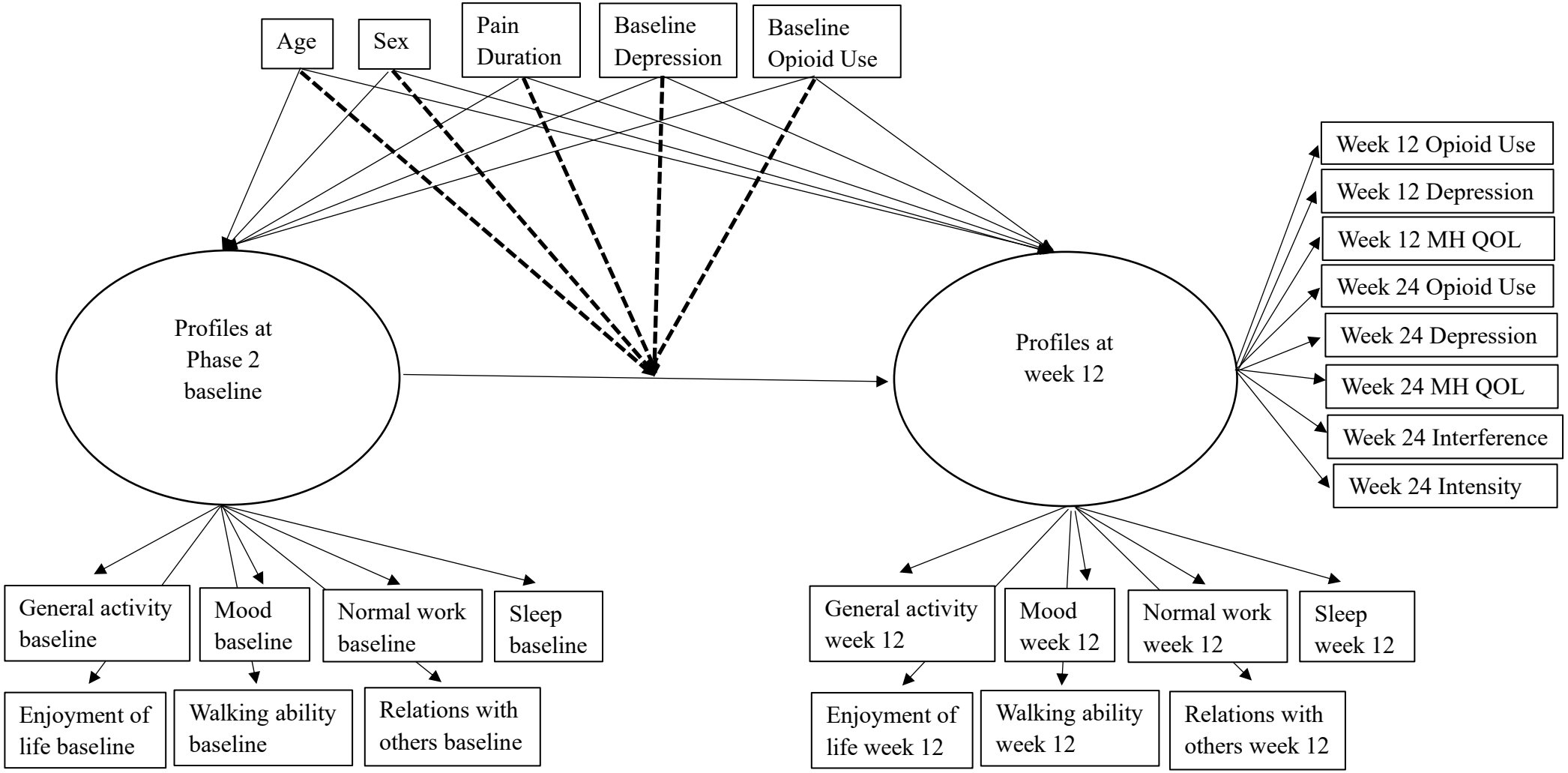
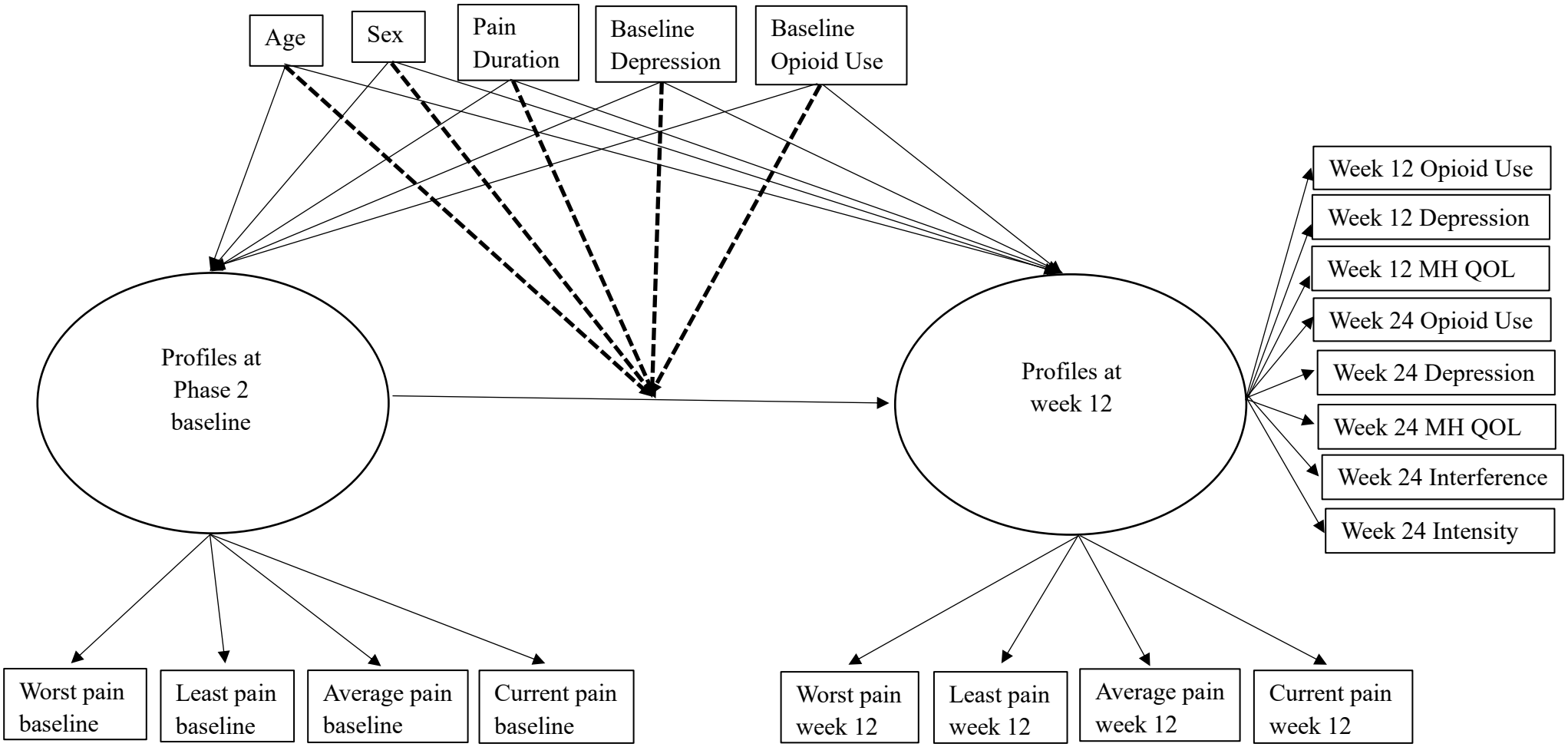


Figure 2. Proposed pain intensity model with covariates predicting profile membership and transition between profiles at Phase 2 baseline and week 12, and profiles at week 12 predicting concurrent and distal treatment outcomes.



Supplemental Table 1. Correlations of average pain intensity and average pain interference at each timepoint in the current study.

Variable	1.	2.	3.	4.	5.	6.
1. Pain intensity, Phase 2 Baseline	--					
2. Pain intensity, Week 12	0.272**	--				
3. Pain intensity, Week 24	0.462**	0.646**	--			
4. Pain interference, Phase 2 Baseline	0.801**	0.215*	0.274**	--		
5. Pain interference, Week 12	0.303**	0.718**	0.458**	0.414**	--	
6. Pain interference, Week 24	0.307**	0.532**	0.646**	0.451**	0.736**	--

Note. * = $p < .05$, ** = $p < .01$.

Supplemental Table 2. Fit statistics for the latent profile analyses at Phase 2 baseline and week 12 for the unconditional pain interference and pain intensity models.

Timepoint	BIC	aBIC	Entropy	LRT	BLRT	Smallest n (%)
Pain Interference Model						
Phase 2 Baseline						
2 Profiles	6192	6123	.961	946.69, $p < .001$	969.16, $p < .001$	76 (39%)
3 Profiles	5945	5850	.927	282.21, $p = .026$	288.91, $p < .001$	57 (29%)
4 Profiles	5847	5727	.932	137.19, $p = .049$	140.45, $p < .001$	31 (16%)
5 Profiles	5813	5668	.950	73.91, $p = .553$	75.66, $p < .001$	2 (1%)
Week 12						
2 Profiles	3494	3425	.936	489.71, $p = .042$	502.54, $p < .001$	44 (37%)
3 Profiles	3378	3283	.943	150.67, $p = .150$	154.61, $p < .001$	23 (19%)
4 Profiles[c]	3307	3187	.951	106.36, $p = .188$	109.14, $p < .001$	4 (3%)
5 Profiles[c]	3293	3148	.961	50.18, $p = .319$	51.49, $p < .001$	4 (3%)
Pain Intensity Model						
Phase 2 Baseline						
2 Profiles	3343	3302	.882	456.12, $p = .004$	473.43, $p < .001$	89 (46%)
3 Profiles	3115	3058	.925	259.62, $p = .063$	269.47, $p < .001$	56 (29%)
4 Profiles	3040	2967	.912	83.39, $p = .007$	86.55, $p < .001$	31 (16%)
5 Profiles	3023	2935	.881	41.03, $p = .441$	42.59, $p < .001$	27 (14%)
Week 12						
2 Profiles	1850	1809	.913	262.78, $p = .002$	273.79, $p < .001$	40 (34%)
3 Profiles	1765	1708	.911	104.57, $p = .054$	108.95, $p < .001$	26 (22%)
4 Profiles	1735	1662	.918	51.73, $p = .197$	53.89, $p < .001$	5 (4%)
5 Profiles[c]	1730	1641	.933	27.76, $p = .171$	28.93, $p < .001$	1 (<1%)

Note. BIC = Bayesian Information Criterion; aBIC = sample size adjusted Bayesian Information Criterion; LRT = Lo-Mendell-Rubin Adjusted Likelihood Ratio Test; BLRT= Bootstrapped Likelihood Ratio Test. A 3-profile solution was not chosen due to several factors, which include inconsistent fit across models and timepoints, the small sample size of the current study, and the tendency for mixture models to overextract profiles. [c] = solution yielded empty cells indicating possible model nonidentification.

Supplemental Table 3. Final profile counts and proportions based on the most likely latent profile membership for all models in the current study.

Model	Phase 2 Baseline Profile N (%)		Week 12 Profile N (%)	
Pain Interference	Low	High	Low	High
LPA[a]	118 (61%)	76 (39%)	74 (63%)[*]	44 (37%)[*]
Unconditional LTA[b]	113 (58%)	81 (42%)	166 (86%)	28 (14%)
Conditional LTA[b]	115 (59%)	79 (41%)	151 (78%)	43 (22%)
Outcome Analysis	--	--	89 (75%)[*]	29 (25%)[*]
Pain Intensity				
LPA[a]	105 (54%)	89 (46%)	78 (66%)[*]	40 (34%)[*]
Unconditional LTA[b]	83 (43%)	111 (57%)	157 (81%)	37 (19%)
Conditional LTA[b]	78 (40%)	116 (60%)	137 (71%)	57 (29%)
Outcome Analysis	--	--	80 (68%)[*]	38 (32%)[*]

Note. [a] = Latent profile analysis; [b] = Latent transition analysis; [*] = does not add up to 194 because analyses cannot account for missing data.