A Longitudinal Study of Anxious and Depressive Symptomology

and Pain Medication Usage

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Dedication

This thesis is dedicated to my wonderful, supportive family.

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Abstract

Evidence suggests that depression and anxiety may be related to pain medication use in a bidirectional manner. Understanding the relationship of these factors is of heightened importance due to the extensive use of long-term opioid pain medication therapy for treatment of adults suffering from chronic pain. The present study, utilizing a large longitudinal sample from the National Survey of Midlife Development in the United States (MIDUS), examined the relationship between depression, anxiety, gender, and pain medication usage in individuals with chronic pain over an almost 20-year span. Structural equation modeling found stability of depression and anxiety in individuals with chronic pain. It also appears that both anxiety and depression may have a bidirectional positive relationship in this population. As expected, pain medication use predicted later use at 10 years. Surprisingly, pain medication use was not strongly related to later negative affect in this sample. However, heightened anxiety was associated with later pain medication use. Gender effects were nonsignificant. Implications for those who are prescribed pain medications over a long term are discussed.

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Chapter 1

Introduction and Literature Review

It is well known that despite recent greater use of psychiatric medications and improved access to mental health services, the occurrence of depression and anxiety disorders have remained remarkably high with lifetime prevalence rates at 16.1% and 12.3%, respectively (Reeves et al., 2011). Additionally, it is also concerning that these disorders share a 59.2% comorbidity rate (Kessler et al., 2003). Moreover, these disorders account for increased family stress, reduced work hours, and elevated medical expenses which are extremely harmful to individuals who suffer from these conditions. Researchers have examined numerous correlates, predictors, and consequences of these disorders. However, relatively limited research has focused on how these disorders may be related to pain and pain medication use. The aim of the current study, using almost 20 years of longitudinal data, is to examine the impact of anxiety and depressive symptoms upon pain medication usage over time. While previous longitudinal studies in community and young adult populations have indicated negative mood may be stable time (Bjerkeset et al., 2008; Lovibond, 1998; Merikangas et al., 2003; Watson & Walker, 1996), this study evaluates stability over a longer period of time, in a sample experiencing chronic pain. Further, it will investigate if the use of pain medication, which is a main line of treatment for chronic pain, affects long-term depressive and anxious symptomology. The following section will briefly review the state of the literature on depression and anxiety, review the literature on pain and pain medication use, summarize the theoretical and empirical research on the bidirectional relationship between these disorders and pain medication use, briefly discuss the possible role of gender as a moderator of these relationships, and conclude with a rationale for the current study.

Review of Depression and Anxiety

Depression is a serious mood disorder which is often contains feelings of sadness, hopelessness, and anhedonia (American Psychological Association, 2013). Depressive disorders include major depressive disorder, dysthymia, and depressive disorders related to other medical conditions or substance or medication use. Risk factors include high trait neuroticism, stressful life events, genetic predisposition, and presence of a comorbid psychological disorder (American Psychological Association, 2013). Indicators of major depression, which is the most common type of disorder, include depressed mood or anhedonia accompanied by at least 4 other symptoms such as significantly altered weight or appetite, sleep patterns, rate of thought and movement, or energy level. It may also include greater feelings of worthlessness or guilt or suicidal ideation and lasts over a period of two or more weeks (American Psychological Association, 2013). Depressive symptoms may be expressed in different patterns. These may manifest in a more anxious pattern, in a melancholic manner, or with manic/hypomanic features (American Psychological Association, 2013). Depressive symptoms may also be induced by medications or substance use. Prevalence rates of depression are high, with 7.6% of Americans over age 12 reporting moderate or severe depression and 3% reporting severe depressive symptoms within the last two weeks (Pratt & Brody, 2014); moreover, the risk of relapse is great (Ramana et al., 1995). Depression is also costly. It is estimated that adult depression annual costs in the U.S. are $238 billion (Egede, Bishu, Walker, & Dismuke, 2016). Mood disorders, which include major depression and dysthymia, are one of the major causes of hospitalization in the US for middle-aged adults (Wier et al., 2009). Moreover, 43% of those with severe depression report problems with work, home, or social interactions; these interferences also may impact those with mild or moderate symptoms. (Pratt & Brody, 2014). It is apparent that certain

gender and age trends occur within depression in the general population. It is most prevalent in adults age 40-59, and especially in females (Pratt & Brody, 2014) at nearly a two to one ratio compared to males (Maier et al., 1999) . This gender difference has been attributed to multiple causes such as biological, psychological, and social factors (Nolen-Hoeksema, 2006). Depression is also difficult to treat as treatment-resistant rates may be around 33% despite numerous modes of intervention (Rush. et al., 2006). Therefore, despite a focus on depression by researchers and numerous treatments, much information is still needed to reduce the impact of this disorder.

Similar to depression, anxiety disorders pose a significant mental health problem, as they are also quite prevalent and economically burdensome. Annual costs in the U.S. are estimated at $48 billion (Shirneshan, 2014). Anxiety disorders share features of exaggerated fear, an emotional response, and anxiety, anticipation of future threat, which may result in hypervigilance or avoidance behaviors, and individual disorders vary by source of fear or anxiety and associated cognitions (American Psychological Association, 2013). In adults, the most common disorders are specific and social phobias, panic disorder, and generalized anxiety disorder. Symptoms similar to these disorders may be induced by medications, substances, or illness (American Psychological Association, 2013). Anxiety disorders have a similar etiology as exposure to a traumatic or stressful event may trigger development; genetic and temperament factors may increase risk (American Psychological Association, 2013). Anxiety disorders are most common in middle age and are much more prevalent in females (Kessler & Chiu, 2005). Common treatments include psychotherapy, stress management training, and antidepressant, anti-anxiety, or beta-blocker medications (National Institute of Mental Health, 2016). However, despite numerous types of treatments, these disorders are quite pervasive and continue to increase health care costs and lower productivity and quality of life. Also, many individuals with one anxiety

disorder often have another comorbid anxiety or depressive disorder at the same time (Brown, Campbell, Lehman, Grisham, & Mancill, 2001). Taken together, it is clear that depression and anxiety continue to deleteriously affect millions of people across the world and necessitate research examining both the predictors and consequences of these disorders. As described below, pain and pain medication use may be critical predictors and outcomes of depression and anxiety.

The Role of Anxious and Depressive Symptoms on the Experience of Pain

Pain has been associated with a variety of mental disorders including anxiety disorders and depression. The biopsychosocial model of chronic pain views this illness, which is affected by biological, psychological, and social factors, as a subjective reaction to disease (Gatchel, Peng, Peters, Fuchs, & Turk, 2007; Gatchel, 2004). Thus, affect is a main component of pain as depression, anxiety, and emotional stress are contributory factors. This model is theoretically supported by Melzack's Neuromatrix Theory of Pain, which recognizes that pain is the result of cognitive, sensory, and affective components which produce pain related experiences and behaviors; thus, pain is not simply the result of sensory stimulation alone (Melzack, 2001, 2005).

Research indicates that anxious symptoms play a contributory role to the experience of pain as heighted anxiety levels have been found to influence pain severity and tolerance (Fernandez & Turk, 1992). Continual anxiety may also lead to heightened physiological arousal leading to extended experiences of pain (Gatchel et al., 2007). Further, anxiety sensitivity is associated with increased pain-associated fear and pain-related escape/avoidance even after controlling for pain severity (Asmundson & Taylor, 1996). To further support anxiety's role in chronic pain, a study of chronic low back pain patients found reductions in pain-related anxiety predicted improvement in pain, pain interference with activity, affective distress, and general daily activity (McCracken & Gross, 1998). It seems anxiety disorders may often precede chronic

pain, although experiences of anxiety may increase with a pain diagnosis (Knaster, Karlsson, Estlander, & Kalso, 2012). In a longitudinal study of individuals with lower extremity trauma, anxiety predicted chronic pain at 24 months (Castillo et al, 2013). Thus, findings indicate that anxiety may have a causal role in chronic pain development and outcomes.

Additional findings also reveal a role of depressive symptoms in chronic pain and pain outcomes. A majority of chronic pain clinic patients report high levels of major depression, and a significant number of individuals with depression report chronic pain (Bair, 2003). Studies have found that depression is associated with chronic pain prevalence (Magni et al., 1994), pain intensity (Haythornthwaite, Sieber, & Kerns, 1991) and pain chronicity (Pincus, Burton, Vogel, & Field, 2002). Research indicates chronic pain may yield depression (Castillo et al, 2013; Magni et al, 1994) and depression may cause chronic pain (Magni et al., 1994). It is possibly a cyclical relationship. However, some findings support the role of depression as a reactive response to pain (Gatchel et al., 2007), and studies have found that depression usually post-dated pain onset (Knaster et al., 2012) and that pain predicted depression in chronic pain patients (Brown, 1990). In contrast, Okifuji and Turk (2016) have proposed a model of the depression-pain relationship reflecting a bidirectional nature that is mediated by sense of control, self-efficacy, and social support to further explain why some, but not all individuals with pain develop these co-occurring conditions. Anxiety may further confound depression levels in chronic pain patients, as changes in pain related anxiety were found to predict changes in depression scores (McCracken & Gross, 1998). Thus current research indicates depression may play a primary or secondary role in long-term opioid usage, but the exact nature of that role is unclear. Overall, though both anxious and depressive symptoms appear to have significant influence on the experience of chronic pain, above and beyond pain intensity.

Pain and Opioid Pain Medication Usage

An analysis of the 2012 National Health Interview Study estimated that 11.2% of adults or approximately 25.3 million American adults experienced chronic pain at a given time, which involves having pain every day for the previous 3 months (Nahin, 2015). Chronic pain is predicted to cost approximately $560-$600 billion annually due to lost productivity and elevated medical utilization expenses in the United States alone (Gaskin & Richard, 2012). Opioid pain medications provide relief for chronic pain via psychological means, via attention and affect, and by impacting neuropharmacological processes (Garland, Froeliger, Zeidan, Partin, & Howard, 2013). It is estimated that a high percentage of chronic pain sufferers use opioid pain medication for long-term pain management, and opioid prescriptions have increased significantly since the 1990's leading to increased risk of addition and overdose (Reuben et al., 2015). The growing trend of long-term opioid pain medication use is concerning as there are adverse effects such as constipation, sleep disturbance, increased risk of fractures, and negative cardiovascular effects (Baldini, Von Korff, & Lin, 2012). Despite the regular prescribing patterns of opioid medications for pain management, little data supports long-term use, leaving few options for individuals with extended periods of pain (Chou et al., 2015); thus, chronic pain and treatment methods are a current focus area of the National Institutes of Health.

Co-Occurrence of Anxious and Depressive Symptoms and Opioid Pain Medication Usage in Individuals with Chronic Pain

In individuals with chronic pain, negative affect may be both an outcome and moderator of pain and motivator of opioid medication usage beyond pain intensity (Sullivan, Edlund, Steffick, & Unützer, 2005). Multiple studies have found those with chronic pain who have comorbid mood and anxiety disorders have higher rates of opioid pain medication usage and may

receive greater doses (Braden et al., 2010; Edlund et al., 2010; Sullivan, Edlund, Steffick, & Unützer, 2005). In a community sample, those depressive or anxiety disorders were more likely to receive prescribed opioid medication for chronic pain (Sullivan et al., 2005, 2006). Additionally, in a comprehensive analysis of individuals within two large health systems, those with mental health or substance use disorders were more typically received opioid prescriptions and, over a five year period, individuals with these disorders experienced greater increases in rates of chronic opioid use (Edlund et al., 2010). Another large study of insured individuals with chronic noncancer pain found those with depression were more likely to receive stronger doses and greater supply but were no more likely to experience greater incidence of use (Braden et al., 2010). While prescription opioid medication use is common in individuals with chronic pain and use may be due to numerous psychosocial components, it is unclear how these factors also impact long-term continued usage of pain medication, and this poses an area of needed additional research. However, overall results imply that a relationship exists between negative mood and opioid use in individuals with chronic pain. As anxious and depressive symptomology may co-occur with chronic pain and opioid medication use, this study aims to further examine how affective symptomology and opioid medication use interact in chronic pain patients over an extended time.

Depressive and Anxious Symptoms as Contributors to Opioid Medication Usage in Individuals with Chronic Pain

As previously mentioned, elevated usage of opioid pain medication in individuals with mental health conditions is often found. Some research indicates depressive symptoms and mental health disorders may also predict extended times of usage and inability to discontinue medications.. A longitudinal community sample study found that continuation of opioid

medication usage was more likely at 3 years in individuals with major depression, dysthymia, generalized anxiety disorder, or panic disorder (Sullivan et al., 2006). Also, a prospective study of back pain, headache, and orofacial pain patients found pain intensity, pain limitations, depressive symptoms, and number of pain sites predicted long-term opioid use at 2 to 5 years after baseline (Von Korff & Dunn, 2008). However, not all studies have yielded similar results. Research conducted on 550,616 veterans who received long-term opioid therapy found age, smaller dose, lower dose frequency, and mental health diagnoses such as bipolar disorder, schizophrenia, or alcohol/substance use disorders were positively associated with discontinuation of prescription opioid use. However, this only impacted a small number of participants as 80% of veterans were still using pharmacotherapy at one year follow-up (Vanderlip et al., 2015). In a study of back pain patients, nonsurgical treatment and smoking predicted long-term opioid usage, but mental diagnosis did not (Krebs et al., 2011). Resolution of these discordant results would allow better risk predictions of those more likely to use medications for extended periods.

It is possible that prescribing patterns reflect an indirect use of opioid medications to regulate mood or stress (Howe & Sullivan, 2014). Some opioid based medications have been shown to provide dose-dependent secondary mood and anxiety regulating effects at initiation, but few long-term studies of effects exist (Bodkin, Zornberg, Lukas, & Cole, 1995; Howe & Sullivan, 2014; Tenore, 2008). Khantzian's "Self-Medication Hypothesis" proposes that individuals utilize substances to control or eliminate negative emotions, and that specific substance preference is based upon alleviation of symptoms (Khantzian, 1997). Koob (2003) later extended this idea proposing that subsequent drug use after initiation may serve to mitigate psychological deficits. In support of this, a recent study found that in individuals with depression, depressive symptoms moderated the relationship between pain severity and increased

likelihood of opioid medication use (Goesling et al., 2015). However, this is a new area of research and additional studies are needed. In summary, theory and research suggest negative affect may impact opioid use initiation and continuation in individuals suffering from chronic pain in attempt to alleviate psychological symptoms. If this is indeed the case, greater emphasis on treatments for psychological symptoms should occur in those suffering with co-occurring pain.

Opioid Use as a Contributor to Further Mental Health Decline

It appears extended opioid pain medication use is associated with many harmful outcomes such as increased risk of overdose or abuse, fractures, myocardial infarction, and sexual dysfunction and this may be dose dependent (Baldini, Von Korff, & Lin, 2012; Chou et al., 2015). It is also possible that long-term usage also impacts mental health. Research conducted on chronic pain patients with osteoarthritic pain did find pain interference, improved mood, better sleep, and higher enjoyment of life were associated with controlled-release oxycodone use at 6, 12, and 18 months (Roth et al., 2000). However, a recent meta-analysis found reduced pain intensity, but no improvements in mood or quality of life were associated with pain medication usage (Eisenberg, McNicol, & Carr, 2006). Other data indicate that extended use may even worsen psychological well-being. One retrospective study conducted 10 years after treatment found non-cancer pain medication users reported poorer quality of life, higher depression but not anxiety, and lower quality coping strategies (Jensen, Thomsen, & Højsted, 2006). Additionally, an epidemiological study found chronic pain, measured by daily use of pain medication and daily report of pain, predicted presence of chronic depression and anxiety disorders and severity of depression at 2 years (Gerrits et al., 2012). A retrospective study noted that individuals taking opioid medications have been found to have heightened risk

of developing depression (Smith et al., 2015). Further support for the belief that pain medication use may contribute to averse psychological consequences comes from an epidemiological study of opiate naive patients with no depression but with chronic pain, who later reported increased onset of depression after initiation of pain medication usage; this was associated with long-term pain medication usage (90 days) but was not dose dependent (Scherrer et al., 2016). A recent review sponsored by the NIH noted a strong need for more research in this area due to the limited number of studies examining long-term prescription opioid use outcomes (Chou et al., 2015).

Overall, data seems to suggest that short-term improvements may be seen in mood and anxiety with initiation of opioid pain medication use (Howe & Sullivan, 2014). However, extended use of opioid pain medications may cause or exacerbate depression and anxiety. There is still a need for additional high quality research in this area as many studies were either retrospective, of small sample size, or of shorter duration; thus, further investigation is merited. Currently, data suggest that long-term effects of opioid pain medication usage should reflect heightened anxiety and depression, as individuals may not learn appropriate coping skills and rely on pain medication instead.

Gender as a Moderator of the Relationship Between Opioids and Negative Affect

Differences attributed to gender may have a strong impact on the relationship between chronic pain, opioid use, and negative affect. As Greenspan (2007) noted in his review of gender differences, females are more likely to experience anxiety and depression, have more pain conditions, and are more likely to suffer pain disability; also, certain medication efficacies vary by sex. Additionally, females are more likely to use opioid medications for chronic pain management. Data from the CONSORT study, which contains information from insurance

claims of 4,000,000 individuals, found that women were more likely to initiate and use prescribed opioids long-term, and this was not associated with pain severity or number of pain conditions (Campbell et al., 2010). These findings warrant further investigation into whether other factors may be associated with these prescribing patterns.

Correlational studies indicate gender also seems to influence the affective experience of pain. In chronic pain patients, female gender was associated with pre-existing depression; however, males were more likely to develop post-opioid initiation depression (Smith et al., 2015). Also, in males, but not females, with chronic noncancer pain, depressive symptoms at one year were related to continued persistence of pain (Magni et al., 1994). To date, studies have found significant differences by gender in experiences of pain, pain outcomes, pain treatments, and affect associated with pain. For example, females may be more likely to use anti-anxiety medications, such as benzodiazepines, concurrently with pain medications (Cropsey et al., 2015). However, further research is needed to understand causes of gender disparities in long-term opioid pain medication usage. These findings lend support to further exploration of gender effects upon the relationship of long-term opioid medication and negative affect. It is possible that the long-term relationship with depression may be stronger in males using pain medications, while anxiety may be of heightened severity in females. At this time, research is mixed, and examination of longitudinal study data may clarify the nature of this relationship.

The Overall Relationship-Summary of the Current Study

It is apparent from previously noted research that the associations between chronic pain, opioid use, and depression and anxiety are quite complex, multifaceted, and, in many cases, multidirectional. However, a majority of the evidence supports the idea that anxious and depressive symptoms may contribute to opioid medication use above and beyond pain intensity.

Additionally, although data is more limited due to the small number of available studies, shorter-term longitudinal studies indicate that use of opioid medication may provoke or intensify levels of negative affect as duration of use increases. It appears no long-term studies have yet examined these effects in a prospective manner. Exploration of this relationship is extremely relevant as depression and anxiety appear to be related to poorer long-term outcomes in those with chronic pain although these effects may vary by gender. Thus, this study seeks to investigate the relationship between depression, anxiety, prescription opioid use, and gender. Specifically it aims to further examine the role of negative affect on opioid use, and the effects of opioid use on subsequent depressive and anxious symptoms over time.

Hypotheses

(See Figure 1)

H1A: Controlling for anxiety at time 1, higher anxiety at time 2 will predict higher pain medication use frequency at time 3.

H1B: Controlling for depression at time 1, higher depression at time 2 will predict higher pain medication use frequency at Time 3.

H2: Higher pain medication use at time 2 will predict higher anxiety and depression at Time 3.

H3: Higher Anxiety at Time 1 will predict higher anxiety at Times 2 and 3.

H4: Higher Depression at Time 1 will predict higher depression at Times 2 and 3.

H5: Higher Pain Medication Use at Time 2 will predict higher pain medication use at Time 3.

H6: Structural models will vary by gender, such that at time 3, depression will be higher in males and anxiety will be higher in females.

Chapter 2

Methods

Participants and Recruitment Procedure

The participants and data for this study will come from the National Survey of Midlife Development in the United States (MIDUS) Study. The MIDUS Study consists of 3 waves of data collection, which were obtained data via a phone interview and subsequent paper survey. The sample obtained in Wave 1 of the Midlife in the United States Survey (Brim et al., 1996) was collected by Harvard University in 1995 and 1996 and sponsored by the John D. and Catherine T. MacArthur Foundation Research Network on Successful Midlife Development. All 7,108 participants were English-speakers in the contiguous U.S. who owned a telephone in their home. Homes were selected at random using random-digit-dialing, and a household listing of all individuals between the ages 25-74 was obtained from the respondent. Individuals were then selected from the list at random and attempts were made to contact the specific individual (n=3,487). Additional subsamples included oversamples from five metropolitan areas (n=757), siblings from the random digit dialing sample (n=950), and a random-digit-dialed twin sample (n=1,914). If the selected individual(s) refused participation, no other household member was subsequently designated. After consenting to participate, a 30-minute telephone interview was conducted with the participant. Then, a questionnaire, with an estimated completion time of 2 hours, was mailed to the participant's home along with a pen and a check for $20. After the questionnaire was mailed, a reminder card was sent 3 days later. A second copy of the questionnaire was mailed 2 weeks later if the initial document had not been returned. Finally, telephone calls were placed after 2 more weeks if a response was not received, and an additional financial incentive was offered. Overall response rate to both portions was 61%.

In Wave 2 (Ryff et al., 2006), conducted in 2004-2006 by the University of Wisconsin Survey Center, 4,963 of the initial participants in Wave 1 were successfully contacted and again participated in a 45-minute phone interview based upon the Wave 1 format. The retention rate was 70%. Methodology and measures were similar to Wave 1 but additional questions relevant to this study were added (described below). Also, participants were now paid $25 for the phone survey. In addition, participants received a letter one week in advance of being called for an interview, which notified them of the project. Updated methods for obtaining the paper surveys were used. When the survey was mailed, $10 was now also included, and participants were still compensated another $25 upon return of the questionnaire. If the questionnaire was not returned within 5 weeks of mailing, an additional copy was mailed to the participant. For those who still did not return the paper survey, an additional copy was mailed after another 3 weeks, and a phone call was made if no response was received 3 months after the first mailing. If there was still no response, another copy of the paper questionnaire was mailed out with a check for $25. Finally, near the end of the survey, those who had still not returned the paper questionnaire were contacted and asked to complete a limited telephone administered version. Main reasons for non-completion of the phone interview included refusals and non-working phone numbers. Other reasons included inability to participate due to health or other related reasons or death, which was later verified with the National Death Index. Average follow-up time was 9 years, ranging from 7.8 to 10.4 years. Of these individuals, 80%, or 4,032, also again completed the paper questionnaire.

In 2013 and 2014, Wave 3 data (Ryff et al., 2014) was collected by the University of Wisconsin Survey Center; 3,294 of the longitudinal study individuals were successfully re-contacted and participated, yielding a retention rate of 66% of Wave 2 participants. Procedures

were similar to the MIDUS Wave 2 methodology, but an additional $2 was mailed with the advance notification letter. Also, a reminder letter was mailed 2 weeks after the paper questionnaire was sent. Additionally, a second packet was sent to non-responders after 4 weeks from the original packet mailing, and a reminder card was sent after an additional 4 weeks. Afterwards, an additional questionnaire packet was sent to those who had still not responded. Of those who did not participate in Wave 3, 179 were ruled ineligible to participate due to mortality, living outside the United States, or due to being physically or cognitively unable to participate. Of those still eligible, 2,732 completed both a 45-minute telephone interview and 100 page paper questionnaires.

For the main portion of this study, participants who endorsed chronic pain in both Waves 2 and 3 were examined, yielding a sample size of 521. If siblings or twins were present in the sample, only one individual's data was used, that of the lower individual ID number. Additional demographic information is reported in Table 1.

Measures

In Wave 1, a structured questionnaire utilizing trained interviewers was used to gather information regarding many factors, including demographics, depression, and anxiety. Via paper questionnaires, data was captured from respondents regarding physical disorders and prescription medication use. In Waves 2 and 3, these questions were repeated and additional questions were added to the paper questionnaire, including those which specifically addressed pain medication usage and presence of chronic pain. In Waves 1, 2, and 3, age at the time of the phone interview was calculated from the date of birth and gender was also recorded. Participants were also asked for additional information such as education level.

Depression and Anxiety In all waves, depression and anxiety were both measured via

phone interview using portions of the World Health Organization's Composite International Diagnostic Interview Short Form (Kessler, Andrews, Mroczek, Ustun & Wittchen, 1998), a modification of the WHO-CIDI (World Health Organization, 1990) which has shown good diagnostic capabilities and demonstrates strong psychometric properties such as test-retest reliability (K≥.68) (Wittchen, 1994) and concordance with clinical assessment (K≥.73) (Janca, Robbins, Cottler, & Early, 1992). To screen for depression participants were asked if they had felt sad and blue for all or almost all of each day for most or all days during a 2-week period over the past 12 months. If so, they were asked if during the two-week period if they were depressed all day, most of the day, half the day, or less than half the day. If this duration was high (all day or most of the day), they were then asked about frequency, i.e. if they felt this way every day, almost every day, less often than that. Those who answered every day or almost every day were then questioned if during the two weeks in past 12 months when the subject felt sad, blue, or depressed, did the participant: …"feel down on yourself, no good, or worthless?" or "lose interest in most things?" Total number of "yes" responses to these questions was used to capture depression severity. Scores ranged from 0-7 depending on the number of symptoms reported; those with no symptoms and those who did not answer the duration and frequency questions were given a score of 0. Variables were treated as continuous.

To screen for anxiety, individuals were first asked how much they worried in the last month if compared to others, and answers ranged from "more, less, about the same, not at all, don't know, or refused". Those who answered that they had some worry then described the frequency by selecting if they worried "every day, just about every day, most days, about half the days, less than half the days, don't know/not sure". Individuals who answered about "half the days", or more then answered questions which assessed anxiety duration, answering whether it

lasted “all day, most of the day, about half the day, or less than half the day”. Those who answered these questions also responded to questions measuring generalized anxiety disorder symptomology (GAD) severity. Those who did not answer these questions received a 0 for this variable. They answered questions such as “How often - over the past 12 months- you were restless because of your worry?” For each selection of “most days”, 1 point was given. Continuous total scores ranged from 0 (low or no symptoms) to 10 (highest score). Variables were treated as continuous.

Pain Presence of chronic pain was determined at Times 2 and 3. Unfortunately, this data was not assessed in Wave 1. In Waves 2 and 3, participants were asked “Do you have chronic pain, that is do you have pain that persists beyond the time of normal healing and has lasted anywhere from a few months to many years?” Those who reported suffering from pain were coded “1” for “Yes”, and others were coded “2” for “No”. Only individuals who reported chronic pain at both time periods were included in this study.

Pain Medication Usage All participants were asked if they had used prescribed pain medications within the past 30 days in Waves 2 and 3. As separate questions assessed use of medications to treat diseases such as arthritis or migraines and non-prescription pain medication usage, the report of pain medication usage was equated with opioid medication usage. Individuals who marked yes for having used pain medications also indicated frequency of use by marking either “Daily”=1, “A few times week”=2, “Once a week”=3, “A few times a month”=4, or “Once this month”=5. This will be treated as a continuous variable.

Data Analytic Plan

Cross-lagged longitudinal structural equation modeling tested causal pathways between the observed variables of anxiety, depression, and opioid use. Analyses were conducted using

MPlus Version 7.2 (Muthén & Muthén, 2015). Structural equation modeling, which allows investigation of several regression relationships simultaneously offers several advantages as it can accommodate more complicated models, especially those which contain several dependent variables and incorporate chains of influence between variables (Streiner, 2005). First, a Confirmatory Factor analysis was conducted to evaluate the measurement properties of the previously proposed model (Figure 1) and to establish measurement invariance over time. It is necessary to establish factorial invariance prior to testing a longitudinal structural model. Given the high correlations among duration, frequency, and severity at each time point, depression was modeled as a latent variable. Table 2 includes means, standard deviations, and correlations among major variables. Similarly, a latent variable for anxiety was created due to strong correlations between anxiety duration, frequency, and severity. Pain medication use was treated as an indicator variable. Parameters were estimated using Maximum Likelihood Estimation. In this sample, there was less than 2% missing data, which was deemed to be missing completely at random, and thus was handled using full information maximum likelihood estimation (FIML).

Four goodness-of-fit indices were used to evaluate the adequacy of the CFA and structural models: the comparative fit index (CFI), the Tucker-Lewis Index (TLI), the standardized root mean square residual (SRMR), and the root mean square error of approximation (RMSEA). Values equal to, or greater than .90 for the CFI and TLI, and values at or lower than .08 for the RMSEA and SRMR, were considered indicators of acceptable model fit. Cross-lagged models were compared using $\Delta\chi2$ difference tests with the weak factorial model with a p value set at .05.

Chapter 3

Results

For the CFA, configural, weak, and strong invariance was established. Results establishing pattern, loading, and intercept invariance and are presented in Table 3. Evaluation of cross-lagged models indicated that the paths from Depression at Time 2 to Pain Med Use at Time 3 (ß=.00) (Hypothesis 1B) and from Pain Med Use at Time 2 to Anxiety (ß=.03) and Depression at Time 3 (ß=.08) were insignificant (Hypothesis 2) along with paths from Anxiety at Time 1 to Pain Med Use at Time 2 (ß=.05). In addition, correlations between Depression at Time 3 and Anxiety at Time 3 with Pain Med Use at Time 3 were insignificant. These paths were pruned from the final structural model with no significant effect to the weak factorial model, $\Delta\chi 2$ with a p value set at .05. The final model is depicted in Figure 2.

H1A, which stated that heightened anxiety would predict later pain medication use, was supported by the SEM model. Thus, it appears that, after controlling for anxiety at baseline, higher anxiety at time 2 predicted higher pain medication use frequency 10 years later (Time 3), (ß=.09, p=.05) (see Table 5). Hypotheses 1B and 2 were not supported. Hypothesis 3 predicted that Higher Anxiety at Time 1 would predict higher anxiety 10 and 20 years later. This was supported as early Anxiety (Time 1) was found to predict Anxiety at Time 2 (ß=.37, p<.001), and Anxiety at Time 2 predicted Anxiety at Time 3 (ß=.37, p<.001). Hypothesis 4 stated that higher Depression at Time 1 would predict higher Depression at Times 2 and 3. Results were also significant as Depression at Time 1 predicted Depression at Time 2 (ß=.26, p<.001), and Depression at Time 2 predicted Depression at Time 3 (ß=.20, p<.001). Hypothesis 5 stated that higher Pain Medication Use at Time 2 would predict higher pain medication use at Time 3. Pain Medication Use at Time 2 was found to predict Pain Medication Use at Time 3 (ß=.39, p=.01),

supporting this hypothesis. Finally, independent samples t-test revealed significantly elevated anxiety and depression duration, frequency, and severity in females at Time 3 (See Table 6), which partially supported hypothesis 6, which had predicted higher depression in males and higher anxiety in females.

For the structural model, within time point correlations between Depression and Pain Med Use at time 3 and Anxiety and Pain Med Use at Time 3 were not significant. These non-significant regression paths and within time point correlations were removed from the final structural model in an effort to create a more parsimonious model that better represented the data. The final model is depicted in Figure 2.

Additional Analyses

While not hypothesized a priori, Depression at Time 1 predicted Pain Medication Use at Time 2 (ß=.12, p=.01). Also, a strong predictive relationship occurred between early Anxiety and later Depression, and early Depression and later Anxiety. Depression at Time 1 significantly predicted Anxiety at Time 2 (ß=.13, p=.01), and Depression at Time 2 predicted Anxiety at Time 3 (ß=.13, p=.01). Similarly, Anxiety at Time 1 predicted Depression at Time 2 (ß=.14, p=.002), and Depression at Time 3 was predicted by Anxiety at Time 2 (ß=.17, p<.001). Other non-hypothesized data analyses tested gender group differences between the Structural SEM models, but these would not converge. Thus, the program was not able to estimate a suitable model based upon gender differences. In addition, covariates of age and number of chronic conditions did not contribute significantly to the model.

To explore if the proposed model might fit better with another sample population, SEM analyses were conducted on individuals who reported no chronic pain, those with chronic pain at time 2 only, and those with chronic pain at time 3 only. Results are included in Table 4. In

comparison to the models tested using the sample with Chronic Pain at T2 and T3, no other samples (No pain, Pain at Time 2, or Pain at Time 3) fit the model as well, and all structural models demonstrated indices of poor fit.

Chapter 4

Discussion

Utilizing data from a representative sample of middle-aged residents of the United States who experience chronic pain, the current study addressed a gap in the literature by examining a model which tested the temporal relationship between pain medication use, depression, and anxiety in individuals with chronic pain over a period of 20 years, expanding previous research studies which looked at these relationships using cross-sectional or short-term longitudinal data. Despite predictions, results did not support a major role of pain medication use on long-term depression or anxiety. Thus, it seems the relationship between negative affect and pain medication use may not be as significant as some other research has indicated, especially since possible confounds of age and number of chronic conditions were considered, but were found to be insignificant. While there was a small effect of Time 1 depression on pain medication use at Time 2, and Time 2 anxiety on pain medication use at Time 3, values were small, indicating that other factors must contribute more significantly to pain medication usage trends. These findings, while unpredicted, appear to support a prior study which found no positive effect of affect on pain medication usage (Krebs et all, 2011), and to dispute studies which have found a positive relationship between negative affect and pain medication usage (Jensen, Thomsen, & Højsted, 2006; Scherrer et al., 2016; Smith et al., 2015). There are several possible reasons for these findings. Some studies examined different populations. The Scherrer study (2016) was also from a large sample and covered over 10 years, but it screened out individuals with a prior diagnosis of depression and only examined those individuals just beginning an opioid pain management regimen. In comparison, information was not available to allow this split in the present study. It is possible that those individuals with no prior diagnosis who are naïve to pain medication may

represent a specific subpopulation, who may experience different temporal changes associated with mood. Further, Jensen, Thomsen and Højsted, 2006 used a sample containing individuals being treated in a pain management hospital, and not the general population. These individuals are likely to have higher pain and disease severity, possibly yielding a different prognosis. Smith et al. (2015) only looked at individuals being treated with opioid pain medication, and not all individuals reporting chronic pain. In addition, participants were required to estimate onset time of mood symptoms, depression diagnoses, and chronic pain, and groups were split according to the timing of depression onset to pain medication diagnosis. This study relied upon accurate reporting of onset of symptoms, which may be subject to reporting bias. Secondly, our study utilized structural equation modeling as opposed to the Smith et al. (2015) study which utilized multivariate logistical regressions to examine group differences. SEM allows evaluation of multiple relationships at once as opposed to sequentially, and incorporates measurement error into the model itself (Gefen, Straub, & Boudreau, 2000).

An interesting relationship was found between pain medication use at baseline and 10 years later, as results showed that that early pain medication use predicted continued use at 10 years, even if age and chronic conditions were considered. This is possibly reflective of the difficulty in weaning off long-term medication interventions, and likely replicates the increased prevalence of long-term opioid prescribing, as previously noted by Boudreau et al. (2009). As the current study incorporated data through 2014, when heightened awareness of long-term opioid use risk was of greater concern and alternative treatments were being more intently explored, it still appears that many sufferers of chronic pain are having difficulty discontinuing opioid medication use for pain.

Importantly, a strong relationship was found between anxiety and depression over time, and it appears that anxiety and depression have a strong, long-term bidirectional relationship chronic pain patients, similar to findings of a 4 year study conducted by Gerrits et al. (2015). The mutual influence of anxiety/depression on chronic pain has been previously noted. Lerman et al. (2014) found a latent anxiety/depression factor predicted pain and pain disability in a longitudinal study. Also, Moffit et al. (2007) found in a large cohort study covering individuals in their initial 32 years of life, people were equally likely to experience onset of depression followed by later anxiety, onset of anxiety associated with later depression, or the onset of anxiety and depression at once. As predicted, anxiety at baseline predicted anxiety at 10 and 20 years. Similarly, results were found for depression, although these results were not as strong. It therefore appears that negative affect, depression and anxiety, may have a trait-like stability in chronic pain sufferers, much as has been found in community samples (Merikangas et al., 2003). Also, while not hypothesized a priori, strong bidirectional predictive effects were found between anxiety and depression over time. This not only indicates stability of mood disorders, but also that they significantly overlap. This suggests that certain common etiological factors such as genetic or social influences may exist and should be further examined. It also indicates that individuals who have chronic pain should be regularly monitored for anxiety and depression concurrently, but that specific treatments for mood disorders might be better implemented irrespective of changes in chronic pain levels. A comparison study examining the long-term effects of psychological interventions for mood disorders is warranted in this population.

Limitations

Several limitations exist that may impact validity and reliability. Constructs of depression and anxiety were based upon unvalidated short versions of previously validated scales

and relied on retrospective reporting. However, the variables used were consistent with the definitions and meanings attributed to the constructs in the literature. Also, this model cannot account for changes in prescribing trends which may have occurred over the past 20 years due to modified prescribing recommendations and medication development and availability. Further, the attrition rate for the entire study was 46% over this 20-year time frame. If 3rd wave attrition trends were similar to the 2nd, individuals who continued to participate were more likely to be White, female, married, and have better overall health and more education (Radler &Ryff, 2010), and this may limit generalizability. In addition, as the sample only consisted of individuals who are residents of the United States, results may not generalize to individuals from other countries. Finally, concurrent use of antidepressants or anxiolytics or other mental health treatments was not considered. Further research may want to incorporate the use of additional medications into the study.

Despite these limitations, the findings of this study highlight the trait-like qualities of negative mood in a chronic pain population. Over a period of 20 years, the results showed that anxiety and depression were relatively stable in both males and females over time. In addition, they also showed that pain medication does not appear to have a significant effect on depression or anxiety. Thus, while interventions targeting negative affect are relevant for individuals engaged in long-term opioid therapies for chronic pain, it does not appear that these will indirectly also impact long-term pain medication use.

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Appendices

Appendix A: Tables

Table 1

Participant Demographics

	Wave 1	Wave 2	Wave 3
Age *(M, SD)*	47.81 (11.03)	56.76 (10.95)	65.83 (10.94)
Number of Chronic Conditions	3.48 (2.96)	3.56 (3.00)	5.11 (4.04)
Gender			
Male	38.8%	38.8%	38.8%
Female	61.2%	61.2%	61.2%

Table 2

Means, Standard Deviations, Correlations

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Depression Duration, Time 1	1																			
Depression Duration, Time 2	.35**	1																		
Depression Duration, Time 3	.32**	.34**	1																	
Depression Frequency, Time 1	.88**	.28**	.29**	1																
Depression Frequency, Time 2	.32**	.88**	.30**	.30**	1															
Depression Frequency, Time 3	.29**	.26**	.88**	.28**	.25**	1														
Depression Severity, Time 1	.84**	.31**	.28**	.93**	.32**	.28**	1													
Depression Severity, Time 2	.33**	.83**	.34**	.31**	.94**	.29**	.35**	1												
Depression Severity, Time 3	.31**	.33**	.85**	.30**	.33**	.95**	.32**	.37**	1											
Anxiety Duration, Time 1	.42**	.27**	.20**	.39**	.25**	.19**	.42**	.24**	.20**	1										
Anxiety Duration, Time 2	.27**	.41**	.23**	.24**	.39**	.23**	.30**	.40**	.27**	.31**	1									
Anxiety Duration, Time 3	.31**	.34**	.48**	.26**	.29**	.44**	.25**	.32**	.44**	.32**	.32**	1								
Anxiety Frequency, Time 1	.33**	.22**	.17**	.28**	.20**	.17**	.31**	.19**	.19**	.78**	.33**	.25**	1							

Table 2. Continued

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Anxiety Frequency, Time 2	.20**	.37**	.19**	.19**	.36**	.20**	.22**	.37**	.23**	.33**	.76**	.29**	.37**	1						
Anxiety Frequency, Time 3	.28**	.29**	.38**	.25**	.22**	.34**	.24**	.24**	.36**	.34**	.34**	.82**	.30**	.37**	1					
Anxiety Severity, Time 1	.35**	.16**	.21**	.24**	.18**	.25**	.39**	.17**	.27**	.50**	.27**	.23**	.47**	.23**	.22**	1				
Anxiety Severity, Time 2	.19**	.27**	.28**	.21**	.30**	.29**	.23**	.37**	.34**	.19**	.42**	.26**	.15**	.38**	.25**	.38**	1			
Anxiety Severity, Time 3	.21**	.26**	.37**	.22**	.28**	.38**	.24**	.32**	.44**	.29**	.25**	.45**	.26**	.25**	.41**	.43**	.57**	1		
Pain Med Use, Time 1	.15**	.20**	.15**	.11*	.17**	.13**	.13**	.16**	.16*	.08	.13**	.09*	.08	.09*	.10*	.05	.11**	.10*	1	
Pain Med Use, Time 2	.19**	.13**	.09	.15**	.10*	0.08	.14**	.10*	.10*	.11*	.13**	.12*	.10*	.08	.05	.40**	.09	.06	.02	1
Mean (SD)	0.93 (1.44)	.76 (1.33)	.78 (1.35)	.49 (1.01)	0.38 (.90)	.10 (.93)	1.07 (2.27)	.81 (2.03)	.92 (2.18)	.67 (1.04)	.62 (.99)	.61 (1.04)	1.86 (1.36)	1.82 (1.33)	1.74 (1.26)	.36 (1.43)	.23 (1.24)	.29 (1.35)	1.80 (2.21)	2.60 (2.21)

** Correlation is significant at the 0.01 level (2-tailed)
* Correlation is significant at the 0.05 level (2-tailed)

Table 3

Fit Indices of Structural Equation Models of Depression, Anxiety, and Pain Medication Use in Individuals Reporting Chronic Pain at Times 2 and 3 (n=521)

Model Type	*Chi-Square*	*df*	*p*	*RMSEA (95% C.I.)*	*SRMR*	*CFI*	*TLI*
Configural Model	402.12	126	<.001	.07 (.06-.07)	.06	.97	.95
Weak Invariance	424.87	134	<.001	.07 (.06-.07)	.06	.97	.95
Strong Invariance	482.93	143	<.001	.07 (.06-.07)	.07	.96	.95
Initial Structural	470.58	140	<.001	.07 (.06-.07)	.08	.96	.95
Final Structural	471.98	143	<.001	.07 (.06-.07)	.08	.96	.95

Table 4

Non-Hypothesized Exploratory Analyses: Fit Indices of Structural Equation Models of Depression, Anxiety, and Pain Medication Use in Other Individuals

Model Type	*Chi-Square*	*df*	*p*	*RMSEA (95% C.I.)*	*SRMR*	*CFI*	*TLI*
			No Pain				
Configural Model	515.20	126	<.001	.06 (.06-.07)	.05	.96	.94
Weak Invariance	410.40	62	<.001	.09 (.08-.10)	.07	.96	.93
Strong Invariance	465.66	67	<.001	.09 (.08-.10)	.07	.94	.92
Structural	442.05	55	<.001	.10 (.09-.011)	.12	.95	.92
			Time 2 Pain Only				
Configural Model	364.18	126	<.001	.09 (.08-.010)	.07	.93	.84
Weak Invariance	212.22	62	<.001	.10 (.09-.012)	.06	.93	.89
Strong Invariance	223.92	67	<.001	.10 (.09-.12)	.06	.92	.90
Structural	384.15	55	<.001	.16 (.15-.18)	.10	.81	.75
			Time 3 Pain Only				
Configural Model	313.68	126	<.001	.07 (.06-.08)	.05	.96	.94
Weak Invariance	196.17	62	<.001	.09 (.08-.102)	.08	.95	.95
Strong Invariance	287.85	67	<.001	.11 (.10-.12)	.11	.92	.89
Structural	226.56	55	<.001	.11 (.09-.12)	.07	.94	.92

Table 5

Final Structural Model Regression Results (Final Pruned Model)

Outcome	Predictor	ß	SE	p
Pain Med Use Time 2	Depression Time 1	.12	.11	.01
Pain Med Use Time 3	Anxiety Time 2	.09	.04	.05
	Pain Med Use Time 2	.39	.04	.01
Depression Time 2	Depression Time 1	.26	.04	.00
	Anxiety Time 1	.14	.05	.00
Depression Time 3	Depression Time 2	.20	.05	.00
	Anxiety Time 2	.17	.05	.00
Anxiety Time 2	Depression Time 1	.13	.05	.01
	Anxiety Time 1	.37	.05	.00
Anxiety Time 3	Depression Time 2	.13	.05	.01
	Anxiety Time 2	.37	.06	.00

Table 6

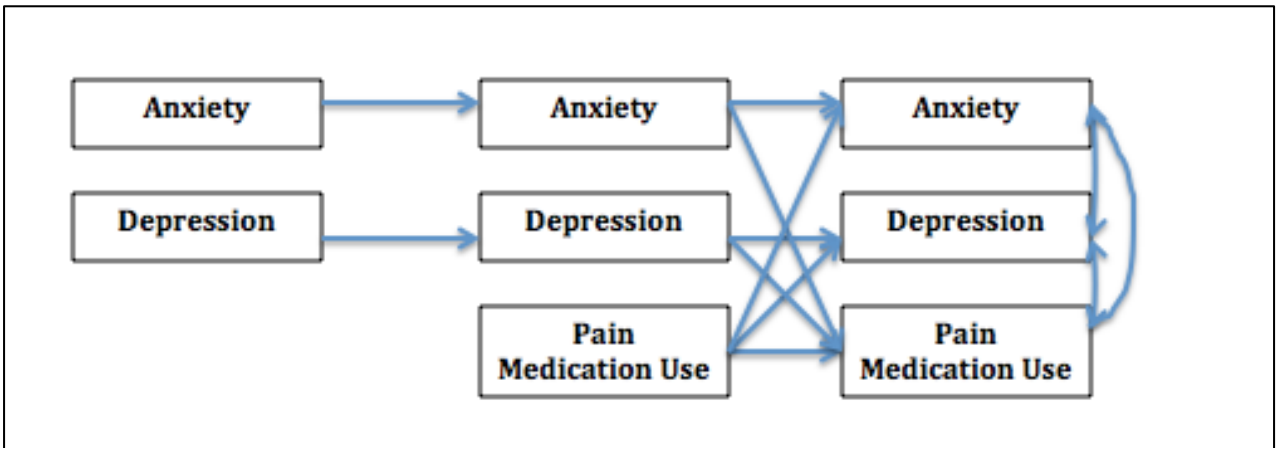
Independent Samples T-Test by Gender

Time	Variable	Type	Gender	Mean (SD)	df	t	p
T1	Depression	Duration	Female	1.20 (1.55)	516	5.28	<.01
			Male	.53 (1.14)			
		Frequency	Female	.63 (1.11)	515	3.88	<.01
			Male	.28 (.80)			
		Severity	Female	1.38 (2.6)	516	3.90	<.01
			Male	.59 (1.59)			
T2	Depression	Duration	Female	.94 (1.44)	515	3.96	<.01
			Male	.48 (1.09)			
		Frequency	Female	.48 (.99)	516	3.03	<.01
			Male	.23 (.74)			
		Severity	Female	1.04 (2.26)	516	3.10	<.01
			Male	.47 (1.60)			
T3	Depression	Duration	Female	.92 (1.41)	514	3.14	<.01
			Male	.55 (1.20)			
		Frequency	Female	.47 (.98)	516	2.01	.05
			Male	.30 (.84)			
		Severity	Female	1.12 (2.38)	516	2.59	<.01
			Male	.61 (1.80)			
T1	Anxiety	Duration	Female	.75 (1.12)	513	2.13	.03
			Male	.55 (.88)			

Table 6. Continued

Time	Variable	Type	Gender	Mean (SD)	df	t	p
		Frequency	Female	1.95 (1.43)	512	2.01	.05
			Male	1.71 (1.21)			
		Severity	Female	.49 (1.67)	516	2.67	.01
			Male	.15 (.92)			
T2	Anxiety	Duration	Female	.70 (1.06)	516	2.48	.01
			Male	.48 (.85)			
		Frequency	Female	1.90 (1.38)	515	1.85	.07
			Male	1.68 (1.23)			
		Severity	Female	.31 (1.78)	516	1.78	.08
			Male	.11 (.85)			
T3	Anxiety	Duration	Female	.71 (1.15)	512	2.89	<.01
			Male	.44 (.82)			
		Frequency	Female	1.87 (1.38)	513	2.80	.01
			Male	1.55 (1.06)			
		Severity	Female	.42 (1.62)	516	2.71	.01
			Male	.09 (.71)			
T2	PainMed		Female	2.08 (2.25)	512	3.67	<.01
			Male	1.36 (2.10)			
T3	PainMed		Female	2.99 (2.15)	460	5.18	<.01
			Male	1.91 (2.16)			

Appendix B: Figures



Wave 1
1995-1996

Wave 2
2004-2006

Wave 3
2013-2014

Figure 1. Proposed Model of Negative Affect in Individuals with Chronic Pain

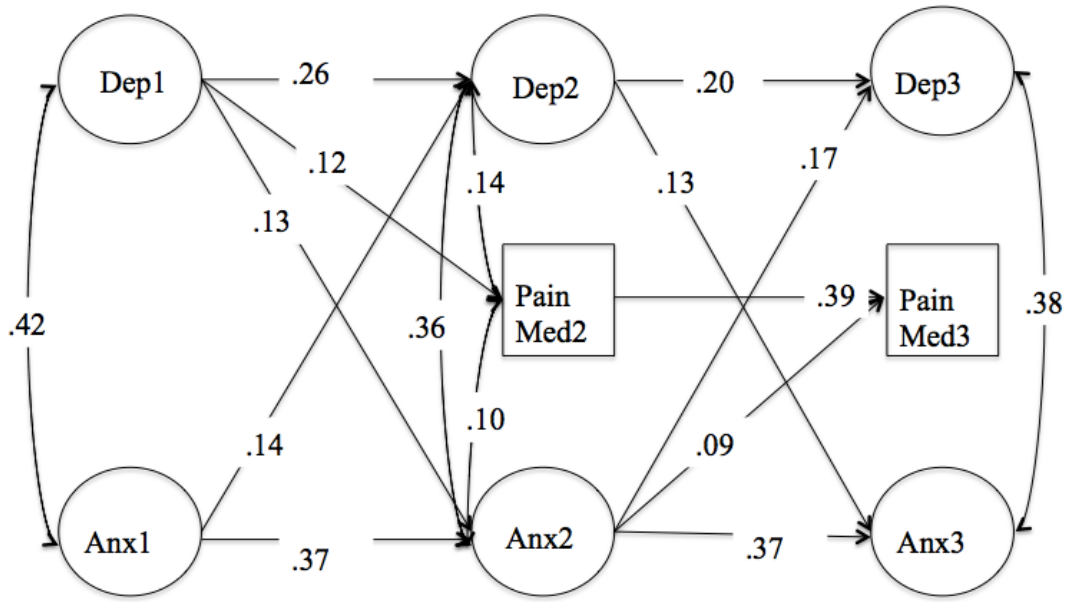


Figure 2. Standardized Structural Equation Modeling Results of Cross-Lagged Model Demonstrating the Temporal Relationship between Anxiety, Depression, and Pain Medication Use

Vita

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