PARALLEL LATENT CHANGE MODELING FOR DEPRESSION AND PAIN TO PREDICT RELAPSE DURING BUPRENORPHINE AND SUBOXONE TREATMENT

By

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To the Faculty of Washington State University:

The members of the Committee appointed to examine the dissertation of NOEL ADAM VEST find it satisfactory and recommend that it be accepted.

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PARALLEL LATENT CHANGE MODELING FOR DEPRESSION AND PAIN TO PREDICT RELAPSE DURING BUPRENORPHINE AND SUBOXONE TREATMENT

Abstract

by Noel Adam Vest, Ph.D.
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Much of what is currently known regarding treatment for opioid use disorder has been derived from heroin users, with very few investigations into the unique processes that may be involved with individuals who primarily misuse prescription opioids. Relapse is common in treatment for opioid use disorder, making the parallel processes related to relapse during treatment critical for examination. Pain and depression often co-occur in substance use disorder treatment, including opioid substitution treatments. Advanced statistical analyses that can simultaneously model these two conditions may lead to targeted clinical interventions. The objective of this dissertation was to utilize a discrete survival analysis with a growth mixture model to test time to prescription opioid relapse, predicted by parallel growth trajectories of depression and pain, in a clinical sample of patients in buprenorphine/naloxone treatment for primary prescription opioid use disorder. The latent class analysis characterized heterogeneity among patients (n=359) in the Prescription Opioid Addiction Study, a Clinical Trials Network project collected from 2006-2009. The results from this secondary analysis suggested that a 4-class solution was the most
parsimonious based on global fit indices and clinical relevance. In order of class size, the 4 classes identified were: 1) typical treatment, 2) high depression and moderate pain, 3) high pain, and 4) low treatment motivation. Odds ratios for time-to-first use indicated no statistically significant difference in relapse between the high pain and the high depression classes, but all other classes differed significantly. These results emphasize the need to monitor the influence of pain and depression during stabilization on buprenorphine and naloxone. Future work may identify appropriate interventions that can be introduced to extend time-to-first prescription opioid use among patients in this clinical population.
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Dedication

To my wife…
CHAPTER ONE: INTRODUCTION

Recently, a national public health emergency was declared regarding the current opioid crisis (Christie et al., 2017). The introduction of the HEAL (Helping to End Addiction Long-term) initiative, a collaborative effort headed by the NIH aimed at combating some of the harm caused by addiction to opioids, will earmark the necessary funds to treat this life-threatening disease. The devastation caused by addiction to opioids has threatened all communities across our nation and resulted in a serious public health problem (Kolodny et al., 2015). Opioid use and misuse is a multifaceted problem that will take a concerted effort to from many different stakeholders (Compton, Jones, & Baldwin, 2016; Hser et al., 2017; Ling, 2017). Despite some recent advancements in treatment of opioid use disorder, many questions remain unanswered, especially regarding prescription opioid use specifically, and its treatment. The significance of this dissertation project is the application of advanced statistical modeling to determine critical time-points during treatment when appropriate interventions can be given to prevent relapse, enhance treatment success, and improve patient outcomes.

1.1 Prescription Opioid Public Health Crisis

The most recent opioid addiction epidemic is just one of the many faced by our nation over the years. We have witnessed past opioid crises when opium dens began opening in the 1700’s, among soldiers after the civil war, and at the turn of the 19th century when there were nearly 50,000 products available over the counter that contained opioids (Kolodny et al., 2015). Over the last century, and even more recently, the availability of opioids has been subject to a push and pull of policy and legislation to try and curb abuse and reduce overdose deaths (Clarke, Skoufalos, & Scranton, 2016; Vadivelu, Kai, Kodumudi, Sramcik, & Kaye, 2018). The most recent opioid crisis can be traced to a controversial article, known as the Portnoy paper, which
was published in 1986 (Portenoy & Foley, 1986). In this case study of 38 participants, Portenoy and Foley (1986) falsely reported that long-term prescription opioid therapies (commonly referred to as pain killers and analgesics) for non-cancer patients were relatively safe. Before this paper was published, opioids were most often prescribed for malignant cancer pain with very few patients receiving them for other chronic pain conditions (Kolodny et al., 2015). After the Portnoy paper, and the improper assurance that the risk for addiction among those prescribed opioids was minimal, the use and misuse of opioids skyrocketed (Brady, McCauley, & Back, 2016). As a result, opioid drugs were commonly prescribed for acute and chronic pain conditions. In fact, the 1990’s was an era when doctors were emboldened to treat pain as the “5th vital sign” in patients, which led to policies that liberalized the use of prescription opioids (Tompkins, Hobelmann, & Compton, 2017). These policies have culminated in the current opioid epidemic, which encompasses one of the biggest public health concerns facing our nation (Jones et al., 2018).

Not all patients who are prescribed opioids becomes dependent on their reinforcing properties. In fact, just a small percentage of individuals who are prescribed opioid analgesics go on to meet diagnostic criteria for opioid use disorder (Han, Compton, Jones, & Cai, 2015). Thus, problems generally tend to occur when genetic predisposition for opioid use disorder (Kreek et al., 2005) meets a large amount of environmental availability (Atluri & Manchikantl, 2014; Fortuna, Robbins, Caiola, Joynt, & Halterman, 2010). Thus, identification of persons vulnerable to the reinforcing effects before, during, and after treatment for prescription opioid use disorder may represent an important step in combating the nationwide opioid problem.

Recently, the development of problems related to prescription opioid use have become a major concern that has resulted in higher rates of fatal overdoses (Hedegaard, Warner, Ph, &
Miniño, 2017) and prevalence of prescription opioid use disorder nationwide (Han et al., 2015; Jones, Mack, & Paulozzi, 2013; Rudd, Aleshire, Zibbell, & Gladden, 2016). According to Wu, Zhu, and Swartz, (2016), among persons with opioid use disorder (OUD), 81.9% claim use of prescription opioids only, with only 9.7% specific to use of heroin and 8.4% claiming OUD of both substances simultaneously. Despite the higher number of patients nationwide who report prescription opioid use only, much of what is currently known regarding opioid use disorder is specific to heroin use, with very few studies exploring whether those findings generalize to primary users of prescription opioids (Monwell et al., 2016). This is especially concerning with regards to treatment, as the pathway into and out of active addiction for individuals misusing prescription opioids appears to be drastically different than individuals who report primary use of heroin (Hser et al., 2017). The rise in the use and misuse of prescription opioids has made it necessary for researchers to examine the harmful effects specific to the drug. Thus, I am interested in the unique processes among primary prescription opioid use disorder patients for this project.

1.2 Treatment for Primary Prescription Opioid Use Disorder is Not Well Understood

Much of what is currently known about opioid pharmacotherapy has been elucidated from studies on heroin use and methadone, with less research specific to prescription opioid use and other opioid pharmacotherapies. With the advent of methadone in the 1960’s, pharmacotherapy for opioid addiction has been an important part of the treatment of opioid use disorder (Amato et al., 2005; Bell, 2012; Veilleux, Colvin, Anderson, York, & Heinz, 2010). Opioid substitution therapy (OST) targets the withdrawal/negative affect stage in the opponent process paradigm (Bell, 2012). The avoidance of withdrawal allows those undergoing OST to focus on the rewarding aspects of daily life rather than spend their time in a constant search for,
and using, opioid drugs. Along with methadone, buprenorphine and naloxone (BUP+N) treatment is a common OST for individuals attempting to discontinue harmful use of opioid drugs (Veilleux et al., 2010). Although methadone is commonly referred to as the “gold standard” among pharmacotherapies (Mattick et al., 2014), BUP+N has been found to increase treatment retention and improve outcomes for those with opioid use disorder (Kolodny et al., 2015). Some additional benefits of BUP+N treatment include: 1) buprenorphine is a partial agonist with high affinity for the mu-opioid receptor, which allows for a ceiling effect and results in less respiratory depression which, in turn, inhibits the risk for overdose (Bell, 2014), 2) prescriptions can be given for up to 30 days which make it preferable to patients who live in rural areas or those that would have problems traveling to a methadone clinic due to family obligations or a job, and 3) it can be taken as a sublingual or a tablet which again allows for use away from the doctor’s office (Connery, 2015). Lastly, because the medication offers increased autonomy and can be taken away from the doctor’s office, BUP+N may be preferable for individuals entering OST for primary prescription opioid use disorder.

Individuals in treatment for opioid use disorder often relapse early in treatment (Stone, Carroll, Rich, & Green, 2018). Tuten and colleagues (2012) found that 50% of individuals in treatment for opioid use disorder relapsed within one month. Likewise, Marcovitz, McHugh, Volpe, Votaw, and Connery (2016) examined 202 patients in BUP+N treatment and found, that among the 23 early treatment drop-outs, over 53% had relapsed on opioids in the first month. This suggests that opioid relapse is a strong predictor of treatment retention for individuals with opioid use disorder. Further, that treatment retention is heavily influenced by relapse in the first 30 days. In a study of privately insured adults, Manhapra, Agbese, Leslie, and Rosenheck (2018) found that for each month of treatment enrollment, the risk for patients discontinuing their
treatment went down by 10%. Treatment completion has also been shown to be related to better long-term outcomes (Gossop, Stewart, Browne, & Marsden, 2002). These findings suggest that relapse is common in treatment for opioid use disorder and can further influence treatment retention, as well as other long-term outcomes. While these findings are important, they do not report on the processes specific to treatment retention for prescription opioid use, or how the treatment process may vary from one individual to the next. Despite evidence suggesting that relapse (or lack of relapse) is an important factor in rates of treatment retention, very little is known about what mechanisms may predict relapse, specifically among individuals with primary prescription opioid use disorder. Thus, a better understanding of processes that may be influencing relapse, and further, whether homogeneous ‘sub-groups’ in treatment may exist, can offer important insight and an improvement in services for patients receiving BUP+N medication. Two conditions which may contribute to relapse among patients in BUP+N treatment are pain and depression.

1.3 Pain and Depression as Risk Factors

Pain and depression are known to co-occur (Bair, Robinson, Katon, & Kroenke, 2003; IsHak et al., 2018) and are often studied in relation to substance use and related problems (Davis, Uezato, Newell, & Frazier, 2008; Michna et al., 2004). In studies examining prescription opioid use among individuals who report pain and depression, the evidence suggests that both conditions contribute to the misuse of prescription opioids. For example, Clark, Cao, and Krause (2017) found that depression was a predictor of prescription medication misuse among 2,522 healthcare enrollees who had been diagnosed with a spinal cord injury in the past year. Additionally, Banta-Green, Merrill, Doyle, Boudreau, and Calsyn (2009) employed a latent class analysis to identify a typical class, an addictive behaviors class, and pain dysfunction class
among individuals in treatment for chronic pain. The pain dysfunction class reported significantly higher pain interference and mental health conditions, including depressive like characteristics. Not surprisingly, the non-typical classes were prescribed opioids at three times the rate of the typical class (Banta-Green et al., 2009). However, despite the documented relationship of depression and pain in previous research among high-risk populations, there is a relative paucity in studies attempting to elucidate how these conditions may influence success in BUP+N treatment.

Pain plays a central role in most of the prescriptions written for pharmaceutical opioids in the United States (Savage, Kirsh, & Passik, 2008; Tsui et al., 2010). As a result, many patients with a history of using opioids also report high levels of pain (Sheu et al., 2008; Speed, Parekh, Coe, & Antoine, 2018). Specific to prescription opioid use, 62% of persons with prescription opioid use disorder report current pain as opposed to just 12% of healthy controls (Barth, Maria, Lawson, Brady, & Back, 2014). This suggests that pain is common among individuals who use and misuse opioids.

Likewise, there is some evidence that pain may also influence treatment progress for individuals in BUP+N treatment (Barry et al., 2013; Griffin et al., 2016), but the available findings are mixed. For example, Potter et al. (2010) found that acute pain severity increased the likelihood of self-reported illicit opioid relapse for patients in BUP+N treatment. They also found that, at 15-day post treatment follow-up, those who reported more pain in the previous 4-weeks were more likely to report a greater number of days using illicit opioids (Potter et al., 2010). Conversely, in a study of 82 participants in office-based buprenorphine treatment, Fox et al. (2012) found that pain was not a significant predictor of treatment retention or increased opioid use after 6 months of treatment. These finding suggest that pain is prevalent in BUP+N
treatment and that it may influence opioid relapse; however, clearly more research is needed. Furthermore, none of the previous research has documented how pain may change over the course of BUP+N treatment. It is true that some experts have called for focused efforts to better understand concurrent pain in the treatment for prescription opioid use disorder (McHugh, Nielsen, & Weiss, 2015).

Another factor that may be implicated in relapse is depression. Depression shows a high co-occurrence among individuals with past year opioid use disorder, with rates as high as 28.7% in the general public (Wu, Zhu, & Swartz, 2016). Depression has been shown to decrease over time among individuals in BUP+N treatment (Dean, Bell, Christie, & Mattick, 2004), but much more research is needed to determine when and how this reduction occurs over time, and further, how depression may influence relapse. This is especially important because depression has been shown to be a strong predictor of overdose among individuals who use substances (Bartoli et al., 2014; Tobin & Latkin, 2003).

Examination of how the combination of depression and pain may influence relapse is also needed, especially given that depression and pain often co-occur (Bair et al., 2003; Pilowsky & Bassett, 1982). However, despite a wealth of evidence documenting depression-pain comorbidity, studies examining the cooccurrence of depression and pain in BUP+N treatment have been scarce. After a thorough search of existing literature, I was able to locate one study that examined the co-occurrence of pain and depression in BUP+N treatment. The researchers examined 328 participates in primary care from 2012 to 2013 (Stein et al., 2015). The BUP+N patients were divided into three groups; acute but not chronic pain (n = 71), mild chronic pain (n = 51), and moderate to severe chronic pain (n = 103). A cross-sectional design which measured the study variables after at least one month of BUP+N treatment was implemented for all
participants. Not surprisingly, the moderate to severe and mild chronic pain groups experienced more depression than the acute group. However, the groups did not differ in their non-prescribed opioid use, but the chronic and mild groups were more likely to report self-administration of cannabis, cocaine, or alcohol to relieve pain (Stein et al., 2015). A drawback of this study was the cross-sectional design which limits the clinical relevance of the findings. Given the high co-occurrence of pain and depression (Nunes, Sullivan, & Levin, 2004), it would be essential to study them in a simultaneous fashion to better understand how they may affect treatment outcomes. Thus, the first Specific Aim of this dissertation project is to correctly identify the growth trajectories of depression and pain among individuals in BUP+N treatment.

1.4 Advanced Statistical Analyses to Inform Clinical Interventions and Research

Taken as a whole, the evidence thus far suggests relationships between pain, depression, and prescription opioid use; however, in order to fully explore how these variables may influence BUP+N treatment, advanced statistical procedures are necessary. Longitudinal modeling may assist in characterizing important timepoints where large fluctuations in depression and pain are influencing relapse among patients in BUP+N treatment. These critical time-points may lead to clinically relevant interventions than can be adapted and implemented in the treatment milieu. Thus, statistical procedures that can model two parallel change processes and their combined effect on relapse simultaneously may be invaluable to physicians and other health care professionals.

While previous researchers have examined depression, pain, and relapse among individuals who misuse prescription opioid medications in a longitudinal framework (Banta-Green et al., 2009; Clark et al., 2017), none have tested whether empirically derived ‘sub-groups’ exist within the overall pattern of change and outcome relatedness over time. The determination
of clinically meaningful sub-groups that represent patterns of depression and pain change over
time would also inform future treatment procedures that could be customized with the type of
patient in mind.

Latent class analyses (i.e., finite mixture modeling) have been implemented to explain
heterogeneous samples in developmental models across time (Nagin, 2005). The method of
growth mixture modeling paired with discrete survival analysis is an ideal choice for my research
question because it allows for the inclusion of the clinically relevant process of relapse.
Investigation of this type originated in cancer research (Ibrahim, Chu, & Chen, 2010) where
variables like immune response to a vaccine, genetic biomarkers, or other related health
outcomes could be evaluated in tandem with relapse-free survival rates. Research implementing
these methods has also been very useful within related areas of adult alcohol and drug use
disorder research (Howe, Cole, Mehta, & Kirk, 2012; Northrup et al., 2014). This is similar to
the change model presented in this project’s first aim, but it differs in one critical aspect which is
that this method searches for ‘clusters’ of similar individual trajectories of change and lumps
them into (potentially) clinically meaningful groupings (Ibrahim, Chu, & Chen, 2010; Muthén &
Muthén, 2017; Anastasios, Tsiatis, & Davidian, 2004). This method of analysis will continue to
deepen our understanding of patient reports of pain/depression and relapse to prescription opioid
use for individuals receiving buprenorphine/naloxone treatment by identifying individual
difference classes that differentiate the treatment process. Thus, the second Specific Aim of this
dissertation project is to employ latent class analysis (LCA) to identify subgroups in the parallel
growth modeling of pain and depression, and their combined influence on time-to-first
use/relapse (survival) among patients in BUP+N treatment.
1.5 Capitalizing on Existing CTN Resources

The introduction of the Clinical Trials Network (CTN) by the National Institute on Drug Abuse (NIDA) in 1999 ushered in a sea change regarding the implementation of evidenced based practices as they relate to substance use disorders (National Institute on Drug Abuse [NIDA], 2010). Realizing that there was an unacceptable gap between research and practice, NIDA and its partners founded the CTN. The CTN currently consists of 13 node sites throughout the country, with the hope of reaching geographically diverse patient populations. The CTN aims to bring real-world interventions and treatments to culturally and ethnically diverse populations in a fast and effective manner. A couple of examples of how the CTN accomplishes these aims is the dissemination library and the data sharing portal (NIDA, 2010). The dissemination library is a comprehensive website where NIDA offers a multitude of free resources based on the findings of CTN studies to clinicians and other researchers. The data sharing portal offers an incredible resource for researchers interested in implementing innovative statistical techniques and analyses. This free data resource allows researchers to hone their skills, answer complex questions, and address knowledge gap areas in a timely and efficient manner.

The CTN represents a multi-million-dollar investment from the federal government to better understand substance use disorder prevention, treatment, and recovery. In order to fully capitalize on that investment, the data sharing resource needs to be viewed as a cache of unlimited possibilities as it relates to statistical modeling and data analyses. Further, analyses of these data provide a unique opportunity to answer novel research questions at a substantially lowered cost. The existing CTN-0030 project, known as the Prescription Opioid Abuse Treatment Study (POATS; Weiss et al., 2010), provides the foundation for this secondary data analysis.
1.6 Prescription Opioid Treatment Study

The POATS project offers an excellent choice for this project because of the focus on primary use of prescription opioids among patients in BUP+N treatment. The status quo as it relates to BUP+N treatment, including POATS, has largely been to focus on abstinence at end of treatment, single outcomes (e.g., percent of opioid-negative urinalyses) as the primary outcome indicator of interest (Weiss et al., 2011). Utilizing the longitudinal nature of the data that’s inherent in clinical trials increases statistical power. As a result, this allows researchers to look at change over time, and identify individuals that are at highest risk for relapse during treatment. While end-point analyses are necessary and clinically important, more sophisticated analyses allow us to determine when treatment worked for specific patients, when relapse occurred, and what predicted change in use over time or time to relapse. This allows researchers, and clinicians, the ability to determine critical time-points when additional treatment or specific interventions could be implemented to enhance overall BUP+N treatment success. Having access to cutting edge analytic techniques along with real data examples, like the POATS, could significantly improve treatment protocols, and in doing so, improve public health.

Concerning prescription opioid users specifically, the primary outcome of the POATS was an evaluation of supplemental psychosocial intervention in the BUP+N treatment (see Wiess, 2011). Unlike what has been found in previous methadone treatment (Mclellan, Arndt, Metzger, Woody, & O’Brlen, 1993), and specific to the use of prescription opioid use disorder in the POATS project, Weiss et al. (2011) found that weekly psychosocial interventions did not show improvement in overall treatment retention or a decrease in illicit opioids use among patients. Further, the influence of chronic pain or higher addiction severity scores did not impact these results. However, the psychosocial intervention did improve treatment outcomes for a
subset of individuals who had ever used heroin (Weiss, 2014). This suggests that prescription opioid users appear to be heterogeneous group and a more personalized care approach may be needed. It also suggests that more research is needed identifying subgroups of patients and specific trajectories over the course of treatment to understand the individual difference factors and trajectories involved in relapse in a more nuanced way that recognizes these individual differences and how they may influence the treatment process.

1.7 Summary and Project Aims

My overall objective of this project is to utilize the longitudinal nature of the data in the CTN-0030 POATS trial to implement advanced statistical techniques to investigate questions regarding the impact of depression and pain, and how these two conditions may impact relapse among individuals in treatment for primary prescription opioid use disorder. Specifically, I am interested in identifying homogeneous patient sub-groups based upon the combined factors of pain and depression. The significance of this study is its potential to determine critical time-points when additional treatment or services can be given, along with individual difference factors that contribute to these trajectories, to enhance overall opioid treatment success through these Specific Aims:

Specific Aim 1 is to correctly identify the simultaneous growth trajectories of depression and pain among individuals in BUP+N treatment.

Specific Aim 2 is to employ latent class analysis (LCA) to identify subgroups in the parallel modeling of pain and depression, and their combined influence on relapse, or time to first use (survival), among patients in BUP+N treatment.
The premise for Specific Aim 1 is that important parallel individual processes (i.e., depression and pain trajectories) are not well understood, specifically as they relate to individuals in BUP+N treatment. The premise for Specific Aim 2 is that latent class analysis of longitudinal data may provide better explanatory power as it relates to heterogeneous treatment outcomes for relapse and offer novel targets for treatment intervention because of the ability to determine clinically relevant subgroups based on constructs of interest (pain and depression).
CHAPTER TWO: METHODOLOGY

This was a secondary analysis of the NIDA CTN-0030 publicly available data set (NCT00316277) and was collected from 2006-2009. There have been many publications that have previously detailed the design and implementation of the Prescription Opioid Abuse Treatment Study (McHugh et al., 2013; Potter et al., 2010; Weiss et al., 2010; Weiss & Rao, 2017). I will briefly describe the details as they pertain specifically to this dissertation project. However, for a detailed description of the study and the primary findings please refer to Weiss and colleagues (2011).

2.1 Participants and Study Design

The study was completed in two consecutive phases. In phase 1 of the study, 3,691 patients were originally screened for study enrollment and 653 participants were randomized to two conditions. In the control condition, participants received standard opioid substitution treatment with BUP+N, and in the psychosocial treatment condition the participants received BUP+N with the addition of opioid dependence psychosocial counseling. The psychosocial treatment group attended twice-weekly individual sessions in which treatment was based on the *Manual for EMM of Opioid Dependence* (Pantalon et al., 1999). The researchers implemented a 2-week BUP+N stabilization period and then 2-week rapid titration off BUP+N and then up to a 8-week follow-up period. Only 6 percent of the 653 participants were successful in phase 1, and the unsuccessful patients were automatically transitioned to phase 2. In phase 2 of the study, which was used for the present project, 360 participants were enrolled, and the schedule included a 12-week stabilization on BUP+N, a 4-week detoxification, and an 8-week follow-up. Similarly, participants were randomized in to a BUP+N group and a BUP+N with counseling group. Because past research has found that individuals in treatment for opioid use disorder often
relapse within the first few weeks of treatment (Tuten et al., 2012), and that the BUP+N stabilization period is vital to patient success in BUP+N treatment for individuals that misuse prescription opioids specifically (Sigmon et al., 2013), I focused only on the 12-week BUP+N stabilization period of phase 2. One participant had no scores across all study variables, as such, the final number of participants was 359.

POATS primary hypothesis was that the BUP+N treatment group with psychosocial counseling would demonstrate greater treatment success that the BUP+N group that received no psychosocial counseling (Weiss et al., 2011). Treatment success was defined as abstaining from opioids in the final week of the study (week 12) and at least 2 of the previous 3 weeks of treatment. Urinalysis was implemented to confirm self-reported abstinence. Missing urinalysis were considered positive for the primary outcome. Consequently, the psychosocial counseling was found to have no effect, so the treatment arms were collapsed into one data set for the purposes of this dissertation project.

2.2 Procedures

POATS participants were recruited from 10 CTN node sites across the country (Weiss et al., 2010). Locations included: Bellevue Hospital Center (New York, NY), McLean Hospital (Belmont, MA), San Francisco General Hospital (San Francisco, CA), UCLA Integrated Substance Abuse Programs (Los Angeles, CA), St. Luke's Roosevelt Hospital (New York, NY) Long Island Jewish Medical Center-Addiction Recovery Services (Glen Oaks, NY), East Indiana Treatment Center (Lawrenceburg, IN), ADAPT, Inc. (Roseburg, OR), Chestnut Ridge Hospital (Morgantown, WV), Behavioral Health Service of Pickens County (Pickens, SC), and Providence Behavioral Health Services (Everett, WA). The node site at McLean Hospital served
as the project hub and provided all support services for study protocols. Data management, safety monitoring, and quality assurance were monitored and approved by NIDA.

Some of the inclusion criteria for the study included 1) had the ability to give informed consent, 2) older than 18 years of age, 3) permission of primary care physician, 4) met criteria for opioid use disorder, 5) if pregnant then was willing to use birth control through study, and 6) appeared to be free of major psychiatric issues. Some of the exclusion criteria included 1) having a high suicide risk in the past 30 days, 2) irregular liver functioning, 3) looming surgical procedure necessary, 4) pregnancy, 5) past 30-day participation in methadone or buprenorphine treatment, 6) other substance use disorder treatment or any substance use disorder requiring medical attention, 7) allergy to study medications, ant 8) legal or other reason that would have prohibited patient ability to remain in the local area during the duration of the study (Weiss et al., 2010).

Methodological considerations concerning individuals with primary illicit use of prescription opioids were carefully weighed for the POATS project. Specifically, researchers wanted to achieve a balance regarding a study sample that would allow for generalizability of study results and inclusion of a distinct patient population (i.e., primary prescription opioid use disorder). For these reasons, special consideration was given to participants with previous use of heroin and those with a history of chronic pain. For heroin use, subjects were ineligible for the study if they had ever administered heroin by injection, had a previous diagnosis of heroin use disorder, or reported use of heroin on more than 4 occasions in the past month. Of the 653 individuals enrolled in phase 1, only 150 (23%) reported some heroin use previously. Pain was an excluding criterion for individuals with a major pain event in the past 6 months, individuals that could not obtain clearance from their primary care physician, and for individuals requiring
ongoing need for pain management with opioids. A total of 274 (42%) of the 653 individuals enrolled in phase 1 reported chronic pain. Randomization for the study was stratified by the presence of lifetime heroin use and the presence of chronic pain.

Participants received a weekly supply of BUP+N drug and were expected to dose one time daily for the duration of the study. A minimum dose of 8 mg and a maximum dose of 32 mg per day was adhered to for all patients. Over the 12-week stabilization study period, the patients were given two urinalyses to test for the presence of the prescribed pharmacotherapy to assure that BUP+N was being self-administered as prescribed. Lost or stolen BUP+N medication was not replaced.

2.3 Measures

Table 1 illustrates the summary statistics for all participants in the phase 2 stabilization stage of study. Demographics measured baseline levels of sex, age, race, education, marital status, and employment status. Also measured were overall treatment success in phase 2; as mentioned previously, treatment success was determined by whether the participant submitted negative (for prescription opioids) urinary drug screens for 3 of the final 4 study visits. Please see Table 2 for a timeline of study variables.

Depression measure

The Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) was implemented to measure presence and severity of depression. Specifically, the measure asks about changes in diet, motivation, sleep habits, and moods. The BDI has 21 items, scored on a 4-point scale, with higher numbers indicating with more severe symptoms of depression. The BDI
Table 1

Summary statistics for all study participants receiving buprenorphine and naloxone treatment in 12-week stabilization period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>58% (208)</td>
</tr>
<tr>
<td>Male</td>
<td>58% (208)</td>
</tr>
<tr>
<td>Female</td>
<td>42% (151)</td>
</tr>
<tr>
<td>Race</td>
<td>91% (325)</td>
</tr>
<tr>
<td>White</td>
<td>91% (325)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>No high school diploma</td>
<td>18% (64)</td>
</tr>
<tr>
<td>High school diploma complete</td>
<td>42% (150)</td>
</tr>
<tr>
<td>Above high school diploma</td>
<td>40% (145)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>27% (97)</td>
</tr>
<tr>
<td>Never married</td>
<td>50% (180)</td>
</tr>
<tr>
<td>Divorced/separated/other</td>
<td>23% (82)</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
</tr>
<tr>
<td>Full-time</td>
<td>60% (217)</td>
</tr>
<tr>
<td>Part-time</td>
<td>19% (67)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>14% (50)</td>
</tr>
<tr>
<td>Other</td>
<td>7% (25)</td>
</tr>
<tr>
<td>Phase 2 treatment success</td>
<td>49% (177)</td>
</tr>
</tbody>
</table>

Note: n = 359. Treatment success = 3 of 4 final urinalysis drug screens were negative for opioid use.

is a well validated measure with strong internal consistency and high discrimination between depressed and non-depressed individuals (Richter, Werner, Heerlein, Kraus, & Sauer, 1998). A total score was calculated by adding all indicators together, the possible range of scores was 0 to 63. Because this project examined change in depression across the treatment milieu, all four time points that were measured during the 12-week stabilization period were implemented in the study analyses.
Table 2

Timeline of study variables during BUP+N treatment for primary prescription opioid use disorder.

<table>
<thead>
<tr>
<th>Assessment/Variable of Interest</th>
<th>Base</th>
<th>1a</th>
<th>1b</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brief Pain Inventory</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine Drug Screen</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Note: X indicates that this urinary drug screen was measured in the main study but not included in these analyses.

Pain measure

Brief Pain Inventory (BPI; Cleeland & Ryan, 1994) is a 9-item scale measuring the intensity as well as the interference in daily activities of pain. For this dissertation project, only the pain intensity measure was used because we were primarily interested in quantifying the amount of current pain the participant was experiencing. Similar to the depression measure, the BPI was administered at 4 time points, about 1 month apart, during the 12-week stabilization period. The BPI measurement tool has been validated across many cultures and clinical populations (Cleeland & Ryan, 1994; Tan, Jensen, Thornby, & Shanti, 2004).

Drug use measure

Urine Drug Screen (UDS) was recorded for relapse (0 = negative, 1 = positive) of prescription analgesic opioids (only) on a weekly schedule during the buprenorphine stabilization treatment milieu. Because there was high variability in early the stabilization period urinalysis results, we did not include the first two urinalysis tests in our longitudinal models. Similar to the original POATS measure of treatment success, we considered any missing
urinalysis result to be positive for opioid use. Lastly, we were not concerned with self-reported use of opioids, opting to rely on the more stringent urinalysis confirmed measure of relapse.

2.4 Data Analyses

The demographic and class probabilities were analyzed using SPSS ver. 25 (SPSS Inc, Chicago, IL, USA). The latent growth curve model (Little, 2013) and latent class mixture model (Nagin, 2005) were analyzed using MPlus version 8.2 (Muthen & Muthen, 2018). Specific Aims 1 and 2 were tested in two separate model building procedures. In the first procedure, I employed latent growth curve model building techniques articulated in Little (2013) to determine the best fitting parallel longitudinal trajectories for the pain and depression measures across the four time points (Figure 1). In the second procedure, I employed discrete-time survival and latent growth mixture modeling to analyze changes in depression and pain trajectories, which predicted relapse (Figure 2).

Parallel latent growth curve model (Specific Aim 1)

Growth models allow researchers to model change in processes over time (McArdle & Epstein, 1987; Meredith & Tisak, 1990). For example, growth models can estimate where a group starts and how the change process develops over time (i.e., is it increasing or decreasing). Statistically, the move to a latent variable model is necessary in order to capture the change (Sterba, 2014). In the latent variable model, a researcher obtains two unobserved latent factors: the intercept and the slope. The intercept is the starting point (when time is 0) and the slope is the rate of change over time (the trajectory). Additionally, a non-linear constraint can be added to the models for quadratic term, which adds a new variable that is the squared value of the original data set (Sterba, 2014). Adding a cubic term or evaluating a piece-wise change model are additional model building techniques that can be implemented in latent growth models (Bollen &
Curran, 2006). These advanced models can be important for clinical evaluations because different stages of the treatment process can be examined. Latent growth curve modeling has become a very powerful statistical tool for modeling change trajectories in substance use disorder research because of the nature of the measurement and the high level of flexibility (Fleming, Mason, Mazza, Abbott, & Catalano, 2008; Needham, 2012; Wills, Sandy, Yaeger, Cleary, & Shinar, 2001).

A parallel latent growth curve model allows the modeling of two growth trajectories simultaneously across time (Duncan, Duncan, Strycker, Li, & Alpert, 1999; Little, 2013). For the purposes of this project, this means that by using a parallel latent growth model, I was able to evaluate two assessments (i.e., both pain and depression) across the BUP+N treatment milieu, in a simultaneous manner. Scores for monthly reports of pain and depression across the 12-week BUP+N stabilization period allowed for 4 equally spaced timepoints for each participant. This technique has become a common statistical tool to measure dual trajectories of change in SUD research (Fleming et al., 2008; Mamey et al., 2015; Worley et al., 2012).

Figure 1 illustrates a diagram of the parallel growth models for the Specific Aim 1 procedure. Model building techniques (Little, 2013) for the growth trajectories were conducted as follows:

**Fixed intercept model**: the “null model” estimates the starting value and common residual variance. The model assumes no change across scores (population mean) and no variability between scores.

**Random intercept model**: estimates the variability around the population mean.
Fixed intercept/fixed slope model: this model allows for no variability in the slope (rate of change) or the intercept (starting value). The addition of the linear slope allows for the evaluation of change across equal time points.

Random intercept/fixed slope model: this model allows for variability around the initial time point, but no variability in the rate of change across time.

Random intercept/random slope model: imposes no constraints on the slope or the starting value and allows for within person change across time. Can also restrict or add correlations of similar
parallel growth constructs. For example, the intercept for pain can be correlated with the intercept for depression.

**Test for quadratic and cubic slope:** this model explores the need for a quadratic and cubic growth factors in order to be certain that the final model selected is the best fitting model.

A solid understanding of this parallel growth model was necessary before I could move to the latent class analysis in the second part of this dissertation project. A thorough investigation of how the developmental processes for pain and depression were related over time informed the expectations regarding the latent class analysis of these dual trajectories.

The chi-square, comparative fit index (CFI), root mean square error of approximation (RMSEA), and standardized root mean square residual (SRMR), were employed to determine adequate model fit, where benchmarks greater than 0.95 and less than .05, respectively, indicate good global fit (West, Taylor, & Wu, 2012). The Bayesian Information Criteria (BIC) was also employed to determine the best fitting model. The intercepts in the models were set to 1 and the slopes for growth were set at 0 for the first measurement, 1 for the second, 2 for the third and 3 for the 4, for both pain and depression. Although I made additions to the model one at a time (depression then pain), for parsimony and brevity sake I reported the parallel additions and constraints together.

*Latent class analyses of parallel growth model and survival (Specific Aim 2)*

Figure 2 illustrates the statistical model implemented for Specific Aim 2. Latent class analysis (LCA; Muthén, 2002) is a statistical analysis procedure that can be implemented to classify participants into meaningful homogeneous subgroups. LCA is also referred to as Latent Transition Analysis and Growth Mixture Modeling; however, I will refer to the model as LCA to limit any confusion. Latent class membership is determined by response patterns evident in the
data, where each class shows a specific response profile. In clinical trials research this can be helpful because the procedure can lead to insight not offered by other statistical techniques (Nagin & Odgers, 2010). For example, LCA can be used to determine the most likely latent class membership for a set of individuals based upon diagnostic criteria. Briefly, the goal of LCA includes determining the number of relevant classes in the most parsimonious model so that the groups may be examined and interpreted in a meaningful way (Geiser, 2013). Lastly, class membership can be used to inform patient typology with regard to external variables; including age, sex, education level, and race/ethnicity (Grimm, Ram, & Estabrook, 2017).

Figure 2 illustrates the discrete-time survival latent growth mixture model. This LCA model utilized simultaneous analysis of parallel growth mixture modeling and discrete-time survival analysis\(^1\) to better understand how depression and pain impact relapse. The measurement model is similar to the model examined for Specific Aim 1; however, the clinically relevant process of relapse was added to address an important marker of treatment success in SUD research (Jackson & Janssen, 2018). Joint modeling of these processes was preferred because the results offer a more efficient and less biased estimate of the effect across time (Ibrahim et al., 2010; Tsiatis & Davidian, 2004). The model allowed testing of the homogeneity of sub-groups among the study participants based upon response patterns for pain, depression, and relapse to opioid analgesics.

**Determining patient typology**

The ideal number of latent classes is often determined by theoretical considerations regarding clinical relevance and prior research (Asparouhov & Muthen, 2014). Typically, the

\(^1\) Because the survival analysis was not directly comparable to the overall treatment success outcome in the original POATS trial, I regressed the discrete survival outcome on the treatment condition to assure that treatment did not have significant an overall effect on survival rates, \(b = 0.23 \pm 0.31, p = .46\).
Figure 2. Discrete-time survival and parallel latent growth mixture modeling. Dotted line ovals represent the potential quadratic and cubic functions across the time points. For ease of understanding, lines were not drawn to each indicator variable from the quadratic and cubic latent variables for intercept and slope. All intercepts set to 1.
multiclass solutions are compared statistically based upon overall model fit. The Bayesian Information Criteria (BIC) is a common comparison fit statistic used to characterize the number of classes in a dataset (Kass & Raftery, 1995). Along with BIC, I also examined entropy, Lo-Mendell-Rubin (LMR) likelihood ratio test, and overall interpretability of the solutions to determine the most parsimonious and clinically distinct model (Asparouhov & Muthen, 2014). Entropy is a measure of class membership likelihood that ranges from 0 to 1 (values closer to 1 are preferred); values above 0.80 indicate good class membership. The LMR test is a likelihood ratio test that offers a measure of the current mixture model (k) and a sample drawn with (k-1) one less latent class (Lo, Mendell, & Rubin, 2001). Models were fit for 1 through 10 latent class solutions. Missing data were handled with Full Information Maximum Likelihood, robust to data missing at random. To remain consistent with the main POATS design, we considered missed urinalyses as positive in the survival data. For each class solution, we allowed the model to estimate mean values for intercept, slope, quadratic, and cubic functions. We then examined the estimates and reset the non-significant values to zero in a revised model. The model proposed in Figure 2 allows for the estimation of growth parameters across unobserved subgroups using latent class trajectories and survival simultaneously.

Lastly, given the latent classes selected for patient typology, overall class inclusion was then calculated to evaluate frequency and percentage of basic demographic variables and treatment success (see Table 9). Because these values were used for general explanatory purposes of different patient types, tests of statistical differences between class selection groups were not performed.
CHAPTER THREE: RESULTS

3.1 Parallel Latent Growth Curve Model

The preliminary data results are displayed in Table 3. These results show the overall means, standard errors, and correlations of each of the time points in the buprenorphine stabilization treatment milieu. Overall, the means for both depression and pain appear to decrease incrementally from time one to time four, with a large decline initially and a smaller decrease from time 2 to 3 and time 3 to 4.

Table 3

Means, standard deviations, and bivariate correlations.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Beck Time 1</td>
<td>20.20 (13.19)</td>
<td>.48*</td>
<td>.46*</td>
<td>.36*</td>
<td>.26*</td>
<td>.12*</td>
<td>.11</td>
<td>.14*</td>
<td></td>
</tr>
<tr>
<td>2. Beck Time 2</td>
<td>10.22 (10.11)</td>
<td></td>
<td>.77*</td>
<td>.68*</td>
<td>.17*</td>
<td>.31*</td>
<td>.27*</td>
<td>.27*</td>
<td></td>
</tr>
<tr>
<td>3. Beck Time 3</td>
<td>9.22 (9.85)</td>
<td></td>
<td></td>
<td>.80*</td>
<td>.18*</td>
<td>.29*</td>
<td>.30*</td>
<td>.31*</td>
<td></td>
</tr>
<tr>
<td>4. Beck Time 4</td>
<td>8.51 (10.79)</td>
<td></td>
<td></td>
<td></td>
<td>.11*</td>
<td>.26*</td>
<td>.22*</td>
<td>.29*</td>
<td></td>
</tr>
<tr>
<td>5. Pain Intensity T1</td>
<td>11.86 (11.04)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.52*</td>
<td>.54*</td>
<td>.49*</td>
<td></td>
</tr>
<tr>
<td>6. Pain Intensity T2</td>
<td>7.33 (8.53)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.72*</td>
<td>.67*</td>
<td></td>
</tr>
<tr>
<td>7. Pain Intensity T3</td>
<td>6.66 (8.06)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.77*</td>
<td></td>
</tr>
<tr>
<td>8. Pain Intensity T4</td>
<td>6.02 (7.91)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. n = 359.
*p < .05

Next, parallel latent growth modeling was employed to examine the effect of two longitudinal processes simultaneously. Table 4 illustrates each of the incremental additions to the model. An intercept only model with residuals held equal was found to be a very poorly fitting model. This means that the constraint on equal residual variances did not hold and subsequent models released this constraint. It also made theoretical sense that only the correlations for intercepts (pain intercept with depression intercept) and slopes be included (the other correlations were non-significant). Figures 3-5 illustrate estimated means and actual means for models 4-6.
Table 4

*Summary of model fit indices.*

<table>
<thead>
<tr>
<th>Model Description</th>
<th>$\chi^2$</th>
<th>df</th>
<th>CFI</th>
<th>RMSEA</th>
<th>SRMR</th>
<th>BIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Intercept only w/ Equal Residuals</td>
<td>740.39</td>
<td>37</td>
<td>.09</td>
<td>.23</td>
<td>.21</td>
<td>18541</td>
</tr>
<tr>
<td>2. Intercept only Residuals Released</td>
<td>323.74</td>
<td>31</td>
<td>.62</td>
<td>.16</td>
<td>.22</td>
<td>17891</td>
</tr>
<tr>
<td>3. Added Slope to Model</td>
<td>195.39</td>
<td>26</td>
<td>.78</td>
<td>.14</td>
<td>.12</td>
<td>17745</td>
</tr>
<tr>
<td>4. Correlated Intercepts &amp; Slopes</td>
<td>191.70</td>
<td>26</td>
<td>.79</td>
<td>.13</td>
<td>.12</td>
<td>17745</td>
</tr>
<tr>
<td>5. Added Quadratic</td>
<td>77.04</td>
<td>24</td>
<td>.93</td>
<td>.08</td>
<td>.05</td>
<td>17625</td>
</tr>
<tr>
<td>6. Added Cubic</td>
<td>37.31</td>
<td>22</td>
<td>.98</td>
<td>.04</td>
<td>.04</td>
<td>17590</td>
</tr>
</tbody>
</table>

*Note.* $n = 359.$

from Table 4. The best fitting model, and therefore kept as the final model, was the model with both the quadratic growth and cubic growth functions. Because the estimated and actual means were nearly identical in the final model (see Figure 5), I concluded that this was the most parsimonious model and that a piecewise approach was not necessary.

![Figure 3. Estimated slope values and actual sample means for pain and depression for the correlated intercepts and slopes model. This corresponds with Model 4 in Table 2.](image)
Figure 4. Estimated slope values and actual sample means for pain and depression for the model with an added quadratic term. This corresponds with Model 5 in Table 2.

3.2 LCA of Parallel Latent Growth Model Predicting Survival Model

Model Selection

Displayed in Table 5 are the model fit indices for 1 through 10 latent classes. Examining BIC values, the 9-class model offered the best solution. However, when examining the classes there appears to be much overlap in the growth trajectories and survival probabilities for many of
Table 5

*Model fit indices and estimated class size for LCA and discrete survival analysis.*

<table>
<thead>
<tr>
<th>Model</th>
<th>AIC</th>
<th>BIC</th>
<th>Δ BIC</th>
<th>Class Size</th>
<th>Entropy</th>
<th>LMR LRT</th>
<th>Par.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Class</td>
<td>22265</td>
<td>22374</td>
<td></td>
<td>100%</td>
<td>0.89</td>
<td>753.62***</td>
<td>28</td>
</tr>
<tr>
<td>2 Class</td>
<td>21518</td>
<td>21666</td>
<td>708</td>
<td>78%, 22%</td>
<td>0.90</td>
<td>731.71***</td>
<td>33</td>
</tr>
<tr>
<td>2 Class Revised</td>
<td>21002</td>
<td>21169</td>
<td>477</td>
<td>62%, 24%, 14%</td>
<td>0.89</td>
<td>509.11**</td>
<td>43</td>
</tr>
<tr>
<td>3 Class</td>
<td>21007</td>
<td>21159</td>
<td>10</td>
<td>62%, 23%, 15%</td>
<td>0.89</td>
<td>502.05**</td>
<td>39</td>
</tr>
<tr>
<td>4 Class</td>
<td>20795</td>
<td>20986</td>
<td>173</td>
<td>58%, 21%, 11%, 10%</td>
<td>0.90</td>
<td>205.07</td>
<td>49</td>
</tr>
<tr>
<td><strong>4 Class Revised</strong></td>
<td><strong>20802</strong></td>
<td><strong>20976</strong></td>
<td><strong>10</strong></td>
<td><strong>58%, 21%, 11%, 10%</strong></td>
<td><strong>0.90</strong></td>
<td><strong>203.92</strong></td>
<td><strong>45</strong></td>
</tr>
<tr>
<td>5 Class</td>
<td>20586</td>
<td>20799</td>
<td>177</td>
<td>51%, 17%, 12%, 10%, 10%</td>
<td>0.89</td>
<td>212.27</td>
<td>55</td>
</tr>
<tr>
<td>5 Class Revised</td>
<td>20606</td>
<td>20800</td>
<td>-1</td>
<td>57%, 18%, 11%, 9%, 5%</td>
<td>0.90</td>
<td>199.34</td>
<td>50</td>
</tr>
<tr>
<td>6 Class</td>
<td>20420</td>
<td>20653</td>
<td>147</td>
<td>46%, 16%, 10%, 10%, 9%, 9%</td>
<td>0.88</td>
<td>158.94</td>
<td>60</td>
</tr>
<tr>
<td>6 Class Revised</td>
<td>20440</td>
<td>20654</td>
<td>-1</td>
<td>48%, 13%, 10%, 10%, 10%, 9%</td>
<td>0.88</td>
<td>170.72</td>
<td>55</td>
</tr>
<tr>
<td>7 Class</td>
<td>20298</td>
<td>20546</td>
<td>208</td>
<td>44%, 16%, 10%, 10%, 9%, 8%, 3%</td>
<td>0.88</td>
<td>106.98</td>
<td>64</td>
</tr>
<tr>
<td>8 Class</td>
<td>20254</td>
<td>20530</td>
<td>16</td>
<td>41, 15, 12, 9, 9, 9, 3, 2</td>
<td>0.88</td>
<td>47.82</td>
<td>71</td>
</tr>
<tr>
<td>9 Class</td>
<td>20180</td>
<td>20495†</td>
<td>35</td>
<td>38, 18, 10, 8, 7, 6, 5, 4, 3</td>
<td>0.86</td>
<td>77.03</td>
<td>81</td>
</tr>
<tr>
<td>10 Class</td>
<td>20163</td>
<td>20517</td>
<td>-22</td>
<td>41, 11, 8, 8, 7, 6, 6, 6, 4, 2</td>
<td>0.87</td>
<td>54.72</td>
<td>91</td>
</tr>
</tbody>
</table>

*Note:* LCA = Latent Class Analysis, BIC = Bayesian Information Criterion, AIC = Akaike Information Criterion, LMR LRT = Lo-Mendel-Rubin Likelihood Ratio Test, Par. = Parameters in model. † is best fit according to BIC. Bold line indicates the model chosen as the overall best fitting class.

The classes. Additionally, 6 of the classes had less than 35 participants and 3 classes had less than 20. This diminished the clinical relevance the sub-groups and made it nearly impossible to interpret the 9-class model. I subsequently worked from larger (k = 8) to smaller class sizes to compare model fit. I also considered the graphs for depression, pain, and time to relapse illustrated in Figure 6. Taking into account the BIC, LMR, and entropy indicators, in addition to the clinical relevance of the subgroups, I settled on the 4-class revised model as the most parsimonious. Entropy was acceptable at 0.90, the LMR-LRT was non-significant, and the estimated classes were of acceptable size and clinically relevant. The 3-class solution indicated a better LMR likelihood ratio score, but the model eliminated a clinically relevant high pain group.
that was evident in the 4-class model. Likewise, the 5-class solution offered decent model fit, but
the inclusion of a group with fewer than 20 people (less than 5% of sample) failed to justify the
clinical interpretability of that class. Table 6 shows the most likely class membership counts for
classes 1 through 4. Average latent class probabilities for the 4-class model were high, between
91.7% and 95.8%, suggesting that model assigned the individual to the most likely class with a
high degree of certainty (see Table 7).

Table 7

*Average latent class probabilities for most likely latent class membership (row) by latent
class (column).*
**Defining the Classes**

As mentioned above, the 4-class model was determined to be most appropriate. A graphical presentation of the four classes across the treatment milieu is available in Figure 6. In Table 8, a test of the significant differences between classes based on survival odds ratios is reported. Lastly, Table 9 shows the most likely class membership for key demographic variables of the sample. Consequently, the following classes were defined by the information available in Figure 6, Table 8, and Table 9.

**Table 8**

*Odds ratio of survival (no opioid use).*

<table>
<thead>
<tr>
<th>Class Comparison</th>
<th>OR</th>
<th>z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1 to Class 2</td>
<td>0.15</td>
<td>-12.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Class 1 to Class 3</td>
<td>0.32</td>
<td>-6.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Class 1 to Class 4</td>
<td>0.03</td>
<td>-30.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Class 2 to Class 3</td>
<td>2.11</td>
<td>1.08</td>
<td>0.277</td>
</tr>
<tr>
<td>Class 2 to Class 4</td>
<td>0.20</td>
<td>-2.96</td>
<td>0.003</td>
</tr>
<tr>
<td>Class 3 to Class 4</td>
<td>0.09</td>
<td>-8.14</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Class 1** represents the typical patient group (red lines in Figure 6). This was the largest proportion of our sample with 214 participants (59.6%). The class should be noted for its survival probability, as it was the most successful in terms of fewest prescription opioid relapses. This was consistent with the overall trend of this group to finish phase 2 successfully (59% finished successfully). This class showed a similar trajectory for both pain and depression. The class showed moderate levels of both pain and depression at baseline, large decreases from
Figure 6. Simultaneous trajectories of pain, depression and relapse (survival) across the 12-week treatment milieu.
baseline to week 4, and then a stable and slight decrease from week 4 to week 12. This makes sense, as this was the general trend in slope for the overall parallel latent growth models for pain and depression reported earlier (see Figure 5). Class 1 differed significantly in odds of survival from all other classes.

**Class 2** represents a chronic/high pain class (blue lines in Figure 6). The class is noted for extremely high and stable pain (chronic pain), and a moderate baseline with stable and decreasing depression from baseline through week 8 and then a small uptick in depression from week 8 to week 12. The trajectory of depression among members of this class was very similar in shape and magnitude to the highly successful group in class 1. The survival rate for this group was relatively low as nearly every class individual had relapsed by week 13. Approximately 40 participants (11.1%) in the sample were representative of this class. Class 2 and 3 did not differ significantly in their odds of survival. Class 2 differed significantly in odds of survival from classes 1 and 4 in their odds of survival.

**Class 3** was classified as a high depression group (green lines in Figure 6). This group showed a decrease in depression from baseline to week 8 and then a small increase in depression from week 8 to week 12. The individuals in this class reported moderate baseline pain intensity that was consistent throughout the treatment milieu. This class was at moderate risk of relapse and did not differ significantly from class 2 in odds of survival (the class did differ significantly from all other classes). Approximately 71 participants (19.7%) in the sample were most likely to be classified to this group. Nearly half (48%) of the individuals in this class completed Phase 2 successfully. The class was noted for its high percentage (67%) of female participants. This is consistent with literature showing that women are more likely to enter into treatment with higher rates of mental illness than men (Chen et al., 2011).
Class 4 was classified as a low treatment motivation group (black lines in Figure 6). The individuals in this class exhibited very little pain at baseline which remained consistent across time. The class reported low baseline depression and the trajectory decreased slightly across the buprenorphine stabilization period. Everyone in this class had relapsed by week 6 of the trial. Approximately 34 people (9.4%) in the sample were representative of this class. This was the smallest class in our sample. As would be expected, only 2 people in this class were successful in phase 2 of the study. The class differed significantly in odds of survival from all other classes. Of note, a large percentage (37%) of individuals reported that they had tried heroin previously (other groups reported 21% - 31%). The mean age was lowest for this class at 30.58 years old.

Table 9

Class membership for select demographic variables.

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Class 1 Typical</th>
<th>Class 2 Chronic/High Pain</th>
<th>Class 3 High Depression</th>
<th>Class 4 Low Motivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Individuals in Class</td>
<td>214</td>
<td>40</td>
<td>71</td>
<td>34</td>
</tr>
<tr>
<td>Male Gender %</td>
<td>137 (64%)</td>
<td>23 (58%)</td>
<td>23 (33%)</td>
<td>25 (73%)</td>
</tr>
<tr>
<td>Age Mean (SD)</td>
<td>32.01 (9.46)</td>
<td>35.14 (9.76)</td>
<td>33.75 (10.34)</td>
<td>30.58 (8.80)</td>
</tr>
<tr>
<td>White Race %</td>
<td>197 (92%)</td>
<td>33 (83%)</td>
<td>65 (92%)</td>
<td>30 (88%)</td>
</tr>
<tr>
<td>Above HS Education %</td>
<td>84 (39%)</td>
<td>30 (75%)</td>
<td>32 (46%)</td>
<td>25 (72%)</td>
</tr>
<tr>
<td>Employed Full-Time %</td>
<td>140 (65%)</td>
<td>21 (53%)</td>
<td>34 (49%)</td>
<td>22 (63%)</td>
</tr>
<tr>
<td>Ever Used Heroin %</td>
<td>48 (22%)</td>
<td>10 (25%)</td>
<td>22 (31%)</td>
<td>13 (37%)</td>
</tr>
<tr>
<td>Phase 2 Treatment Success %</td>
<td>127 (59%)</td>
<td>14 (35%)</td>
<td>34 (48%)</td>
<td>2 (6%)</td>
</tr>
</tbody>
</table>

*Note: These data were generated for explanatory purposes only. HS = High School; Treatment success = 3 of 4 final urinalysis drug screens were negative for opioid use.*
CHAPTER FOUR: DISCUSSION

This dissertation project makes a significant contribution to the literature by yielding four important insights into BUP+N treatment. First, I identified the most common trajectory for pain and depression across a 12-week BUP+N stabilization treatment. Second, I employed latent class analysis to identify a four-class solution for the simultaneous processes of pain, depression, and relapse in BUP+N treatment. Third, individuals were successfully parsed into clusters which included a 1) typical treatment cluster, 2) a high depression and moderate pain cluster, 3) high pain and low depression cluster, and 4) a low motivation cluster. The four clusters had unique patterns across pain, depression, and relapse which increases the clinical utility of these findings. Fourth, three of the four groups differed significantly from each other in regard to their propensity to relapse (i.e., odds ratios in time to first use). This suggests that relapse was common among patients and that each class appeared to be relapsing for different reasons. Lastly, I characterized the key demographic variables for each cluster to offer a highly detailed description of group membership. The differences between classes validates the importance of considering co-occurring pain and depression as a fundamental part of the clinical profile of individuals entering into BUP+N treatment. These results also point to the relevance of modeling time to first use as a fundamental part of the BUP+N treatment milieu. To my knowledge, this is the first study to examine the dual change trajectories of pain and depression and their influence on relapse for individuals with primary prescription opioid use disorder in BUP+N treatment.

The use of parallel growth trajectories allowed for the simultaneous evaluation of two conditions that often co-occur in BUP+N treatment. The methodological approach and data analyses employed in this study offer new insights that can’t be examined when studying these phenomenon independently. This technique can provide clinicians and researchers the necessary
tools to better understand how these constructs are related. Likewise, the implementation of LCA to segment the data into trajectory classes offers a powerful statistical tool for summarizing large amounts of data into a format that is easy to understand. In an applied context, clinicians may now better understand how depression and pain can influence relapse rates, which may inform treatment interventions specific to the characteristics of the patient involved.

As to the specific results for the parallel latent growth model of pain and depression among patients in 12-week stabilization BUP+N treatment, the best fitting model was a slope with quadratic and cubic function for both processes (pain and depression). The results suggest that for both depression and pain, for a large majority of the patients, there appears to be a steep overall drop from baseline to the 4th week, followed by a more steady and gradual decline from the 4th to the 8th week, as well as from the 8th to 12th week. These trajectories of pain and depression across the stabilization period were inline with expectations as buprenorphine has been shown to decrease both pain (Daitch et al., 2012; Schmidt-Hansen, Bromham, Taubert, & Arnold, 2013) and depression (Bodkin, Zornberg, Lukas, & Cole, 1995) in clinical studies. These results were also consistent with our current understanding of the co-occurrence of pain and depression (Nunes et al., 2004).

The novelty of this project lies squarely in the results for specific aim 2. The simultaneous modeling of three clinically distinct, yet relevant, processes across the BUP+N treatment program allowed for specific conclusions regarding the progress of each class. Although we looked explicitly at the dual processes of pain and depression in this analysis, the technique can easily be transferred to other applications where two change processes occur simultaneously and directly effect a discrete survival outcome of interest. Likewise, while we were interested in relapse (time to first prescription opioid use), other statisticians may model recidivism, other
types of drug relapse, or onset of a disease state, for a more rich understanding of the longitudinal nature of these processes. The LCA results offer a glimpse into why some individuals may be successful across the treatment milieu and, consequently, where clinicians may want to increase services in a patient specific manner based upon reports of pain or depression. Additionally, the LCA offered a four-class solution which is consistent with other LCA studies examining persons who use/misuse prescription opioids (Green, Black, Serrano, Budman, & Butler, 2011; Northrup et al., 2014). Specifically, Green et al. (2011) identified a prescribed misusers group, a use as prescribed group, a medically healthy abuser group, and an illicit use group in a national sample of adults entering into substance use disorder treatment. Similarly, in a reexamination of phase 1 of the POATS trial, Northrup et al. (2014) found a four class solution was the most parsimonious. The four classes were characterized as 1) a high craving and high withdrawal group, 2) a moderate craving and withdrawal group, 3) a high baseline craving with low trajectories for craving and withdrawal group, and 4) a low baseline with low craving and withdrawal trajectories.

Our findings suggest that treatment for prescription opioid use disorder is more complex than the presence or absence of use over the stabilization period. Rather, there exist different subgroups of patients in treatment, with some more likely to have difficulties with pain and some to have difficulties with depression. Over 30% of the patients fell into classes where pain and depression were likely to influence rates of relapse. Thus, pain and depression were a somewhat common experience among patients as they progressed through BUP+N stabilization.

4.1 Class Summaries

For a more thorough explanation of each group, I offer a detailed investigation of the clinical relevance of all four classes:
The typical class: At 60% of the BUP+N treatment sample, this was the most representative and largest class. The trajectories for pain and depression in this class were characterized by a sharp decrease in the first four weeks of stabilization on BUP+N, that was followed by a leveling off over the rest of the treatment milieu. This trajectory pattern was similar to what was found previously among the patients in phase 1 of the POATS project. Northrup et al. (2014) found that patterns of withdrawal showed a strong decrease to begin the study (in phase 1 there was only a 2-week BUP+N stabilization) before the levels began to increase again. The same trajectory was not found for the experience of craving. This suggests that pain, depression, and withdrawal may share brain pathways that are important during the initial stages of BUP+N treatment. Noteworthy is that 65% of the individuals in this highly successful class were employed full time, yet only 39% had schooling beyond a high school diploma. This suggests that the typical treatment class may be characterized as a “blue collar” occupational group, although future research will be needed to mete out the nuance of this finding. Lastly, the typical treatment group was the most successful with regards to overall phase 2 treatment success. Remember that phase 2 treatment success was achieved if 3 of the final 4 urinalyses were negative for opioid drugs (Weiss et al., 2011). Thus, future research will be need to tap into this high success group and identify other predictors of treatment success. Additionlly, a qualitative approach that allows individuals from this group to elaborate on how and why they feel they were successful in getting through the stabilization period may offer insight that a quantitative approach can’t capture.

The high pain class: At 11% of the sample, this group experienced high baseline pain that did not let up over the duration of the BUP+N treatment. Depression in this class followed a trend that was very similar to the typical treatment group; rapid decrease in depression early in treatment,
followed by a stable and slow decrease from week 4 to week 12. The high pain class was also very likely to relapse across the treatment milieu. Despite the high relapse (survival) rate, 35% of the individuals were successful in phase 2. This suggests that treating relapse as a part of the recovery (treatment) process may be beneficial for individuals in BUP+N medically managed care. For the individuals in the high pain group, relapse was likely viewed as a tool to evaluate treatment progress which then allowed for future treatment planning to reduce or eliminate use in subsequent weeks. The high pain group was educated at a fairly high rate (75% above high school diploma), yet only about half (53%) were employed full-time. This suggests that the high pain ailment for individuals in this group may be limiting their ability to work.

The high depression class: At 20% of individuals, this class was the second largest subgroup of the overall treatment sample. The group was characterized by high baseline reports of depression that subsided gradually until week 8, and then increased very minimally from week 8 to week 12. The class also reported a moderate but steady level of pain across the entire treatment milieu.

The relapse rate of this group was not significantly different than the high pain group but was higher than the typical treatment group. These findings were consistent with what has been found in previous research with primary care patients (Stein et al., 2015). Importantly, the class was predominantly female (67%). This finding makes sense given the high rate of females that enter into substance use disorder treatment with elevated levels of mental health conditions (Marsh, Cao, & D’Aunno, 2004), including what has been reported previously in regard to the POATS project (McHugh et al., 2013). This suggests that the experience of BUP+N treatment may be fundamentally different for females with depression, yet their treatment progress may look similar to their peers.
Overall the high depression group provides a perplexing result relating to survival. The group, as a whole, saw decreases in depression across the treatment milieu, yet the relapse rates remained relatively high and steady. Perhaps this means that individuals with high initial rates of depression represent a group of patients that may require careful consideration and referral to a psychiatrist or other health care professional to adequately address antidepressant medications or psychosocial interventions for their depressive symptoms during BUP+N stabilization. Further research will be required to flush out the nuance of these findings.

The low motivation class: This class consisted of only 9% of the BUP+N treatment sample, yet was arguably the most important from a clinical standpoint. Researchers and clinicians have long searched for strategies to engage individuals with seemingly little to no motivation to sustain treatment for individuals with substance use disorder (DiClemente, Schlundt, & Gemmell, 2004; Faberman, 2004). From our results, it appears that neither pain nor depression was playing a role in the rates of relapse during treatment for this class. These individuals started low in pain and depression, and there was very little change across the stabilization period. Despite the low rates of pain and depression, all of the patients had relapsed (survival) by week 6 and only 2 patients were able to finish the treatment successfully. The class was also characterized as highly male (73%), well educated (above 73% with high school diploma), and employed at a rate similar to the typical group (63% compared to 65%). Interestingly, the class also reported the highest percentage of individuals having used heroin previously (37%). These findings suggest that identifying individuals entering into treatment for primary prescription opioid use disorder that have previously used heroin may be helpful for intensive treatment planning among this high risk group.
4.2 Clinical Implications

The clinical utility of these results may be profound for health care providers working with BUP+N treatment populations. These findings provide a clearer picture of what may be prompting relapse in BUP+N treatment. Where previous research and methodological strategies have informed clinicians that patients were relapsing, the strategy outlined in this project helps identify who was vulnerable to relapse and what parallel processes may be influencing relapse. Strategies like this will be essential as the health care field moves to fully implement a public health model of treating substance use disorders (Buck, 2011). The approach outlined in this project examines the BUP+N stabilization period from a larger lens. In this strategy, relapse was not considered as the end-all-be-all outcome measure for treatment success; rather, relapse was simply a tool to gauge progress in treatment, and when, during treatment, specific interventions may be appropriate. Future research will be needed to fine tune the approach outlined in this dissertation to evaluate other parallel processes and their effect on relapse among other substance use disorder treatment populations. Thus, this project has laid the groundwork for such forthcoming study designs.

Importantly, this study confirms the previous research suggesting that the first month of BUP+N stabilization is vital to overall treatment retention and success (Marcovitz et al., 2016; Stone et al., 2018; Tuten et al., 2012). In fact, an examination of the survival plot (relapse) in this study shows that the first 3 weeks of BUP+N treatment were the most unstable for patients. After week 3, the pattern of relapse is nearly identical for the typical, high depression, and high pain groups. This suggests that the first few weeks of BUP+N treatment may offer a prime target for clinical interventions that will reduce relapse rates and increase commitment to abstinence. Evidence based practices such as contingency management (Stitzer & Petry, 2006) and
mindfulness meditation (Witkiewitz, Bowen, Douglas, & Hsu, 2012) offer potential techniques that may be effective during this high-risk period. It is clear that future research is needed to fully understand the mechanisms that may be involved during this early stabilization in BUP+N treatment.

The dissertation project also adds to the literature with regards to the characterization of pain and depression among a large contingent of treatment seeking BUP+N patients. Because nearly 60% of the sample were grouped in a single class, this means that a majority of the patients followed a treatment progression with few relapses and similar trajectories of pain and depression. This suggests that a large contingent of patients enter into BUP+N treatment with moderate levels of pain and depression, but these individuals report that both conditions subside in a predictable pattern over the treatment milieu. Understanding this typical class pattern may offer clinicians a blueprint to work from regarding normative rates of depression and pain across the BUP+N stabilization period. Additionally, these findings suggest that this clinical sample represents a relatively homogeneous group of prescription opioid use disorder patients. Lastly, I believe that it is important to point out that both the high depression and pain groups differed significantly in their rates of relapse when compared to the typical group. This suggests that “suffering”, whether emotional or physical, was impacting relapse.

Finally, two important clinical questions remain unanswered; first, among the low motivation group, if neither pain nor depression were impacting relapse, then what was causing the highest relapse rate? Second, how can these individuals be motivated to engage in, and complete treatment? Examining the demographic variables for the low motivation class gives some indication of why they may be struggling. Surprisingly, they were well educated and many were employed full-time. This leads to speculation that this may be a “white collar” class that
was shielded from the negative consequences (i.e., employment, social, legal) of the other classes. Perhaps the class does not have to provide proof of abstinence (i.e., urinalysis) as a condition of employment as other classes may have had to do. Similarly, the class may be motivated by the legal system for their initial (as opposed to multiple) brush with the law. Additionally, they were the youngest of the classes which may be an area for future inquiry. Future research may also incorporate a prescription opioid use motives measure to evaluate whether these individuals were continuing their prescription opioid use for enhancement or coping motives. Lastly, because these individuals appear to be in the precontemplation stage of change (Faberman, 2004; Prochaska & Di Clemente, 1982), interventions that generate ambivalence may be more suitable for this class.

4.3 Limitations

Similar to any research project, the findings reported here must be considered in light of some limitations. First, this was a secondary analysis of data collected from 2006-2009 which may limit generalization to current BUP+N treatment protocols. Although the measures implemented in the current study offer a valid representation of the key variables, novel strategies and interventions may have improved treatment modalities and now offer better overall outcomes for patients. Second, I focused on the dual change trajectories of pain and depression; however, there were other relevant variables that we could have included in the model. Future research will determine whether change trajectories for catastrophizing, withdrawal, quality of life, risky sexual behaviors, and other mental health conditions may also influence prescription opioid relapse. Third, I was only interested in relapse to prescription opioids. This may limit the findings for relapse as it relates to other drugs during BUP+N treatment. Specifically, use of cannabis may be a relevant outcome measure due to the ongoing debate on whether cannabis
provides a safe alternative to treat prescription opioid use disorder (Humphreys & Saitz, 2019). Fourth, inherent among LCA studies is the challenge of determining the number of latent classes. No uniformly accepted technique for selecting the number of classes has been adopted, but the examination of model fit indices as well as graphical representations across models, strengthened the model determination. Lastly, I focused only on the 12-week BUP+N stabilization period in this study. For a more robust understanding of the long-term effects of the change processes investigated in this study, a full examination of the follow-up data is necessary. The classes identified in the current analysis, may offer insights that were not identified by the original POATS researchers (Weiss & Rao, 2017). Despite these limitations, this exploratory study offers insights that are not available in studies using more traditional methodological techniques.
CHAPTER FIVE: SUMMARY AND CONCLUSIONS

The opioid epidemic has devastated our communities and ravaged families across our country. The search for solutions among treatment providers and researchers is eminently important. This project capitalizes on recent advances in statistical modeling, computer hardware, and computer software that allow for simultaneous modeling of multiple change mechanisms across time. The aims of this dissertation were to address heterogeneity among patients in BUP+N treatment for primary prescription opioid use disorder. These results suggest that researchers who have studied BUP+N treatment may have overlooked important differences in pain and depression and how they relate to relapse for different types of patients. This dissertation project suggests that patients that are prescribed and being stabilized on BUP+N may be experiencing treatment in qualitatively different ways. Responding to patient needs in BUP+N treatment may involve a more nuanced approach that considers patient reports of pain and depression when treatment planning. This method may be beneficial when compared to the one-size-fits-all approach that is often employed in BUP+N treatment. While 60% of individuals fell into a typical treatment patient pattern and appear to have been helped by BUP+N stabilization, other patients were not helped at all. The challenge for researchers moving forward is to identify treatment interventions which will increase the number of patients in the typical class that were most likely to respond positively to BUP+N treatment services.
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