Title
Long-term Opioid Therapy in Veterans with Chronic Non-Cancer Pain

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LONG-TERM OPIOID THERAPY IN VETERANS WITH CHRONIC NON-CANCER PAIN

by
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DISSERTATION
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As a clinician, I have committed my professional career in helping reduce pain and suffering and restore the function and quality of life of veterans. These efforts would not be possible without the confidence and trust of these individuals who shared their stories and exhibited unwavering faith in our abilities. It is my hope and conviction that I continue this commitment through research as a mean of reaching many more for generations to come.

LONG-TERM OPIOID THERAPY IN VETERANS WITH CHRONIC NON-CANCER PAIN

Ariel Baria

ABSTRACT

Background: Veterans with chronic non-cancer pain (CNCP) are a vulnerable population whose care remains a challenge for clinicians, policymakers, and researchers. For many of these veterans, the use of long-term opioid therapy (LTOT) to manage CNCP has steadily decreased while stricter opioid prescribing guidelines have increased in response to the "opioid epidemic". **Purpose:** The aims of this study were to 1) adapt Gatchel and colleagues' biopsychosocial model to study CNCP in the veteran population, 2) review current evidence on the effectiveness of LTOT for improving pain and physical functioning in veterans, 3) investigate the trajectories of pain, opioid dosage, and physical functioning among veterans prescribed LTOT and 4) examine whether these trajectories differ by sociodemographic characteristics (i.e., age, marital status, employment, living situation), and mood (anxiety and depression). **Methods:** This study identified physical, psychological, and social factors that contribute to CNCP in veterans and reviewed 12 studies out of 474 articles on the effectiveness and safety of opioids prescribed longer than 3 months in the veteran population. This study also analyzed data from a randomized clinical trial that compared opioid prescribing practices (liberal versus conservative dosing) in 134 veterans for 12 months in an outpatient VA pain clinic. To examine pain intensity and opioid use for longer-term, additional 24-month data were collected retrospectively on veterans who remained on LTOT. Regression models were used to test change over time in the later 24 months of follow-up for pain intensity and opioid use (log-transformed). Second, the effects of sociodemographic characteristics were tested in the first 12 months only, since these

characteristics were not collected in the later years after the original RCT analysis. **Results:** The Biopsychosocial Model of CNCP in Veterans described the most prevalent biological pain conditions (e.g., musculoskeletal disorders, osteoarthritis, low back pain, headaches, polytrauma, chronic post-surgical pain, traumatic brain injury, neuropathy, and amputation), psychological stressors (e.g., post-traumatic stress disorder, depression, anxiety, substance abuse), and social factors (e.g., homelessness, social isolation, disability, decreased access to medical care). The current literature does not demonstrate strong evidence to support the effectiveness of LTOT for improving pain intensity and physical functioning in veterans prescribed opioids over a 12-month period for CNCP. This study found that pain intensity and prescribed opioid dosage did not significantly change in the later 24 months of follow-up among veterans with CNCP but there was a significant increase in their physical functioning during the 12-month period ($p<0.05$). In the multivariate model, an increase in depression scores was associated with an increase in pain intensity ($\beta=0.06$, $P=0.003$) and physical disability ($\beta=1.48$, $P<0.0001$) for veterans prescribed LTOT for CNCP. **Conclusion:** The biopsychosocial model of CNCP for veterans is a useful and relevant conceptual framework to guide clinical care and future research for LTOT. The literature review indicated the paucity of evidence supporting the use of LTOT for improving pain and physical functioning and over 12 months. The findings of this study described the relative stability of pain intensity, physical functioning, and opioid dosage in veteran with CNCP. In addition, depression plays an important role in the management of veterans with CNCP and highlight the need of concurrent management of both conditions.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

(ADEs)	Adverse Side Effects
(ADLs)	Activities of daily living
(ADRB)	Aberrant drug-related behaviors
(AHRQ)	Agency for Healthcare Research and Quality
(APAP)	Acetyl-Para-Aminophenol (acetaminophen)
(BAI)	Beck Anxiety Index
(BLS)	Bureau of Labor Statistics
(BPI)	Brief Pain Inventory
(BPS)	Biopsychosocial
(CAM)	Complementary alternative medicine
(CARF)	Commission on Accreditation of Rehabilitation Facilities
(CDC)	Center for Disease Control and Prevention
(CI)	Confidence interval
(CINAHL)	Cumulative Index for Nursing and Allied Health Literature
(COT)	Chronic Opioid Therapy
(CNCP)	Chronic non-cancer pain
(CP)	Chronic Pain
(CPP)	Chronic Postoperative Pain
(CPRS)	Computerize Patient Records System
(DOD)	Department of Defense
(EMR)	Electronic medical records
(HADS)	Hospital Anxiety and Depression Scale

(HPACT) Homeless Patient Aligned Care Team

(HR) Hazard ratio

(HRME) High Risk Medication in the Elderly

(IASP) International Association for the Study of Pain

(ICD-9-CM) International Classification of Disease, Clinical Modification – 9th Revision codes

(IEDs) Improvised explosive devices

(IHCP) Integrative Health Clinic and Program

(IRB) Institutional Review Board

(IQR) Interquartile ranges

(LOT) Long-term Opioid Therapy

(LTO) Long Term Opioid

(LTOT) Long-term opioid therapy

(MAR) Missing at random

(MCAR) Missing completely at random

(MDD) Major depression disorder

(MED) Morphine Equivalent Dose

(MEDD) Morphine equivalent daily dosing

(MEM) Morphine Equivalent Milligram

(MHC) Mental health clinics

(MNAR) Missing not at random

(MSD) Musculoskeletal Disorder

(NDE) New depression episode

(NHIS) National Health Interview Survey

(Non-CPP) Non-Chronic Postoperative Pain

(NOT) No-term Opioid Therapy

(NPCD) National Patient Care Database

(NR) None Reported

(NTO) No Term Opioid

(OAU) Opioid Analgesic Use

(OD) Overdose

(ODI) Oswestry Disability Index

(OEF/OIF) Operation Enduring Freedom/Operation Iraqi Freedom

(OME) Oral morphine equivalent

(OND) Operation New Dawn

(OR) Odds ratio

(OSI) Opioid Safety Initiatives

(PDMP) Prescription Drug Monitoring Program

(PTSD) Post-traumatic stress disorder

(RCT) Randomized clinical trial

(RMDQ) Roland-Morris Disability Questionnaire

(SA) Sustained Action

(SCD) Service-connected disability

(SD) Standard deviation

(SHEP) Survey of Healthcare Experiences of Patients

(SOT) Short-term Opioid Therapy

(SPSS) Statistical Package for the Social Sciences

(SR)	Sustained Released
(SUD)	Substance use disorders
(STO)	Short Term Opioid
(TBI)	Traumatic brain injuries
(TF)	Theoretical Framework
(US)	United States
(VA)	Veterans Affairs
(VACO)	VA Central Office
(VAS)	Visual analog scale
(VBA)	Veterans Benefit Administration
(VCP)	VA Choice Program
(VHA)	Veterans Health Administration
(VISN)	Veterans Integrated Service Network
(WCP)	Without Chronic Pain

CHAPTER 1

INTRODUCTION

INTRODUCTION

Chronic non-cancer pain (CNCP) in the veteran population is highly prevalent and remains a challenging problem for clinicians, researchers and policymakers (1, 2). Because of military experience, many veterans have CNCP that is often severe and difficult to manage. In the past three years, the use of long-term opioid therapy (LTOT) has seen stricter guidelines and regulations for the management of both chronic and acute pain (3). The alarmingly high prevalence of opioid abuse, misuse, and overdose deaths and the lack of evidence to support its long-term effectiveness have contributed to a substantial reduction in opioid prescribing (4). In addition, the rationale for clinical use in veterans with CNCP continues to gain greater scrutiny because of the "opioid epidemic". These conditions have created a major vacuum for treatment options for improving pain, function, and quality of life for this vulnerable population. Given this tremendous impact to the care of veterans with CNCP, the overall purpose of this study was to examine the utility of LTOT and identify the biopsychosocial factors associated with opioid use.

In Chapter 2, an adaption of Gatchel and colleagues' biopsychosocial (BPS) model of CNCP for veterans is described. Although various conceptual models exist and describe the complex pain experience (2, 5, 6), Gatchel and colleagues' biopsychosocial (BPS) model provides a heurist framework easily adaptable in veterans with CNCP. As a result of military experience, veterans are exposed to high rates of musculoskeletal injuries, trauma, psychological stressors, and social factors that contribute to the magnitude and impact of CNCP. The BPS model of CNCP in veterans summarizes research findings that support the biological, psychological, and social components of the revised model. In this model, the most common type of CNCP include: injuries from musculoskeletal overuse, osteoarthritis, low back pain,

headaches, polytrauma, chronic post-surgical pain, traumatic brain injury, neuropathies, and amputation. The psychological factors seen in veterans with CNCP include post-traumatic stress disorder, depression, anxiety, substance abuse. Lastly, the social dysfunction common in veterans include: homelessness, social isolation, disability, decreased access to medical care. The chapter concludes with a discussion of important implications for the use of this revised model in clinical practice and future directions for research.

In Chapter 3, a literature review of the most recent evidence for the effectiveness and safety of LTOT is summarized. Many literature reviews have focused on the evidence for the effectiveness, harm, and risk of adverse effects of LTOT for the management of CNCP in the general population. However, few have focused on the veteran population. This review included studies that evaluated the effectiveness and safety of opioids prescribed longer than 3 months for the management of CNCP in the veteran population. Out of 474 articles found, 12 studies were selected for inclusion in this review. For veterans prescribed opioids over a 12-month period, current literature does not demonstrate strong evidence for significant improvement in primary pain outcomes (i.e., pain intensity, function). This review highlighted the gap in literature for the effectiveness of LTOT in veterans including studies that extend beyond 12 months. In addition, this literature review provided limited evidence on the biopsychosocial factors that contribute to LTOT in veterans with CNCP. This information is clinically important for assessing and monitoring veterans prescribed LTOT for adverse effects, aberrant drug-related abuse, and other risks associated with physical, physiological, and social co-morbidities.

Chapters 4 and 5 described the findings of a retrospective, secondary data analysis of 134 veterans who were prescribed LTOT in a single blind randomized clinical trial (RCT) (7) for 12 months and additional retrospective analysis of pain intensity and opioid dosage for 24 months.

The main purpose of the original RCT was to compare the effect of different opioid prescribing practices (i.e., liberal versus conservative prescribing) in veterans with CNCP. The current study investigated the trajectories of pain intensity and opioid dosage in veterans prescribed LTOT for 36 months and examined whether the trajectories differed by sociodemographic characteristics (i.e., age, marital status, living situation, employment) and mood (depression and anxiety). In Chapter 5, physical functioning and disability trajectories are investigated for 12 months with the same sociodemographic characteristics and mood covariates investigated. Given the paucity of evidence supporting the effectiveness of LTOT for CNCP, the study findings may improve our understanding of important factors that contribute to pain relief and opioid use. In addition, while most studies are limited to 12 months or less, this study evaluates LTOT up to 36 months.

Lastly, Chapter 6 provides a synthesis and discussion of study findings, the clinical implications, limitations, and future research recommendations. By using the BPS model of CNCP in veterans as a theoretical framework, examining the current literature, and investigating the trajectories of pain intensity, opioid dosage, and physical function and disability in veterans prescribed LTOT, this clinically relevant information may provide an evidence-based approach to optimizing LTOT and improve care of veterans with CNCP. More studies are needed on CNCP and the effectiveness of long-term opioid therapy in this vulnerable population.

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CHAPTER 2

ADAPTION OF THE BIOPSYHOSOCIAL MODEL OF CHRONIC NON-CANCER PAIN IN VETERANS

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ABSTRACT

Population: Veterans with chronic non-cancer pain (CNCP) are a vulnerable population whose care remains a challenge for clinicians, policymakers, and researchers. As a result of military experience, veterans are exposed to high rates of musculoskeletal injuries, trauma, psychological stressors (e.g., post-traumatic stress disorder, depression, anxiety, substance abuse), and social factors (e.g., homelessness, social isolation, disability, decreased access to medical care) that contribute to the magnitude and impact of CNCP. In the veteran population, sound theoretical models are needed to understand the specific physiological, psychological, and social factors that influence this unique experience. **Purpose:** This paper describes an adaption of Gatchel and colleagues' biopsychosocial model of CNCP to veterans and summarizes research findings that support each component of the revised model. The paper concludes with a discussion of important implications for the use of this revised model in clinical practice and future directions for research. **Conclusion:** The adaption of the biopsychosocial model of CNCP for veterans provides a useful and relevant conceptual framework that can be used to guide future research and improve clinical care in this vulnerable population.

KEY WORDS

chronic non-cancer pain; veterans; biopsychosocial model; opioids; substance use disorder; depression; post-traumatic stress disorder; military

INTRODUCTION

Chronic non-cancer pain (CNCP) is defined as pain that persists or recurs beyond the usual course of acute illness or injury or greater than 3 to 6 months and affects the individual's well-being (1, 2). While 30% of the United States (US) adult population experiences CNCP, 50% of veterans enrolled in the Veterans Health Administration (VHA) have CNCP (3). In 2011, the number of veterans with CNCP was estimated at 1.44 million (4). In addition, CNCP is highly prevalent in veterans who served in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) (5). Nearly half of these veterans report high rates of musculoskeletal pain and CNCP from traumatic blast injuries (3, 6). Compared to non-veterans, veterans with CNCP tend to experience more complex pain conditions with higher rates of psychiatric and social problems that include depression, post-traumatic stress disorder (PTSD), work disabilities, and substance use disorders (SUD) (3, 7).

Given the impact of CNCP in the veteran population, clinicians and policymakers agree that sound theoretical models are needed to understand the multitude of factors that influence this experience (3). The purpose of this paper is to describe an adaption of Gatchel and colleagues' review of the biopsychosocial (BPS) model of CNCP to veterans and summarize research findings that support each component of the revised model. The paper concludes with a discussion of the use of the model in clinical practice and research.

BPS Model of CNCP

Based on Engel's BPS model of health and illness (8) and other researchers (9), Gatchel and colleagues re-conceptualized the complex interactions among the biological, psychological, and social processes associated with CNCP (10). Although various conceptual models of CNCP

exist (11, 12), Gatchel and colleagues' model provide a heuristic approach that is easily adapted to veterans with CNCP.

According to Gatchel and colleagues (10), an individual's biopsychological experience of CNCP includes central and peripheral interactive processes influenced by his/her genetic predisposition (see Figure 1.1). The BPS model of CNCP describes these central processes as interactions among biologic, cognitive, somatic, and affective inputs. Efferent feedback from central processes interacts with peripheral processes that affect an individual's immune response to pain through changes in autonomic and endocrine systems. As illustrated in Figure 2.1, afferent feedback from peripheral processes sends input to central processes, which further contributes to an individual's experience of CNCP. In addition, a set of sociocultural influences can significantly affect an individual's pain perception and level of disability. These social factors include: environmental stressors, activities of daily living, interpersonal relationships, social support, isolation, family environment, social expectations, cultural factors, medicolegal and insurance issues, previous treatment experiences, and work history.

Dimensions of the BPS Model of CNCP for Veterans

Figure 2.2 illustrates an adaption of Gatchel and colleagues' BPS model for veterans with CNCP. In this revised model, the physiological and psychological processes, as well as, the sociocultural factors unique to veterans are identified (3). These physiological processes include: injury and trauma experienced during active military duty as well as the long-term consequences of these injuries. The mental health disorders that are common in veterans with CNCP include: PTSD (13-18), SUD (17, 19-29), depression (13-15, 20, 30, 31), and anxiety (14, 17, 20, 30, 31). The social factors that are common in veterans with CNCP include: poor social support,

isolation, homelessness, disability, and the limited access to timely and appropriate pain care (3, 23).

Biological Factors that Contribute to CNCP in Veterans

Military training and rates of injuries

Unintentional injuries from acute and overuse musculoskeletal trauma result in more than two million medical encounters annually across the four military services (32). These injuries result in more disability discharges than any other health condition (33). Almost 50% of military service members experience one or more injuries annually and more than half of these injuries are related to exercise, physical training, or sports activities (34). A survey of trainees in the US Army found that the leading causes of injury in men and women were: physical training (24% of injuries for women, 26% for men), road marching (23% for women, 24% for men), and obstacle courses (4% for women, and 5% for men) (35).

The most common injuries in military personnel are musculoskeletal-related including overuse or stress syndromes (23.8%), muscle strains (8.6%), ankle sprains (6.3%), overused knee injuries (5.9%), and stress fractures (3.0%) (36). In addition, low back pain, tendonitis, iliotibial band syndrome, and patellofemoral syndrome are common causes of CNCP (36). The factors associated with increased risk of training and non-combat injuries include: higher frequency and intensity of physical activity, more strenuous activity, an individual's poorer level of physical fitness, and personal health risk behaviors (e.g., sedentary lifestyles, tobacco use), all of which are influenced by demographic characteristics such as gender and age (i.e., women and older individuals are at higher risk) (32).

Combat related injuries in military personnel

Currently, over 90% of soldiers survive combat-related injuries (e.g., penetrating wounds, mine blast injuries from improvised explosive devices (IEDs)) (3, 17, 37). Compared to the Vietnam era, exceptionally high rates of musculoskeletal disorders and other painful medical conditions are being diagnosed in military combat personnel (3, 17, 38). These pain conditions are often associated with PTSD and traumatic brain injuries (TBI) (3, 17, 38, 39). Known as "polytrauma", these injuries are described as two or more life threatening injuries to any physical region or organ system, that results in physical, cognitive, psychological or psychosocial impairments, and functional disability (38).

Using data from 359 veterans who returned from OIF, OEF, and Operation New Dawn (OND) tours and from the Polytrauma System of Care Registry (17), the most common pain complaints were headaches (59%) and low back pain (33%). In an earlier study of 340 OIF/OEF veterans (38), the three most common medical conditions were: CNCP (81.5%), PTSD (68.2%), and persistent post-concussive symptoms (PPCS; 66.8%) (38). Of note, 42.1% of the sample was diagnosed with all three conditions (38). The most common locations for CNCP were: back (58%), head (55%), shoulder (21%), neck (19%), and knee (18%). These CNCP conditions were often associated with functional disabilities and psychological distress, family discord, and vocational issues that persisted long after the veterans have completed active duty service (3, 38).

Types of CNCP in Veterans

In the 2010-2014 National Health Interview Survey (NHIS), a comparison of pain severity among veterans and non-veterans found that 65.5% of veterans reported CNCP in the past 3 months; with 9.1% classified as severe (40). Veterans reported higher prevalence of back pain (32.8% versus 28.5%) and joint pain (43.6% versus 31.5%) compared to non-veterans (40).

In a Musculoskeletal Disorder (MSD) Cohort Study (14), over 5 million veterans had one or more MSD diagnoses. The top three CNCP diagnoses were: non-traumatic joint disorder (26.5%), back disorder (25.4%), and OA (20.9%) (14).

Based on the Centers for Disease Control and Prevention's combined 2011, 2012, and 2013 Behavioral Risk Factor Surveillance System database, arthritis was found to be the most common CNCP condition in veterans compared to non-veterans (25.6% versus 23.6%) (41). The highest prevalence rate for arthritis (i.e., OA, rheumatoid arthritis, gout, lupus, fibromyalgia) were found in veterans 45 to 65 years of age (40.3% in women and 36.0% in men) and in veterans 18 to 44 years of age (17.3% in men and 11.6% in women) (41). According to Cameron et al (42), women veterans experienced an adjusted OA incidence rate that was nearly 20% higher (rate ratio 1.19 [95% CI 1.17-1.21]) than men. In addition, African American veterans had a significantly higher incidence of OA than those in the White and "other" race categories.

In a 2014 study of retired OIF/OEF veterans (N = 310,256) who received service connection disability (SCD) through the Veterans Benefit Administration (VBA) (43), 159,893 veterans reported back pain, 14,094 reported arthritis pain, 22,583 reported arthritis with back pain, 4,583 reported multiple CNCP conditions other than arthritis pain, and 1,533 reported other pain disorders. Among this cohort of OIF/OEF veterans, CNCP secondary to arthritis and back pain was associated with an increased risk of developing medical comorbidities (i.e., diabetes, hypertension, hyperlipidemia, obesity) and increased utilization of pain clinics and pain medications.

Rates of Chronic Comorbid Conditions in Veterans with CNCP

The physical consequences of CNCP have a significant impact on veterans' overall health-related quality of life, disability, and other chronic conditions (40). Veterans with CNCP

develop a significant number of concurrent health conditions, including physical problems due to deconditioning and weight gain (i.e., hypertension, obstructive sleep apnea, diabetes), sleep disorders, SUD, mental health disorders, cognitive dysfunctions, and functional disability (40, 44). According to Goulet and colleagues (14), 48.0% of veterans in the MSD cohort (N=5,237,763) reported diagnoses of hypertension (48%), diabetes (19.4%), and coronary artery disease (16.2%). Furthermore, a significant portion of these veterans was classified as overweight or obese (7, 14, 43). Compared to veterans without pain, veterans with CNCP were significantly more likely to use tobacco and report increased amounts and frequency of alcohol consumption (7). Poorly managed comorbidities among veterans with CNCP may result in additional physical disabilities, psychological and social stressors, and worsening of pain symptoms (3, 7, 43, 44).

Rates of Surgical Complications in Veterans with CNCP

Veterans with CNCP experience a higher risk of complications and poorer surgical outcomes secondary to concurrent medical and psychiatric comorbidities and functional disabilities compared to veterans without CNCP (45, 46). Increased rates of perioperative and postoperative complications and worse surgical outcomes were found in veterans with CNCP undergoing rotator cuff (46), lumbar spine (47, 48), knee arthroscopic (15), and bariatric (49) surgeries. The most common risk factors for poor surgical outcomes included: older age, functional dependence, smoking, presence of comorbid medical conditions (i.e., diabetes, chronic obstructive pulmonary disease, use of chronic steroids), presence of multiple CNCP conditions (i.e., OA, musculoskeletal pain), use of chronic opioid therapy, and PTSD (46-48).

In a study of 145 OEF/OIF veterans who underwent elective knee arthroscopy, the use of an opioid preoperatively was the strongest predictor for the development of chronic post-surgical

pain (CPSP) (15). PTSD occurred in at least 32% of the veterans with CPSP (95% CI, 25%-41%) and was identified as a likely risk factor (15). In addition, PTSD among this group of veterans was associated with smoking; increased preoperative and postoperative opioid use; and increased demand for opioids in the immediate postoperative period.

Combat related extremity injuries may require multiple surgeries for limb reconstruction and/or amputation (45, 50). Among a cohort of combat Veterans followed in a Limb Preservation Clinic between 2011 and 2013 (37), the median number of surgeries was 8 (range 3 to 19). These veterans had increased rates of CNCP from neuropathic etiologies and joint OA that required extensive rehabilitation (45). In addition, CNCP was found to be to a significant predictor of depression, PTSD, and decreased quality of life among this group of veterans with limb threatening lower extremity trauma (37, 51).

Summary of Pertinent Biological Factors

As illustrated in Figure 2.2, veterans with CNCP experience numerous injuries and trauma that can affect the physiological processes involved in nociception and perception of pain. From injuries sustained during physical training, sports activities, military combat or non-combat trauma, or from the long-term sequelae of these injuries, veterans with CNCP are at significant risk for functional disabilities, multiple comorbid medical conditions, and worse surgical outcomes. Common injuries that result in CNCP among veterans include musculoskeletal disorders, arthritis, low back pain, headaches, poly-trauma, TBI, neuropathies, amputations, and CPSP. Moreover, with the long-standing theaters of war, younger veterans and women are at greatest risk for CNCP (32, 42, 52).

Psychological Factors that Contribute to CNCP in Veterans

The BPS model of CNCP highlights the psychological factors that impact an individual's responses to CNCP (see Figure 1.1). The dynamic interactive processes that occur among physiological, psychological, and social factors are important in determining how an individual will modulate and perceive pain symptoms, as well as their subsequent responses and behaviors (53). According to Gatchel and colleagues (10), the most common mental health disorders in individuals with CNCP are depression, anxiety, and SUDs. The longer an individual experiences CNCP, the greater the role that these mental disorders play in his/her physical disabilities and suffering (53).

As illustrated in Figure 2.2, mental health disorders in veterans with CNCP are common and unquestionably important factors that influence management (7, 30, 54). Veterans are at higher risk because of their exposure to military conflicts and associated psychological stress and trauma (30, 31). These disorders may become amplified in veterans with CNCP which results in even higher rates of depression, anxiety, PTSD, SUDs, and other mental health disorders.

Depression in Veterans with CNCP

According to data from the National Alliance on Mental Illness (55), the prevalence of depression among veterans is approximately 14%. For veterans with CNCP, this rate increases significantly and ranges from 15% to 57% (13-15, 20, 30, 31). In a sample of 359 Iraq and Afghanistan-era veterans with CNCP (17), the prevalence of a mood disorder (i.e., major depression, dysthymia, bipolar disorder) was 45%. Over half of these veterans reported the onset of symptoms after deployment. While 88% of these veterans reported ongoing mental health problems, only 65% reported active treatment for these conditions.

Depression rates vary among subgroups of veterans with CNCP including: veterans with CNCP and hepatitis C (49%) (56); CNCP from spinal disorders (64% mild depression, 40% moderate or severe depression) (57); CNCP from MSD (19.9%) (14); CNCP in OIF/OEF veterans (60%-62%) (13, 31, 58); and veterans with CNCP and concurrent use of prescription opioids (24% for current depressive disorder, 43% for past depressive disorder) (20). In addition, several studies investigated the risk for a new or recurrent diagnosis of depression among veterans prescribed opioid therapy (59, 60). The risk of recurrent depression doubled with opioid use even after controlling for pain, psychiatric disorders, and opioid misuse (59). Moreover, the duration of opioid use (i.e., greater than 30 to 90 days) and the type of opioid prescriptions (i.e., morphine, codeine, hydrocodone, oxycodone) were associated with an 18% to 33% greater risk for new depression diagnosis compared to an individual that took opioids for 30 days or less.

Anxiety Disorders in Veterans with CNCP

In veterans with CNCP, anxiety and catastrophizing symptoms predict pain severity and maladaptive behaviors (31). Anxiety may exacerbate an individual's fear response, magnify pain symptoms, and contribute to the negative affective processes associated with CNCP (30, 53). Hypersensitivity, catastrophizing, and hypervigilance may be signs of an anxiety disorder in individuals with CNCP (31). In order to cope with CNCP, individuals with anxiety may exhibit maladaptive or avoidance strategies as well as behaviors associated with helplessness, vulnerability, and hopelessness (17). These maladaptive behaviors may lead to increased pain and worse functional disabilities (10).

The prevalence of anxiety among veterans with CNCP is highly variable (i.e., 6.9% to 53.0%) (14, 17, 20, 30, 31). In a sample of 159 veterans with CNCP who participated in the Integrative Health Clinic and Program (IHCP) (30), the pretreatment prevalence rate of anxiety

was 53.0% for moderate to severe and 46.8% for severe based on the Beck Anxiety Index (BAI). In another sample of 96 veterans with CNCP (61), the mean baseline BAI score was 19.50 (SD = 11.23), which indicates moderate to severe levels of psychological stress and anxiety. Both of these intervention studies, that used nonpharmacological treatments, mind-body interventions, and complementary alternative medicine (CAM) therapies for the management of CNCP, found a reduction in baseline anxiety levels post-treatment (30, 61).

In a sample of OEF/OIF veterans with CNCP (17), the prevalence for non-PTSD Anxiety Disorder (e.g., panic disorder, social phobia, obsessive-compulsive disorder, generalized anxiety disorder) was 44%. Among veterans with CNCP (31), the prevalence and severity of anxiety varied depending on the presence of other comorbid medical conditions and mental health disorders. In a study that evaluated for differences in veterans' beliefs about pain and coping strategies (62), compared to veterans with only CNCP, veterans who had CNCP and PTSD exhibited greater maladaptive coping responses and beliefs, higher anxiety sensitivity, and increased feelings of vulnerability. These findings suggest that veterans with CNCP and PTSD believe that they have less control over their pain symptoms; their emotions have a greater impact on their pain behaviors; and that they are more likely to catastrophize about their CNCP (62).

PTSD in Veterans with CNCP

PTSD is a disorder that develops after exposure to actual or threatened death, serious injury, or sexual violence resulting in a broad host of symptoms associated with this exposure (63, 64). In the general population, the prevalence of PTSD is 6% in men and 12% in women (16). Among subgroups of veterans, the prevalence of PTSD can vary from 9.1% to 18.7% in Vietnam era veterans (16); 11% to 30% in combat veterans (16); and 4% to 18.5% in OIF/OEF

veterans (16, 62). PTSD is often associated with TBI, military sexual trauma, sleep problems, SUDs, CNCP, and other psychiatric disorders (16, 55). For veterans with CNCP, the prevalence for co-occurring PTSD rises exponentially and can range from 27% to 80% (13-18).

Numerous studies have investigated the negative associations among co-occurring PTSD, CNCP, and other mental health disorders among veterans. Compared to those without PTSD, veterans with CNCP and PTSD reported higher pain scores (18, 31); demonstrated increased utilization of healthcare resources; and had a higher number of comorbid conditions (16, 17). In a sample of 241 OIF/OEF veterans with MSD (31), veterans with comorbid PTSD reported a poorer quality of life, greater functional disabilities, and a higher rate of mental health disorders than veterans with only CNCP (31). The majority of veterans with CNCP and PTSD viewed their pain as a core component of their life and identity, which negatively impacted their responses to treatments and compromised their ability to manage their symptoms (31).

According to Outcalt et al. (13), PTSD and major depression disorder (MDD) have strong independent (but additive) associations with CNCP. These associations among CNCP, PTSD, and MDD resulted in a tripling of the likelihood of disability outcomes and suicidal thoughts and behaviors among veterans with CNCP (13). For veterans with CNCP, PTSD, and depression, evidence-based guidelines recommend that each disorder must be managed independently by a multidisciplinary team (13).

In addition, Iraqi and Afghanistan veterans with CNCP and PTSD have a higher likelihood for experiencing the adverse effects of opioids and poorer clinical outcomes (e.g., overdose accidents) than veterans with only CNCP (65). Compared to veterans without PTSD, veterans with CNCP and PTSD were more likely to be prescribed opioids and at higher dosages one year after a pain diagnosis (65).

Substance Use Disorder (SUD) in Veterans with CNCP

Providing medical treatment to individuals with a history of CNCP and SUD remains extremely challenging (19). This situation is particularly true for veterans where co-occurrence rates range from 52% to 77% (17, 19-29). For these veterans, substances including alcohol, opioids, marijuana, and other illicit drugs are commonly overused or misused in order to cope with the mental and physical stressors that are associated with military service and deployment (16, 17, 23, 55). In addition, veterans with co-occurring CNCP and SUD may exhibit increased drug-seeking behaviors, concurrent mental health disorders, and functional and social disabilities that add to the difficulties of managing both conditions.

Numerous studies have investigated the associations between CNCP and SUD in the veteran population. In one study (19), veterans with CNCP and SUD had more severe medical and mental health problems and higher rates of health care utilization than veterans with only CNCP. These problems included higher rates of depression, anxiety, disabilities, suicidal ideations, and hallucinations. Furthermore, these veterans with CNCP and SUD had more behavioral and cognitive problems and problems with opioids, sedatives, and cannabis misuse than veterans with only CNCP. Similar findings were reported in a randomized clinical trial in which veterans with CNCP and SUD had poorer pain-related functional outcomes and were more likely to be diagnosed with PTSD and depression than veterans with only CNCP (21). These veterans were more likely to be prescribed opioids despite minimal evidence to suggest clinical improvements.

A number of studies have investigated the risk of opioid misuse, abuse, and overdose in veterans with CNCP and SUD (23-28, 66). In one study of 127 veterans with CNCP (25), those with a history of SUD were more likely to exhibit medication misuse behaviors (e.g., overusing

their opioids, requesting early refills, borrowing pain medications from others). In a similar study of 343 veterans (66), 35.5% reported an aberrant opioid behavior which included using alcohol (24%), using street drugs (11.7%), and/or sharing prescription pain medications (16.3%) to manage pain. Among these veterans, a history of SUDs or mental health disorder; younger age; a higher number of non-pain symptoms; and higher pain severity and interference scores were predictors of substance misuse and aberrant behaviors.

Veterans with CNCP and SUD who were prescribed long-term opioids were more likely to have an increased number of pain diagnoses, higher pain intensity scores, more catastrophizing symptoms, and lower self-efficacy scores than veterans who were not prescribed opioids or were on short-term opioid therapy (28). In veterans with CNCP, the risks of adverse outcomes from opioids are significant and include higher mortality rates, as well as increases in hospital admissions and emergency room visits for falls or fractures (67). In addition, risks of overdose and death among veterans with CNCP are increased when higher doses of opioids are prescribed (68), long-acting opioid formulations are used (69), and benzodiazepines and opioids are prescribed concurrently (70).

Summary of Pertinent Psychological Factors

The role that mental health disorders play in the perception and modulation of pain may be more significant in veterans with CNCP. As illustrated in Figure 2.2, these mental health disorders are numerous, highly prevalent, and uniquely problematic in veterans with CNCP because of the clinical challenges associated with effective management of these co-occurring conditions. For veterans with CNCP and co-occurring PTSD, depression, anxiety, SUDs, or other mental health disorders, the interactions between the biological and psychological processes significantly influence pain behaviors; worsen pain symptoms; and result in more functional disabilities.

Furthermore, these psychological comorbidities may limit a veteran's ability to cope with CNCP and contribute to the multitude of social problems.

Social Factors that Contribute to CNCP in Veterans

Gatchel and colleagues (10) identified the importance of social factors that contribute to the challenges that individuals with CNCP face (see Figure 1.1). These social factors can interact with physiological and psychological processes to further influence an individual's responses to illness and disease (8, 10). Instead of viewing these factors individually, a key element of the BPS model of CNCP is an examination of the interactions among these biopsychosocial factors (10). These interactions are especially important in veterans with CNCP because of the multitude of social problems they experience as they transition from active duty to civilian status. As illustrated in Figure 2.2, some of the most common social problems experienced by veterans include: homelessness and social isolation, unemployment and disability, and poor and limited access to medical care and resources (3, 23).

Homelessness and Lack of Social Support and Isolation in Veterans with CNCP

In terms of homelessness, veterans account for 11% of the entire adult homeless population (71). Between 39,000 to 63,000 veterans are homeless on any given night (71, 72). Another 1.4 million veterans are considered at risk for homelessness because of a myriad of social problems including: poverty, lack of social support, and dismal living conditions in overcrowded or substandard housing (71, 73). Although the number of homeless veterans declined by 47% from 2009 to 2016 (71), the majority of homeless veterans are still living in emergency shelters, transitional housing programs, or safe havens.

The majority of homeless veterans are young (i.e., 18 and 30 years of age (9%), 31 and 50 years of age (41%) (73)), single, and predominantly males (91%) as compared to females

(8%) (71). Hispanic and African Americans veterans account for 45% of those homeless even though they account for only 3.4 % to 10.4% of US veterans, respectively (73). In addition, while nearly half of the homeless veterans served during the Vietnam era, a significant number of veterans served in more recent conflicts in the Persian Gulf War and Iraqi OEF/OIF. In 2010, the number of OIF/OEF/OND homeless veterans was estimated to be 12,700.

Homeless individuals face numerous obstacles to healthcare delivery including: lack of transportation; problems with appointments; fragmentation of healthcare services; lack of trust in clinicians; social isolation and poor social support; and other competing primary care needs (74). A significant number of homeless veterans have mental health disorders, SUD, and other co-occurring disorders including CNCP, TBI, and PTSD (23, 55, 72, 73). According to the National Coalition for Homeless Veterans (73), 51% of homeless veterans have multiple disabilities, 50% have a serious mental illness, and 70% have a history of past or active SUD. In a sample of 3,543 homeless veterans seen in thirty-three Homeless Patient Aligned Care Team (HPACT) clinics between October 2013 to March 2014 (74), homeless veterans averaged 3.4 annual primary care visits with HPACT compared to 1.8 clinic visits in a regular primary care clinic, and 1.5 visits in specialty care clinics (i.e., chronic pain clinic, orthopedics, neurology). Moreover, approximately 82.2% were receiving concurrent mental health services and substance abuse treatments.

In a large study of 62,459 veterans in a large metropolitan region (72), the health care needs and utilization rates of homeless veterans were significantly higher than veterans with stable housing. Compared to veterans with stable housing, homeless veterans had higher utilization rates for specialty care visits (e.g., chronic pain (3.0% versus 6.7%), hepatitis C (2.1% versus 4.5%), and infectious disease (1.1% versus 2.4%)). Furthermore, homeless veterans had a

higher number of emergency room visits (i.e., 2.8 visits/patient) than veterans with stable housing (i.e., 1.9 visits/patient).

In addition, veterans experience social vulnerabilities related to lack of social support and isolation (23, 74). Some veterans may distrust the VA system due to experiences with lost paperwork, poor organization, limited access to resources, and fears of stigma or loss of benefits from service-connected disability (SCD) when they seek treatment for mental health disorders or SUD (23). Furthermore, the frequent moves and deployments associated with military service disrupt social relationships including: friendships, family dynamics, and other social networks. In a sample of recently separated OIF/OEF veterans interviewed about the challenges of civilian readjustments (23), a major recurring theme was the practice of self-medication with various substances (i.e., alcohol, opioids, illicit drugs) in order to cope with the feelings of being socially isolated and having untreated mental health disorders (i.e., PTSD, TBI, depression) and CNCP.

In a similar study of post-deployment and re-integration into civilian life of 356 OIF/OEF veterans (75), 20% of these veterans reported problems with social support defined as inadequate or nonexistent social support networks and 37% reported difficulty with relationships and social isolation from friends, coworkers, family, or significant others. These veterans reported CNCP (72%), difficulty sleeping (62%), changes in cognition (61%), vocational issues (53%), poor education (49%), limited finances (42%), anger (30%), and substance abuse (23%). The majority of these veterans reported a combination of interconnected medical and psychosocial problems that had negative effects on their health and ability to cope with these conditions (75).

Medical Access Problems in Veterans with CNCP

Access to healthcare is major priority for the VHA following reports of multiple deaths as a result of delays in medical care (76). In numerous studies, delays in care (e.g., medical and

mental health services) for veterans and system barriers were identified (77-80). With the influx of veterans seeking care in the VHA, many VA facilities are not equipped to handle the large number of veterans because of insufficient funds and an aging infrastructure. Furthermore, with an increasing number of veterans deployed in the Middle East and other parts of the world, coupled with the aging veteran population, the VA continues to be overburdened and unable to provide appropriate and timely care (3, 77).

In a sample of 359 combat veterans from two polytrauma centers (77), 62.4% of veterans reported barriers to VA care because of stigmatization (i.e., embarrassment associated with using VA services; being a burden to the system, perception of welfare or non-entitlement); and access difficulties including: long wait times (26.7%), distance from VA facilities (12%), increased paperwork/hassles (10.3%), lack of information about services (9.5%), and limited hours of services (3.3%). The most concerning barrier to care among this group of OEF/OIF veterans was long wait times for appointments, which doubles the odds of veterans not enrolling in the VA for care (77). In addition, veterans who reported that distance was a barrier to accessing care were seven times less likely to utilize the VA.

In a study that investigated the barriers and facilitators to accessing multimodal chronic pain treatments (78), twenty-five veterans with CNCP reported five key themes, namely: uncontrolled impact of pain on all aspects of their lives; reliance on opioids and challenges in obtaining these drugs despite insufficient evidence for their efficacy; poor access to and beliefs about non-pharmacological therapies; frustration with the VA for their healthcare; and poor social support and isolation. These veterans expressed frustration about the lack of access to pain care because of poor care coordination, lack of empathy from their clinicians, limited resources, poor education, and uncovered expenses for treatments.

In an attempt to provide veterans with increased access to medical care, the Veterans Access, Choice, and Accountability Act was passed in 2014 that allows the VHA to extend community-based care through the VA Choice Program (VCP). This program allows veterans to access healthcare in community or private medical facilities that are listed in the VCP. While this program has reduced VA appointment backlogs and improved wait times, significant problems have emerged in the delivery of non-VA care (79, 80).

In a study of veterans who received specialized care through the VCP (80), four central themes emerged regarding the delivery of care, namely: difficulties with enrollment, ongoing support, and billing with third-party administrators; lack of choice in location of treatment; fragmented care and coordination between the VA and community providers; and VA providers expressed reservations about sending veterans to community providers. These reservations were related to the ability of private sector clinicians to manage the multitude of medical problems and comorbidities among veterans (e.g., mental health disorders, SUD, TBI, and PTSD). In addition, VA clinicians were concerned for the well-being of vulnerable veterans especially individuals who were older and/or homeless and may have difficulties negotiating a new system. Duplication of services and costs related to unnecessary treatments, medications, or overbilling of fees were additional concerns voiced by VA clinicians (79, 80).

Poverty, Unemployment, and Disability in Veterans with CNCP

Social problems such as poverty, unemployment, and disability have a significant impact on the health of veterans including those with CNCP (75, 81). These problems are associated with poor access to medical care and resources, lack of social support networks, and higher medical and psychiatric comorbidities, which result in increased mortality rates among veterans (75, 81-83). In 2015, the poverty rate among veterans was 6.9% for men and 9.4% for women

(84). This rate was highest among veterans ages 35 to 54 years compared to all other age groups. Furthermore, Post-9/11 and peacetime veterans have higher poverty rates than veterans from other military conflicts (84).

According to a 2016 report from the Bureau of Labor Statistics (BLS) (85), the overall unemployment rate for veterans was 5.1%. This rate is significantly higher among veterans with disabilities, female veterans, homeless veterans, veterans who are ≥45 years of age, and veterans from various ethnic groups (e.g., African American, Native American Indian, Hispanics) (81, 86). Of the 453,000 unemployed veterans during this period, 60% were ≥45 years of age, 36% were 25 to 44 years of age, and only 4% were 18 to 24 years of age. In comparison to non-veterans with similar sociodemographic characteristics, veterans ages 18 to 65 years of age have higher unemployment rates (86).

The five most common hypotheses for the high unemployment rates among veterans include: poorer health because of increased physical and mental disabilities; poorer sociodemographic characteristics of individuals who choose to enlist in military service; employer discrimination towards veterans; mismatch in the skills of veterans that are not transferable to civilian jobs; and expected higher unemployment rates for veterans recently discharged or retired from active duty (81, 86). In a study of 12,129 veterans ages 18 to 50 years, those who were unemployed longer than 27 weeks, reported a higher number of days with poorer physical and mental health than long-term unemployed civilians (83). Similar findings were reported in a study of 1007 veterans who completed the 2010 Medical Expenditure Panel Survey (81). Compared to Veterans without disabilities, those with disabilities (i.e., any disabilities, social and cognitive disabilities) had significantly higher rates of unemployment. Moreover, veterans with disabilities (e.g., CNCP, PTSD, TBI, and SUD) had more difficulties finding and

keeping jobs; had significantly lower incomes and poorer health status; and required more assistance with activities of daily living (ADLs) and instrumental ADLs than Veterans without these conditions.

In terms of disabilities, approximately 4.6 million (22%) veterans have a service connected disability (SCD) (85). Veterans with SCD are awarded disability ratings by the US Department of VA or Department of Defense (DOD) based on the severity of the physical and/or mental health conditions acquired during their active military status. In 2016, approximately 30% of veterans with SCD were rated 0% to 30% and 37% were rated $\geq$60%. In 2013, the most common SCD conditions in veterans were: tinnitus, hearing loss, PTSD, scars, knee limitations, lumbosacral and cervical strain, diabetes, sciatic nerve paralysis, ankle limitations, and degenerative arthritis of the spine. Although higher rates of disabilities were found among older veterans, younger veterans experienced higher rates of disabilities than their non-veteran counterparts (87). These disabilities were associated with higher rates of social, physical, and mental health problems that contributed to the challenges of reintegration into civilian life.

In a study of 2943 Marines who recently transitioned to civilian life (88), the prevalence of self-reported functional disability ranged from 4.4% for employment problems to 40.1% for financial problems. Among this group of veterans, the number and severity of PTSD symptoms were significant predictors of multiple functional disabilities and posed the greatest impairment to a successful transition to community living. In addition, the delays in processing SCD ratings and associated compensation is a persistent bureaucratic problem for the VHA. The significant number of unprocessed SCD claims has resulted in financial difficulties for a large numbers of veterans (84). According to the 2015 National Centers for Veterans Analysis and Statistic Report (84), veterans who receive a SCD benefit had a significantly lower poverty rate than non-veteran

disabled individuals. This statistic demonstrates the importance of SCD benefits in helping certain groups of veterans avoid poverty.

Summary of Social Factors in Veterans with CNCP

Social factors are often overlooked as major contributors to an individual's experience of CNCP. As illustrated in Figure 2.2, social factors are numerous and equally important as physiological and psychological factors in the management of CNCP. For certain groups of veterans with CNCP, the various physical and psychological factors may be secondary to more pressing social needs (i.e., housing, family and other social responsibilities, or financial burdens). The BPS model of CNCP considers these factors collectively and examines the interactions among these factors that are unique to veterans' CNCP experiences. Furthermore, if these social factors are addressed, treatment outcomes may improve.

Conclusions

The revised BPS model of CNCP for veterans provides an important conceptual framework that allows for a more thorough evaluation of the physiological, psychological, and social factors that contribute to this experience. As illustrated in Figure 2.2, these factors are numerous and the interactions among them provide the conceptual basis for veterans' experiences of CNCP. Findings from the research reviewed in this paper support the adaption of this revised BPS model of CNCP for this particularly vulnerable population. This conceptual approach has numerous clinical implications and provides opportunities for future research.

Clinical Implications of the Adapted of BPS Model of CNCP for Veterans

In the VA and DOD clinical settings, the BPS model of CNCP provides tremendous support for the importance of multidisciplinary pain teams; the use of multimodal approaches in pain management; as well as a theoretical rationale for prioritizing the needs of veterans with

CNCP. Since a significant number of injuries and trauma occur during active duty training, combat, and non-combat settings, early interventions may improve long-term outcomes. Primary and secondary prevention strategies should be directed at reducing the impact of common injuries and trauma (3). In addition, improved coordination, education, and collaboration is needed between DOD and VA services across the continuum of care.

Based on evidence from the BPS model, VA Central Office (VACO), DOD, and other government agencies are taking steps to implement initiatives and treatment guidelines to improve the care of veterans with CNCP (54). Some of these initiatives include: VA Stepped Care Models (3), the National Pain Strategy (89), Opioid Safety Initiatives (OSI) (90), VA/DOD Opioid Prescribing Guidelines (90), and the CDC Guideline for Prescribing Opioids for Chronic Pain (91). The VA and DOD have expanded pain programs to include various types of treatment (e.g., acupuncture, CAM, chiropractic care, interventional pain procedures) and the use of telemedicine to deliver timely interventions to veterans living in rural regions of the country (3, 90, 92). To improve veteran's self-efficacy with pain management and address the biopsychosocial factors within an interdisciplinary team setting, the number of Commission on Accreditation of Rehabilitation Facilities (CARF) accredited pain programs in the VA has increased (90).

In both the DOD and VA, rehabilitation, mental health, and social services remain important for veterans with CNCP. Expansion of these programs is needed to combat the opioid epidemic, reduce long-term disability, address the multitude of social problems, and improve mental health (3). Lastly, because of the increasing number of veterans seen outside the VA system, clinicians in the private sector can utilize this BPS model to address the unique physiological, psychological, and social factors that contribute to CNCP in these individuals.

Directions for Future Research

When applied to veterans, the BPS model of CNCP provides direction for a number of avenues of research. Studies that investigate primary and secondary prevention for common injuries and trauma may reduce the long-term effects of CNCP in veterans (3). In addition, the BPS model may direct the prioritization of research for combat casualty care (e.g., acute and reconstructive care, limb salvage, posttraumatic, and rehabilitation care) (93). Within the framework of the BPS model, studies that explore factors associated with veteran's resilience, self-efficacy, motivation, and recovery may improve pain treatment outcomes.

Qualitative and quantitative studies are needed to explore the BPS factors that influence CNCP in veterans with various sociodemographic characteristics. For example, researchers can investigate the impact and management of pain conditions (e.g., phantom limb pain, post-concussive headaches) in specific veteran population (e.g., nursing home veterans, Hispanic OEF/OIF veterans) within the context of this model. Studies that explore the lived experience of vulnerable veteran populations (i.e., female veterans, polytrauma, homeless) should remain research priorities. Furthermore, key stakeholders including patients, providers, and policymakers, may provide additional insights into BPS factors in various settings.

Studies are needed that investigate the impact of recent VA/DOD initiatives and CDC guidelines on pain care in veterans especially among those with co-occurring CNCP and opioid use disorder/SUD. In addition, the paucity of studies that investigate the long-term effectiveness and safety of opioids in veterans remain insufficient (94, 95). Outcomes studies are needed for specific CNCP interventions (i.e., acupuncture, yoga, ketamine infusion, virtual reality stimulations) in order for clinicians to support their use (96). Furthermore, these studies should

develop and investigate measurement tools that evaluate the impact and outcome of CNCP (e.g., instruments that evaluate social integration and patient engagement) (93, 97).

Of note, the Department of VA Office of Health Services Research and Development established priorities for rehabilitation research (97). Their research plan, which highlights the importance of physiological functions (e.g., molecular, cell, tissue, and organs), as well as physical and mental functions and various aspects of social and community integration can be used within this CNCP framework.

In summary, veterans with CNCP are a vulnerable population whose care remains a challenge for clinicians, policymakers, and researchers. The use of this model, in practice and research, may lead to improvements in both the assessment and management of CNCP.

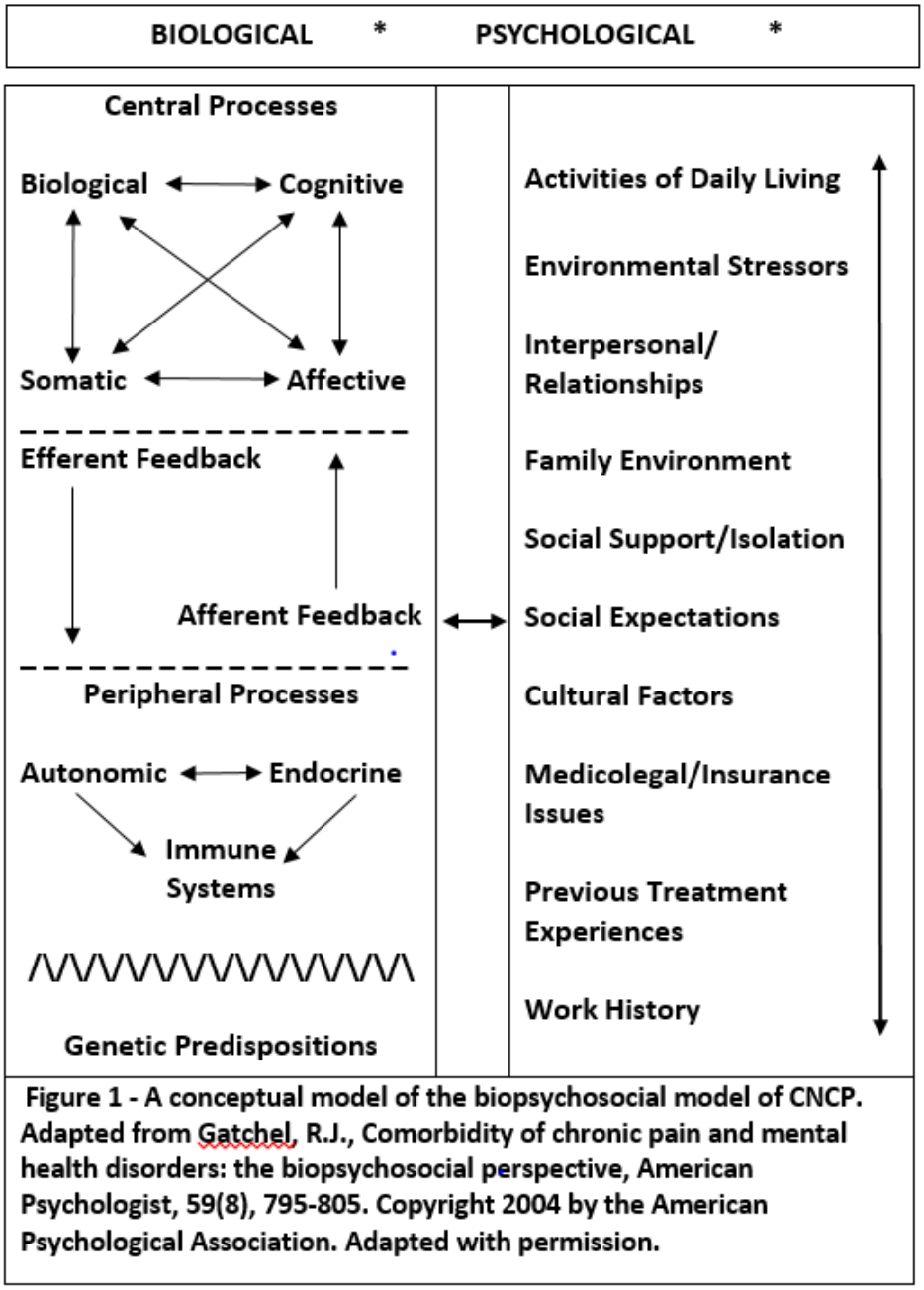

Figure 1 - A conceptual model of the biopsychosocial model of CNCP. Adapted from Gatchel, R.J., Comorbidity of chronic pain and mental health disorders: the biopsychosocial perspective, American Psychologist, 59(8), 795-805. Copyright 2004 by the American Psychological Association. Adapted with permission.

FIGURE 2.1: A CONCEPTUAL MODEL OF THE BIOPSYCHOSOCIAL MODEL OF CHRONIC NON-CANCER PAIN

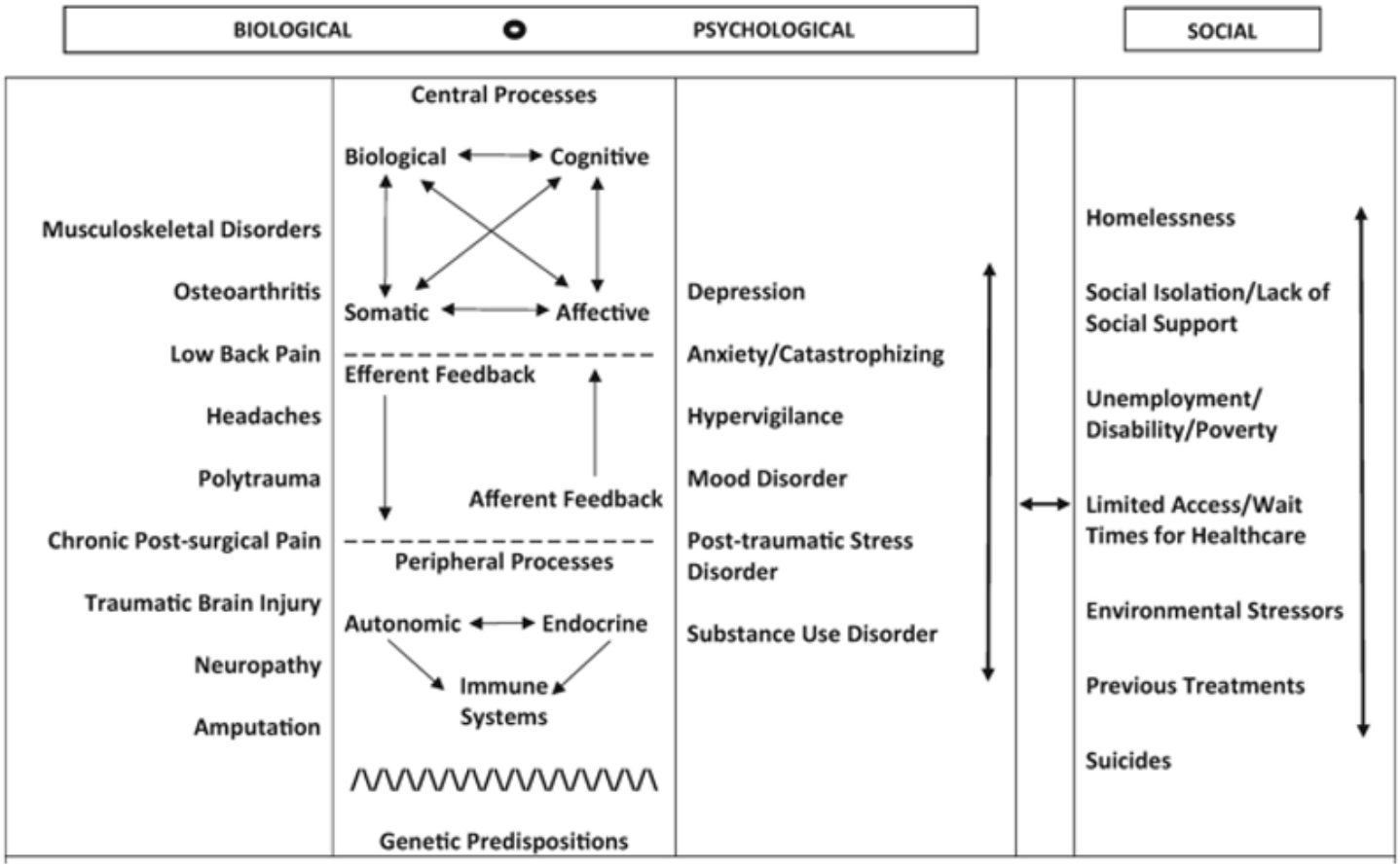

FIGURE 2.2 THE BIOPSYCHOSOCIAL MODEL OF CHRONIC NON-CANCER PAIN IN VETERANS

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CHAPTER 3

LONG-TERM OPIOID THERAPY FOR THE MANAGEMENT OF CHRONIC NON-CANCER PAIN IN VETERANS: A COMPREHENSIVE LITERATURE REVIEW

ABSTRACT

Background: The use of long-term opioid therapy (LTOT) for the management of chronic non-cancer pain (CNCP) is a common practice among veterans. However, the opioid epidemic and the increasing reports of adverse side effects and overdose death have questioned the effectiveness and safety of this treatment. **Methods:** This comprehensive literature review evaluated the effectiveness or safety of opioids prescribed longer than 3 months for the management of CNCP in the veteran population. Studies of opioid use in acute and cancer pain, addiction treatment, and non-veteran populations were excluded. Out of 474 articles found, 12 studies were included in this review. **Results:** Five studies investigated both the effectiveness and safety of LTOT in veterans with CNCP while seven studies reported only on adverse effects or safety. The effectiveness studies included two randomized clinical trials, two retrospective cohort studies, and one cross-sectional study. Among these studies, only one reported significant result for improving pain intensity while the remaining studies did not show strong evidence to support the effectiveness of LTOT for improving pain and physical functioning. The seven studies that reported on adverse effects and opioid abuse risks were retrospective cohort studies. These studies reported multi-organ adverse side effects (i.e., gastrointestinal, cognitive, psychological, and cardiovascular). **Conclusions:** For veterans prescribed LTOT for CNCP, this literature review identified a paucity of evidence for the effectiveness of LTOT for improving pain and physical functioning in this vulnerable population. In addition, this review highlighted the importance of monitoring veterans prescribed LTOT for adverse effects, aberrant drug-related abuse, and other risks associated with physical, physiological, and social co-morbidities.

Keywords: veteran(s), chronic non-cancer pain, opioids, long-term opioid therapy, analgesics, effectiveness, opioid safety

INTRODUCTION

The International Association for the Study of Pain (IASP) defines chronic pain as that which persists beyond the usual course of acute illness or injury (or beyond 3 to 6 months), and affects the individual's well-being (1, 2). Of the 4 million veterans receiving care through the Veterans Health Administration (VHA), an estimated 1.44 million have chronic non-cancer pain (CNCP) (3). Compared to the prevalence of CNCP in the general population (i.e. 30%), the rate for chronic pain in veterans is higher, especially among specific subgroups (i.e., female veterans (67.9%) (4), middle-aged and older veterans (36.3% to 47.4%) (4, 5), and Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans (81.5%) (6)). These rates continue to increase as the number of veterans with CNCP age, and as the number of injuries accrue from on-going military conflicts (7).

Veterans experience complex and challenging CNCP conditions as a result of physical injuries, co-occurring mental health disorders, and social difficulties (7-9). Compared to the general population, veterans report higher rates of musculoskeletal pain, including arthritis (25.6% versus 23.6%) (4), low back pain (32.8% versus 28.5%) and other joint conditions (43.6% versus 31.5%) (10). In addition, veterans are 1.5 times more likely to report severe CNCP than the civilian population. Veterans aged 18 to 39 years have 3.1 times the odds of severe CNCP compared to the same age non-veteran cohort (10). These severe CNCP conditions were often associated with functional disabilities, psychological distress, family discord, social isolation, and vocational barriers (7, 11).

In the current management of moderate to severe CNCP, opioids are the most commonly prescribed analgesics and the majority of these prescriptions are written by primary care providers (12-14). Opioids inhibit and modulate pain symptoms via the central nervous system

and nociceptive neural circuitry. Opioids are classified as agonists, antagonists, mixed agonists-antagonists, and partial agonists that bind to opioid receptors distributed throughout the body (15, 16). The binding of opioids to opioid receptors produces intracellular effects that inhibit nociceptive transmission and the release of excitatory neurotransmitters (15). Analgesic opioid response varies significantly among individuals and may depend on factors such as genetic characteristics, molecular mechanisms of opioid receptor signaling, and other factors that contribute to pharmacological and behavioral effects (e.g., analgesia, reward, depression, anxiety, and addiction) (16).

During the previous two decades, opioid prescriptions for the management of CNCP in the general population had increased by 30% to 58% (17, 18). This increase coincided with key events including the U.S. Congress proclamation of the "Decade of Pain Control and Research" (19), the intense focus on pain standards by the Joint Commission on Accreditation of Hospital Organization, the release of pain management guidelines by expert panels, and the aggressive marketing by pharmaceutical industries (including makers of Oxycontin and COX-2 Inhibitors) (17, 18, 20). In addition, clinicians and pain organizations advocated against the under-treatment of pain and early research suggested that opioids were effective for acute and chronic non-cancer pain; these factors contributed to the routine use of opioids for CNCP (21-23). In contrast, more recent studies suggest that opioids, especially when used long-term and at higher doses, can have adverse effects (i.e., arrhythmias, thyroid disease, hypogonadism, falls, and hyperalgesia (20, 24, 25) and may contribute to increased risk of abuse, overdose, and diversion (21, 26)).

Several systematic and comprehensive reviews (20, 23, 24, 27) have investigated the safety and effectiveness of LTOT for management of patients with CNCP. According to a review by Manchikanti et al. (24), only four studies investigated opioid therapy for CNCP lasting 6

months or longer. They concluded that the strength of evidence for LTOT was weak for improving pain levels, physical function, and quality of life. The authors concluded that clinicians should be cautious when considering LTOT for CNCP because of potential adverse side effects on multiple organ systems, including respiratory depression, cognitive impairment, sexual dysfunction, hyperalgesia, and gastrointestinal problems.

Chou et al. (20) conducted a recent systematic review of 39 studies comparing the harms and effectiveness of LTOT (>3 months) versus placebo, no opioid, or non-opioid therapy. The review found that no study had examined the effectiveness of LTOT on pain relief, function, or quality of life for more than one year. 19 studies suggested that LTOT is associated with increased risk for opioid abuse or addiction, overdose, fractures, cardiovascular events, endocrinological harms, and motor vehicle accidents. Furthermore, several studies demonstrated that higher doses were associated with increased risk. While evidence supports a dose-dependent risk of LTOT, none of the studies evaluated the effectiveness of risk mitigation strategies for overdose, addiction, abuse, or misuse.

The VHA and Department of Defense (DOD) have been quick to respond to evidence suggesting that veterans are at high risk for adverse effects from LTOT (28-33). In 2013, the VA Undersecretary of Health issued the Opioid Safety Initiative (34) which mandated all VA facilities curtail the rising prevalence of LTOT and reduce the risk of opioid overdose, deaths, and misuse among veterans. The Center for Disease Control and Prevention (CDC) Opioid Safety Practices (35) and VHA and DOD Practice Guidelines for Opioid Therapy for Chronic Pain (29) were released in 2016 and 2017, respectively. Intended for primary care clinicians, these guidelines recommended lower opioid dosage limits for patients prescribed LTOT for

CNCP and placed a greater emphasis on implementing risk mitigation strategies, promoting patient education and safety, and reducing adverse effects.

Given the alarming trends in opioid abuse, overdose, and opioid-related deaths, along with high levels of opioid prescription, the safety and effectiveness of LTOT is in question (36). Although there have been a number of literature reviews (20, 22-24, 27) on the effectiveness, harm, and risk of adverse effects of LTOT for CNCP, few of the current literature reviews have focused on veterans. The purpose of this review is to evaluate the effectiveness and safety of LTOT for the management of CNCP in the veteran population.

METHODS

In collaboration with a professional librarian, a systematic and comprehensive literature search was performed using three databases: PubMed, Cumulative Index for Nursing and Allied Health Literature (CINAHL), and PsycINFO. Key terms used included veteran(s), chronic non-cancer pain, opioids, long-term opioids, chronic opioid therapy, and opioid analgesics. English language articles published between January 2005 and January 2019 were searched. Relevant studies from prior systematic reviews (20, 24, 27), recent LTOT clinical guidelines (29, 35, 37) and their reference lists were also reviewed. This review includes studies that evaluated the effectiveness or safety of opioids prescribed longer than 3 months for the management of CNCP in the veteran population. Studies of opioid use in acute and cancer pain, addiction treatment, and non-veteran populations were excluded.

Figure 3.1 illustrates the search and selection process for this literature review. A total of 474 articles were found in the three databases and additional sources reviewed. After a review of study abstracts and titles, 16 studies were selected for full-text review. 4 studies were excluded due to limited sample size, duration/timeframe, or qualitative study design. The twelve studies

that remained were comprised of five studies on the effectiveness and seven studies that investigated adverse effects and safety associated with LTOT in veteran with CNCP.
Data extraction was conducted to describe the studies for the following characteristics: setting/location, study design, study sample (i.e., size, study groups or subgroups by opioid treatment type, age, gender, race/ethnicity, and marital status), type of CNCP conditions, opioid used, follow-up period, data collection method, and measurement tools.

Data synthesis was performed to assess the overall strength of evidence for the effectiveness and safety of LTOT specific to the veteran population. The Grading System by Agency for Healthcare Research and Quality (AHRQ) was used to evaluate the quality of each study. The AHRQ Grading System aims to ensure methodologic consistency in evaluating the strength of evidence and facilitates guideline development or clinical decision-making (38, 39). Evidence was graded as high, moderate, low, or insufficient on the effectiveness, comparative effectiveness, and harms of different health interventions or treatments (38).

In addition, the review was based on four domains that included risk of bias, consistency, directness, and precision. Risk of bias refers to the individual study design and conduct, whereas, consistency refers to the degree in which other studies have reported similar effects. Directness of a study refers to the ability of the study effect or intervention(s) to directly link the outcome(s) and precision refers to the degree of certainty. When appropriate, additional domains included dose-response association, presence of confounders, strength of association, and publication bias. Because of the small number of studies, the variability of study designs, and methodological variations, a meta-analysis was not performed.

RESULTS

Table 3.1 provides a summary of twelve studies included in this review. Five studies (14, 40-43) investigated both the effectiveness and safety of LTOT in veterans with CNCP. Seven studies (3, 12, 13, 25, 44-46) reported only on adverse effects or safety with LTOT among veterans. The five studies that reported on the LTOT effectiveness included two randomized clinical trials (RCT) (42, 43), two retrospective cohort studies (14, 40) and one cross-sectional study (41). Among these studies, only one (41) reported statistically and clinically significant results supporting the effectiveness of LTOT. All seven studies that reported on adverse effects and risks were retrospective cohort studies.

Effectiveness of LTOT in Veterans with CNCP

Mahowald et al. (41) conducted a cross-sectional interview study on veterans' opioid use and a retrospective analysis of opioid prescription in the previous 3 years (1994 – 1997). A total of 230 veterans with CNCP from various spine diseases (e.g., intervertebral disc disease, spinal stenosis, low back pain after surgery, compression fracture) were identified from the Minneapolis VA Orthopedic Spine Clinic. Of those, 152 (66%) veterans were prescribed opioids in the previous 3 years and were divided into short-term opioid (STO) use (<3 months) and long-term opioid (LTO) use (>3 months) groups. Of the 152 veterans taking opioids, the mean reduction in spinal pain severity score went from 8.3 to 4.5 ($P<0.001$). Among the subgroups, veterans in the LTO reported significantly greater reduction in pain severity (from 8 to 3.9) compared to the groups of STO (from 8.6 to 5.0) or no opioid use (from 7.7 to 4.9). In addition, veterans in the LTO group were significantly more likely to report at least 50% reduction in pain severity than the STO group (69% vs. 45%, $p = 0.018$). Lastly, during the qualitative interviews, 54% of veterans in the LTO group reported that their pain medication helped "a lot" compared to

only 40% and 10% in the STO and no opioid group, respectively. In summary, in this sample of veterans, LTOT was associated with greater reduction in mean pain scores when compared to short-term use or no opioid use in veterans with CNCP from spine disease.

Wu et al. (14) conducted a retrospective analysis to determine the effectiveness and safety of LTOT in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans ages 18 to 30 years old. From the VA Data Warehouse, outpatient prescriptions and electronic medical records were collected in a sample of 173 veterans who were prescribed LTOT. In this sample, only 18 veterans receiving long-acting opioids met their inclusion criteria for evaluating LTOT effectiveness and safety. The study measured pain outcomes by visual analog scale (VAS) 3 months before initiation of long-acting opioids and after 6 months. Response to opioid therapy was defined as maintenance of a pain score of 0 or 30 percent reduction in pain scores between 1-3 months after initiation of long-acting opioids. After initiation of long-acting opioid, median pain scores did not show a statistically significant improvement from baseline at 1, 3, and 6 months in this small sample of veterans. In addition, only 4 (22%) patients met the study's definition of opioid responders, whereas 7 (39%) patients discontinued their opioid use. In this sample of OEF/OIF veterans, LTOT was not associated with improvements in median pain score after initiation of long-acting opioids.

Naliboff et al. (42) conducted a single-blind RCT that assigned 140 veterans with CNCP to different prescribing strategies for LTOT: conservative stable dosing versus liberal escalating dosing. The study was conducted at a multidisciplinary VA pain clinic and took place monthly or quarterly for one year. The four primary outcomes included pain severity, pain relief from medications, pain-related functional disability, and opioid misuse behaviors. Patients assigned to the liberal escalating dosing were found to have an 80% increase in opioid dosage over 12

months, compared to only a 16% increase in the conservative dose group. 21% of the escalating dose group reported greater reduction in pain symptoms with LTOT over time compared to only 2% of the stable dose group. However, there was no significant difference in the improvement of functional disability or usual pain between groups.

Burgess et al. (40) conducted a retrospective cohort study in veterans with CNCP, examining the association between pain outcomes and perceived opioid medication effectiveness among blacks and non-Hispanic white veterans. Using the 2007 VA Survey of Healthcare Experiences of Patients (SHEP) and the VA National Patient Care Database (NPCD), the study investigated veterans who were treated for CNCP with and without opioid medications and their perceived effectiveness on pain interference. The study included 1,622 blacks and 13,758 non-Hispanic whites who were prescribed opioids 3 months after a chronic musculoskeletal pain diagnosis. The primary outcomes were pain interference with normal work and self-rated effectiveness of pain treatment. According to the results, black and non-Hispanic white veterans who received opioid prescriptions reported statistically significant greater pain interference scores compared to veterans who did not receive LTOT. However, receipt of opioid prescription was not associated with perceived treatment effectiveness except for those veterans who reported mild pain intensity (i.e. pain score 1-3).

Krebs et al. (43) compared the effectiveness of opioid versus non-opioid medications for improving pain and function in veterans with chronic back, hip, or knee osteoarthritis pain. This pragmatic RCT enrolled 240 veterans who were randomly selected to receive a prescribing strategy of opioid versus non-opioid medications over a 12-month period. The primary and secondary outcomes were function and intensity, respectively. The authors concluded there was no statistically significant difference in pain-related functional outcomes among veterans

prescribed opioid versus non-opioid medications (p = .58). The difference in the mean Brief Pain Inventory (BPI) Interference score among the two groups was 0.1 (95% CI, -0.5 to 0.7).

In addition, more veterans in the non-opioid medication group (53.9%) reported greater improvement in BPI severity scores compared to veterans prescribed opioids (41.0%); a difference measuring -12.8% (95% CI, -25.6% to 0.0) (p = 0.05). Quality of life measures including overall physical and mental health scores did not differ significantly between groups, except for anxiety scores. After 12 months, veterans in the opioid group reported lower mean anxiety scores of 2.5 compared to 2.8 (p = 0.02). The authors concluded that LTOT was not superior in improving pain-related functional outcome compared to non-opioid medications in this sample of veterans with CNCP.

Adverse Effects, Safety, or Risk Associated with LTOT in veterans with CNCP

Four studies (13, 14, 41, 43) reported on adverse effects related to LTOT in veterans with CNCP. According to Wu et al. (14), 28% of veterans who were prescribed LTOT reported adverse effects such as nausea/vomiting, opioid-induced hyperalgesia, decreased libido, constipation, and sedation. Similarly, Mahowald et al. (41) found the most common adverse effects among veterans on opioids were constipation (49%) and sedation (31%), with less than 15% reporting dizziness, itching, or headache. The highest percentage of opioid adverse effects were found in veterans taking LTOT (73%) compared to short term use (59%) or no opioid use (31%). In both studies, adverse effects from opioids such a codeine, oxycodone, propoxyphene, tramadol, morphine, meperidine, fentanyl, and hydrocodone were treated homogeneously. Krebs et al. (43) reported more adverse effects in the opioid group compared to the non-opioid group in the 12-month period (difference 0.9).

In a retrospective cohort study of veterans with CNCP who were prescribed methadone (n=92) and morphine (n=90), veterans taking methadone reported more adverse side effects (34%) compared to veterans taking sustained release morphine (26%) (13). The adverse effects included changes in cognition (e.g., memory loss, dizziness, fatigue, drowsiness, and insomnia), mental health (e.g., aggressiveness, depression, panic attacks, irritability, and drug-seeking behavior), gastrointestinal (i.e., diarrhea, nausea, vomiting, and constipation), and cardiopulmonary effects (i.e., high blood pressure, difficulty breathing, prolonged QTc interval, shortness of breath). The study also found that most veterans prescribed either methadone or morphine SR discontinued the opioid for several reasons, including adverse side effects, inadequate pain relief, and non-compliance.

Six studies (13, 41-44, 46) evaluated the safety of LTOT related to opioid abuse, misuse and aberrant drug-related behaviors (ADRB) among veterans with CNCP. Krebs et al. (43) found no significant difference between veterans prescribed LTOT and non-opioid medications for adverse outcomes or potential misuse measures (i.e., Addiction Behavior Checklist, positive urine toxicology screen or unexplained drug, alcohol or illicit drug use, positive misuse behavior or prescription monitoring program). However, Mahowald et al. (41) reported that only 5% (n=3) of veterans prescribed LTOT had behaviors indicative of drug tolerance, loss of control over opioid use, or opioid abuse behaviors. According to Macey et al. (13), non-adherence with LTOT was reported in 9% of veterans who were taking methadone compared to 4% taking morphine SR (13). Naliboff et al. (42) reported similar findings of noncompliance with medication (15%) or noncompliance with clinic procedures (4%) in veterans prescribed LTOT. In addition, 10% of substance misuse or non-compliance discontinuations of LTOT in this study were due to alcohol or illicit substance abuse.

In a retrospective cohort study of 800 veterans with CNCP who were prescribed LTOT, Sekhon et al. (44) reported 22.9% of veterans had ADRB (i.e., report of lost or stolen medications and/or use of multiple sources to obtain opioid, urine drug toxicology positive for illicit drugs or unreported opioids confirmed, or more than one request for early refills). The study found that the risk of ADRB was higher for those who are $\geq$ 40 years of age, who have an anxiety and/or bipolar disorder or past or current history of non-opioid substance abuse, or who are prescribed morphine equivalent dose > 200mg/day. In a study by Lovejoy et al. (46), a number of veterans exhibited aberrant behaviors such as suspected active substance abuse (44%), inappropriate urine drug results (37%), opioid misuse behaviors (15%), non-adherence (11%), and concerns for diversion (4%). In addition, veterans with substance use disorder (SUD) diagnosis were more likely to have their LTOT discontinued due to aberrant behaviors than veterans without SUD diagnosis (odds ratio (OR) = 1.79, 95% CI = 1.28-2.51).

Two studies reported additional risks in veterans prescribed LTOT and the association with psychiatric and medical comorbidities (64, 45). In a large retrospective cohort study of veterans (n = 70,997), Salas et al. reported that veterans who are prescribed LTOT (>90 days opioid use) were at an increased risk for new depression episode (NDE) compared to veterans prescribed short-term opioids (1-30 days). The incidence rate for NDE in women was 36.7/1000 in person-years and for men was 15.4/1000 in person-years ($p < .001$). In addition, the risk of NDE was higher in female veterans (hazard ratio [HR] = 1.79; 95% CI: 1.45-2.22) than male veterans (HR = 1.25; 95% CI: 1.16-1.34). Among female veterans, LTOT duration was significantly associated with higher pain score, maximum morphine equivalent dosage, greater healthcare utilization, CNCP diagnosis of arthritis and back pain, and psychiatric comorbidities (i.e., post-traumatic stress disorder (PTSD), anxiety disorders, SUD).

In a retrospective cohort study, Morasco et al. (25) compared three groups of veterans with CNCP who were prescribed high-dose opioid (≥ 180 mg morphine equivalent per day, n = 478), traditional-dose opioid (5-179 mg morphine equivalent per day, n = 500), and no opioid (n = 500). They found that patients in the high-dose group had a greater number of documented diagnoses for pain conditions (such as fibromyalgia, arthritis, and low back pain) compared to the other groups. The high-dose group also demonstrated the highest frequencies of psychiatric diagnosis (including major depressive disorder, any alcohol or substance use disorder, nicotine disorder, and other anxiety disorder).

DISCUSSION

In recent years, the use of LTOT in the management of CNCP has changed significantly as a result of multiple factors. The "opioid epidemic", the paucity of evidence to support long-term opioid effectiveness, and increasingly stringent regulations have brought about a rethinking of how, for whom and when opioids should be prescribed. For most pain providers, this national debate has been a welcome discussion. However, these questions have become a conundrum for primary care clinicians. This situation is particularly palpable in the VA, where mandates to reduce opioid prescriptions have created dilemmas for patients, clinicians, and administrators. Based on the body evidence against the use of LTOT coupled with the continued rise in the prevalence of opioid use disorder and overdose, the national opioid prescribing rate in the VA system has been reduced by as much as 71% between 2012 to 2018 (47).

To assist healthcare providers, the purpose of this literature review was to evaluate the effectiveness and safety of LTOT in veterans with CNCP. The literature review findings suggest that LTOT may be a less appropriate option for managing CNCP in the veteran population. A majority of studies that investigated LTOT effectiveness in veterans did not provide convincing

evidence for improving pain intensity, function, quality of life measures or patient satisfaction over a 3 to 12-month period (14, 40, 42, 43). In addition, the two RCTs comparing opioid prescribing strategies and opioids versus non-opioid treatments did not find statistical significance in favor of LTOT. In fact, for veterans prescribed opioids over a 12-month period, the findings suggest that there is no statistically significant difference in primary pain outcomes (i.e., pain intensity, function) when compared to non-opioid treatment. Furthermore, these findings suggest that LTOT can provide only a modest improvement in pain relief from medication despite higher opioid dosage escalation.

However, upon a closer review of these studies, some veterans did report improvements in function and pain intensity with LTOT. In fact, reductions in mean pain score/intensity ranging from 9% to 51% have been reported in veterans prescribed LTOT (41-43). According Naliboff et al., approximately 44% of veterans reported a greater than 1.5% reduction in pain with opioid medications (42). In addition, approximately 52% of veterans reported a greater than 10-point improvement in functional disability scores (i.e., Oswestry Disability Index) (42). Similar findings were reported by the SPACE randomized clinical trial (43), where reductions in pain-related functional scores decreased 37% after 12 months post treatment in veterans prescribed LTOT. In this study, function was measured by the Brief Pain Inventory (BPI-interference scale) where higher scores indicate worse functioning. These findings suggest that certain group of veterans with CNCP do benefit from LTOT in both pain intensity and improvements in function. In these studies, majority of these veterans were male, mean age of 50 years old, and reported CNCP from chronic back, other musculoskeletal pain (i.e., hip or knee osteoarthritis) and complex or mixed pain including neuropathic pain.

In comparison to the general population, numerous studies have also reported similar findings of pain improvements related to intensity and function (22-24). In a meta-analysis review of LTOT effectiveness and side effects, Furlan et al. (23) reported that opioids were more effective than placebo for pain relief and function in patients with nociceptive, neuropathic or fibromyalgia (standard mean difference (SMD) –0.60, 95% confidence interval (CI) –0.69 to –0.50). In addition, strong opioids (i.e., morphine and oxycodone) was significantly more effective than naproxen and nortriptyline for pain relief over a 1-16 weeks follow-up (SMD –0.34, 95% CI –0.67 to –0.01). Manchikanti et al. (24) reviewed the effectiveness of LTOT for a minimum of one year and found at least a 30% reduction in mean pain intensity scores and that opioids are effective in a small proportion of patients. Although the overall evidence for opioid effectiveness was weak in some of the studies, their findings suggested that those patients who remained on LTOT experience clinical significant pain improvements (24).

For safety and adverse effects, all or most of the studies provided striking evidence that clinicians should take extra precaution when prescribing LTOT for veterans with CNCP. In addition to the multi-organ system potential adverse effects, the rate of ADRB and opioid use disorder remains alarmingly high. For veterans especially among males, the long term adverse effects of opioid use can cause significant concerns with hypogonadism and other endocrine dysfunction, decrease in libido including erectile dysfunctions, and cardiopulmonary conditions (9). Because of the high prevalence of hypertension, diabetes, sleep apnea and other concurrent medical conditions related to physical deconditioning and weight gain, veterans with CNCP may be at greater risk of exacerbating these conditions when prescribed LTOT compared to those veterans who are not (9, 48, 49) .

In addition, veterans with CNCP have high prevalence of SUD and other mental health problems (i.e., depression, PTSD, anxiety), cognitive dysfunctions, and social problems (i.e., homelessness, poor social support and isolation, and medical care access problems) (9). These medical and social problems may worsen in veteran prescribed LTOT because of the increase risks of ADRB, opioid misuse or abuse, and non-compliance reported in these studies. Moreover, other studies have reported on the risks of unintentional overdose and death among veterans (36, 50-52). These risks increase exponentially when benzodiazepines and opioids are prescribed concurrently (51), higher doses of opioids are prescribed (36), and long-acting opioid formulations are used (52).

LIMITATIONS OF OPIOID STUDIES IN VETERANS

The studies on veterans included in the literature review have notable limitations. Firstly, 10 out of 12 veteran-specific studies reviewed were observational and utilized retrospective cohort design (n=9) or cross-sectional (n=1) designs. The following studies (13, 14, 25, 40, 41, 44-46) relied heavily on medical records or on data analysis at a single point in time and can infer only association and not causation (53). Furthermore, observational studies are susceptible to three broad types of bias including selection bias, information bias, and confounding variables. For example, Wu et al. (14) excluded 4127 veterans in their review of LTOT effectiveness and safety. After further exclusion of veterans prescribed long-acting opioids, only 18 participants were included in their analysis to determine opioid responders versus non-responders. Selection and information bias may have also affected the studies conducted by Mahowald et al. (41) where sample groups were not equivalent (i.e., large samples in no opioid or short acting opioid group in comparison to veterans prescribed long term opioid medications). Burges et al. (40) relied on a sample of veterans who completed SHEP survey to determine perceived opioid

effectiveness and the association with race. Confounding variables that may affect these study findings include the effects of opioid prescribed outside of the VA system, pain relief from short-acting opioid medication, or other treatments not included in the VA medical records. In addition, missing data from veterans who are excluded in these studies, veterans who did not respond to survey, or those who have limited medical records may further affect study results.

In order to reduce bias and confounding variables associated with cross-sectional or retrospective cohort studies, the following studies (42, 43) utilized randomization in their study design. However, these studies have noted limitations related to a lack of placebo control or an appropriate comparison group to investigate LTOT effectiveness and safety. Even though placebo control studies may pose ethical and study feasibility concerns, placebo control may provide a better distinction between the therapeutic effects, adverse effects, and safety of LTOT while minimizing confounding variables. For example, Naliboff et al. (42) compared opioid prescribing strategies and their effects on pain intensity and function without a placebo or non-opioid comparison group. In addition, high attrition or opioid discontinuation rate of 27% (n=38) of the sample may have affected the ability to identify differences in treatment outcome among groups. As a potential limitation in their study, Naliboff et al. (42) also commented on the relatively small outcome improvements in their study because a majority of the veterans were already prescribed opioids at study baseline irrespective of their randomized group.

Secondly, the majority of studies categorized CNCP as homogenous conditions, whereas in reality CNCP is composed of multiple pathophysiological entities, not all of which may respond to LTOT. Based on an individual's level of nociceptive and neuropathic pain etiology, opioid inhibition and modulation of these pain foci may depend on the individual's biological and genetic characteristics (16, 54). Furthermore, biopsychosocial factors such as mental health

disorders (5, 42, 55-58), and social factors (7, 30) also contribute to the veteran's pain experience. Veterans are a vulnerable population whose military experience may place them at risk for injuries and trauma related to active duty training (59), combat related injuries (6, 7, 60), non-combat injuries (5), pain as a result of other medical comorbidities (e.g., hypertension, obstructive sleep apnea, diabetes) (48, 49), and post-surgical complications from limb reconstruction and/or amputation (61, 62).

Several studies illustrate this point. Burgess et al. (40) studied veterans prescribed opioids for chronic musculoskeletal pain related to back, neck, or joint pain; Wu et al. (14) identified veterans receiving opioids for non-malignant pain or pain not related to drug detoxification purposes. These non-specific pain conditions provide little information to distinguish pain etiologies that may or may not respond more effectively to LTOT. Two studies (41-43) reported LTOT for the management of low back pain and hip and knee osteoarthritis, with the majority of the sample diagnosed with low back pain. However, low back pain diagnosis encompasses a broad range of etiologies that may include spinal stenosis, radiculopathies, facet arthropathies, myofascial pain or spasms, degenerative disc disease, spondylosis and other conditions. These low back pain conditions could have varying responsiveness to opioid therapy based on the degree of the nociceptive and neuropathic inputs and/or in combination with other factors associated with pain pathways (i.e., transduction, transmission, perception, and modulation). Studies that did not take these factors into consideration may have had difficulty finding difference in outcomes from treatment algorithms including those utilizing LTOT.

Similarly, most of these veteran-specific studies also classified opioid medications homogenously, without addressing the pharmacodynamic and pharmacokinetic differences between drugs. These studies reported LTOT based on morphine equivalence and overlooked the

possibility that certain opioids may provide better outcomes than others for specific individuals and CNCP conditions. The use of opioids for pain modulation via mu and kappa receptors has been shown to be more effective in nociceptive pain stimuli than in neuropathic pain conditions (16). Most veterans recruited in these studies may have a combination of pain pathologies resulting in varying degrees of nociceptive, neuropathic, or mixed transmission affecting the response to LTOT. The effectiveness of LTOT in these individuals may elude investigators until a better understanding of these confounding variables are addressed.

Manchikanti et al (24) reviewed the effectiveness and adverse effects among individual opioids including hydrocodone, oxycodone, morphine, tramadol, methadone, transdermal fentanyl, codeine, oxymorphone, buprenorphine, and tapentadol. This review found fair evidence for the effectiveness of Tramadol for osteoarthritic pain; however, for all other opioids, the evidence was poor based on either undetermined effectiveness, weak positive evidence, or negative evidence for managing all other pain conditions. In addition, concerns for safety and adverse effects were common in these studies; this highlights the importance of careful patient selection when prescribing of LTOT.

Thirdly, some of the LTOT outcome measures used in the reviewed studies were limited and require further validation specifically for their ability to measure and distinguish differences in treatment effectiveness. Some of the primary measurable outcomes used among these veteran studies were pain intensity, function, and interference. For instance, Burgess et al. (40) used the VA Survey of Healthcare Experiences of Patients (SHEP) to determine an association between pain outcomes related to pain interference and perceived opioid treatment effectiveness. Wu et al. (14) used median pain scores using the visual analog scale to determine effectiveness of LTOT in young veterans. The SHEP survey or a reduction in median pain score may not

accurately measure opioid effectiveness in veterans with CNCP. In order to measure effectiveness for treatment interventions including the use of LTOT, these measurements should accurately assess the veteran's pain experience and be validated in various veteran populations with CNCP.

Lastly, in the sample demographics of the reviewed studies, male veterans far outnumbered females, non-Hispanic white men than other minority groups, and older veterans than younger veterans. These disproportions in sample demographics may limit the generalizability of the study findings in a substantial number of veterans with CNCP. In addition, the high rate of participant attrition in the two RCTs may have influenced their study outcomes against LTOT effectiveness. In this literature review, studies that investigated safety, adverse side effects, or risks of LTOT outnumbered those that evaluated its effectiveness. This discrepancy may be due to the high cost of conducting RCTs for LTOT effectiveness, especially for a period of 12 months or greater. Compared to RCTs, observational or retrospective cohort studies that investigate adverse effects, safety, or risks are less expensive to conduct, less time-consuming, and less demanding in regard to veteran sampling and recruitment. In addition, the pharmaceutical industry may not be inclined to fund RCTs especially if the study outcomes do not favor their specific drug or affect financial profits.

Based on the AHRQ Grading System (see Table 3.2 & 3.2), the strength of evidence for LTOT effectiveness and safety in veterans with CNCP was typically low or insufficient for most studies. The limited RCTs that investigated LTOT in veterans in addition to problematic study design contributed to the weak or limited evidence to support their use. It is worth noting that opioid guidelines and federal regulations are based on these limited studies found in both the

veteran and general population. These guidelines and regulations may negatively impact those subsets of the population that may benefit from LTOT for improving function and quality of life.

IMPLICATIONS FOR CLINICAL PRACTICE

As healthcare providers, understanding safe and effective opioid prescribing is key to providing high-quality and compassionate patient care. Our review highlights some of the many factors to consider, such as appropriate CNCP indications, the presence of comorbidities and contraindications that may worsen with LTOT. For example, identifying the risk of ADRB and concurrent diagnosis of depression in a veteran with CNCP may inform the decision to implement opioid risk migration strategies. This comprehensive work-up in combination with thorough physical, psychological, and social assessments are important decision-making parameters that inform our ability to identify appropriate candidates for LTOT and reduce the risk of adverse effects.

Based on this literature review, the use of LTOT requires ongoing assessment and examination of risk factors throughout the veteran's continuum of care. Clearly, in both veteran and general population studies, opioid therapy can be effective in managing certain types of pain conditions compared to non-opioid treatments or placebo. In some circumstances, LTOT may be the only remaining treatment option that allows the veteran to function and maintain an acceptable quality of life. According to this review, clinicians must understand the limitations as well as the benefits of LTOT in order to responsibly and optimally use them in their patients. The veteran studies in this review provide guidance for recognizing which veterans will respond clinically to LTOT without significant adverse effects, versus those who will require more intense monitoring for adverse effects and implementation of abuse mitigation strategies.

Lastly, veterans who are being considered for LTOT for CNCP should be provided with mental health assessments for depression, PTSD, and aberrant drug behaviors or opioid use disorders (12, 32, 42, 44-46). In a multidisciplinary team setting, treatment recommendations should require a multimodal approach for veterans to gain functional independence, achieve mental health well-being, and improve social integration (7). These recommendations are extremely important in younger veterans (e.g., OEF/OIF veterans) with CNCP in order to reduce the significant medical and psychiatric comorbidities associated with military traumas and injuries.

GAPS IN THE LITERATURE AND FUTURE RESEARCH

Several gaps in the literature are apparent in this scientific literature review. The need for more prospective longitudinal studies that investigate LTOT in veterans with CNCP is evident. These studies should include head-to-head studies comparing opioid formulations with a non-opioid group and/or placebo arm in various subgroup of veterans with different CNCP conditions. Given that CNCP is a long-term disorder, these studies must extend beyond 12 months especially in regard to opioid effectiveness and safety related to tolerance, misuse, ADRBs, and other systematic adverse effects such as hypogonadism and cardiopulmonary effects in veterans. Since conducting RCTs have prohibitive monetary and time costs, large cohort studies over an extended period may provide additional evidence to inform our ability to identify veterans' characteristics and key predictors in favor of or against the use of appropriate LTOT.

One research priority could investigate the key predictors that informs our ability to identify individuals that will respond favorably to LTOT and exhibit minimal adverse events. An attempt to identify these predictors could results in positive outcomes and determine who should be prescribed LTOT versus those individuals who should not. For example, appropriate social

and family support, spiritual awareness, an improvement in functional gain with treatment, an increase in self-efficacy or the ability to self-manage their symptoms, and/or a strong sense of resilience and coping mechanisms may be predictors of outcomes for veterans with CNCP. Understanding these variables may improve clinical goals of promoting functional independence and improvement in quality of life.

Identifying key variables that would mitigate the risk of opioid abuse, misuse, or addiction should continue to be research priorities. Additional studies should focus on specific CNCP conditions that responds to LTOT and other conditions that do not. The current status quo of limiting opioid medication to everyone will need to be revisited since some patients do respond to LTOT without adverse events. Investigating the trajectories of these predictors over time may provide additional information that could improve the ability to identify veterans who are appropriate candidates for LTOT.

In this literature review, measurements used to evaluate LTOT effectiveness were limited and require further development. An important element in investigating any outcome is the reliability and validity of measurement tools. For veterans with complex biological, psychological, and social factors, these instruments must be able to clearly and confidently assess these factors within the context of CNCP and LTOT. Chou et al. (20) also recommended validation of instruments that accurately measures predictors and risks in order to determine how treatment affects patient outcomes. New measurements that investigate resilience and social integration may be predictors specific to veteran's CNCP experience and can be used as an appropriate conceptual framework for targeting better outcomes for LTOT. Investigating these variables could directly affect veterans' use of LTOT and the risks of adverse effects or harm.

Additional studies are needed to explore LTOT in veterans over 12 months and in other minority groups (i.e., female, Hispanic, African Americans, OEF/OIF combat veterans). These studies may provide greater insight for understanding the effectiveness and potential adverse effects that may occur in specific veteran populations. In addition, these studies may provide an opportunity to explore prescribing strategies that may help reduce conditions related to opioid tolerance, opioid induced hyperalgesia, and other systemic adverse effects.

Individualized patient-centered care has become an important catch phrase in medicine and nursing and in particular, for veterans with CNCP (7). The use of LTOT is one potential intervention in the arsenal of treatments available to manage pain symptoms. However, additional research priorities should include advancing other pain treatments such physical rehabilitation, integrative health and healing techniques (e.g., mindfulness training, acupuncture, yoga), and interventional procedures. Successful management of CNCP will require optimal utilization of these treatments in combination with pragmatic use of opioids in selected patients (7, 20).

CONCLUSIONS

In conclusion, the use of LTOT in veterans with CNCP remains a challenge for clinicians, policy makers, and researchers. Balancing appropriate pain relief with risk mitigation will need closer scrutiny and further investigation going forward. Our review of the literature highlights a lack of evidence supporting the effectiveness of LTOT in veterans with CNCP; however, these studies did underscore the importance of monitoring veterans prescribed LTOT for adverse effects, aberrant drug related abuse, and other risks associated with physical, psychological, and social co-morbidities. Based on this review, significant clinical implications

were identified and gaps in the literature examined to ensure veterans with CNCP received the most appropriate evidence-based care available.

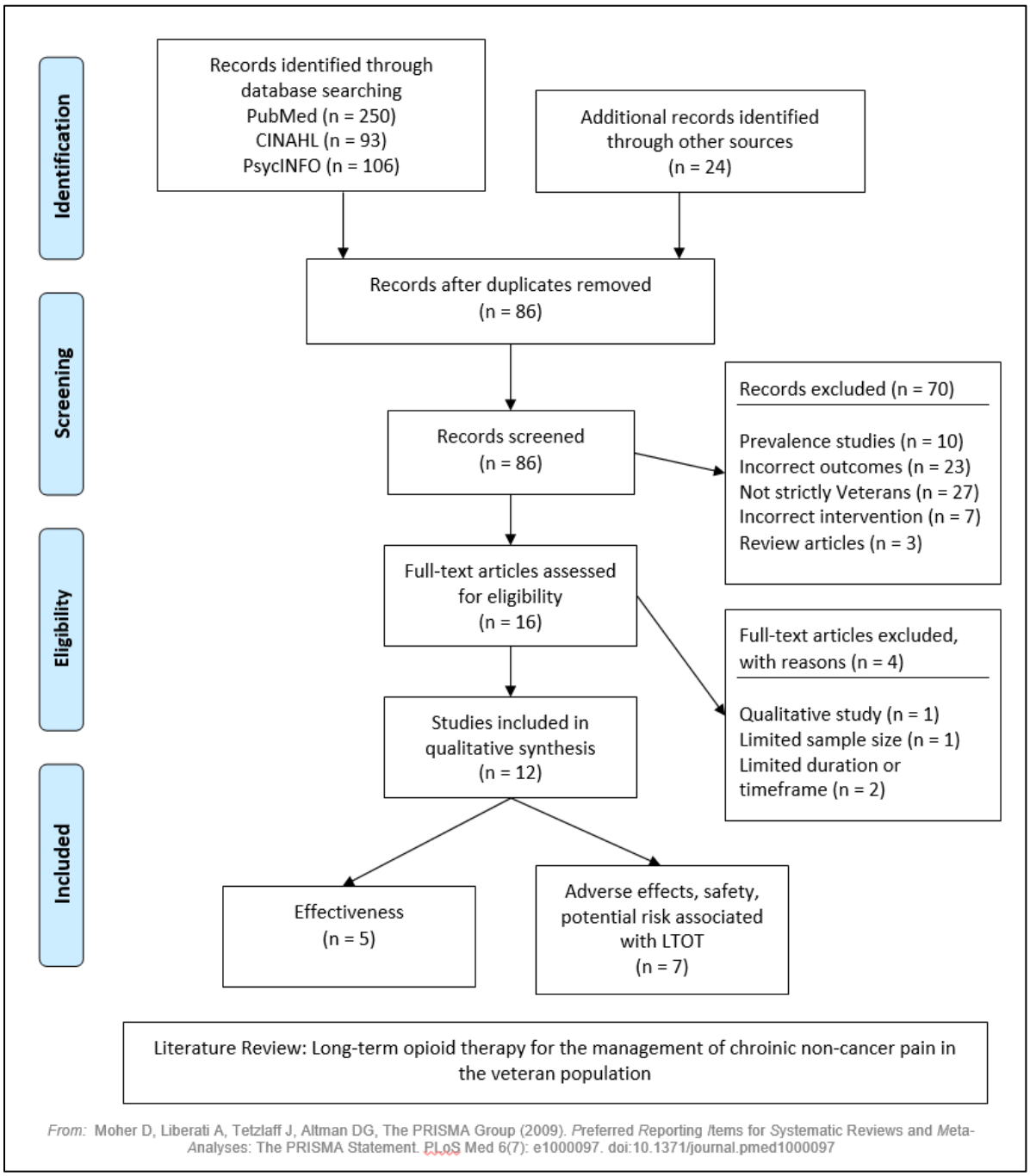

FIGURE 3.1: PRISMA RESEARCH PROCESS FLOW DIAGRAM - LITERATURE REVIEW: LONG-TERM OPIOID THERAPY FOR THE MANAGEMENT OF CHRONIC NON-CANCER PAIN IN VETERANS POPULATIONS

TABLE 3.1: Studies of Long-Term Opioid Use in Veterans with CNCP

Author/Year/Title	Design & Setting	Sample (Veterans)	Type of CNCP and Opioid	Demographics	Follow up period	Data Collection/ Measurements	Outcome: Effectiveness/ adverse side effects, safety, and risks associated with LTOT	Comments
1.								
Mahowald et al. (2005) (41) Opioid use by patients in an Orthopedics Spine Clinic	Retrospective cohort study Setting: Outpatient Orthopedic Spine Clinic in Minneapolis Veterans Affairs Medical Center	N = 230 Long-term = 58 Short term = 94 No opioid = 74 Attrition = 4	Type of CNCP Chronic spine pain: stratified Type of Opioid Codeine, Oxycodone, Propoxyphene, Tramadol, Morphine, Meperidine, Fentanyl, Hydrocodone	Mean Age = 59 +/- 14 Male = 92.2% Ethnicity = NR	April and December 1997 Medication use was analyzed retrospectively for 3 years	Data Collection Medical and pharmacy records obtained from CPRS. Measurements: Opioid use (preparation, dosage, number of pills per day, number of days taken per week, and source of prescription), patient interviews, operative reports, and radiologic imaging studies.	Effectiveness: Opioids reduce back pain severity score from 8.3 +/- 1.5 to 4.5 +/- 2.2 (mean +/- SD) ($P < 0.0001$). 69% of LTO vs 45% STO reported at least 50% reduction in pain severity ($P < 0.018$). ADEs/Safety/Risks: No significant increase in tolerance. No increase abuse behavior for patients with or without history of addiction. Constipation (49%) Sedation (31%) Other: dizziness, sedation, nausea, itching, headaches, confusion.	Small number of patients, study not controlled
2.								
Wu et al. (2010) (14) Opioid use in young veterans	Retrospective cohort study Setting: Outpatient VA Palo Alto Healthcare System	N = 4270 LTOT = 173 Met criteria for inclusion = 18	Type of CNCP: CNCP not stratified Type of Opioid: Oxycodone SA Morphine SA Hydrocodone/ Oxycodone/ Codeine with APAP	Age = 18 to 30 Mean = 25.9 (+/- 2.69) Male = 91% White = 69.9%	January 01, 2003 to October 1, 2008	Data Collection: Data warehouse from Veterans Integrated Service Network (VISN 21) Measurements: Pain score VAS 0-10 scale. Median pain scores, Mean number of opioids and prescribers, types of prescribers, presence of urine drug testing, opioid treatment agreement, ADEs.	Effectiveness: Veterans prescribed long-acting opioids did not have a significant change in median pain score in 1 or 3 months ($p = .25$, $p = 1.0$). 4 patients met criteria for effectiveness. 7 discontinued or switch to another agent during the study. ADEs/Safety/Risks: 5 patients (28%) experienced ADEs which include nausea/vomiting, opioid-induced hyperalgesia, decreased	Small number of patients (N = 18) for opioid effectiveness. Study not controlled

							libido, constipation & sedation.	
Author/Year/Title	Design & Setting	Sample (Veterans)	Type of CNCP and Opioid	Demographics	Follow up period	Data Collection/ Measurements	Outcome: Effectiveness/ adverse side effects, safety, and risks associated with LTOT	Comments
3.								
Naliboff et al. (2011) (42) A randomized trial of 2 prescription strategies for opioid treatment of chronic nonmalignant pain	Randomized clinical trial Setting: Outpatient Chronic Pain Clinic, VA Greater Los Angeles Healthcare System	Total N= 134 ED (Escalating Dose) = 64 SD (Stable Dose) = 70 Attrition = 1	Musculoskeletal: SD = 54 (77%) ED = 50 (78%) Neuropathic: SD = 13 (19%) ED = 12 (19%) Complex: SD = 3 (4%) ED = 2 (3%) Type of Opioid: All types of opioid (hydrocodone, oxycodone, codeine, morphine, methadone, oxycontin, combined) reported as morphine equivalent dosages	Age: SD: 52.4 +/- 7.1 ED 52.7 +/- 7.9 Gender: SD Male= 69 SD Female= 1 ED Male= 57 ED Female= 7 Ethnicity: NR	Monthly and quarterly follow-up for up to 1 year	Measurements: Morphine equivalent of opioid dosages, 10-cm VAS, usual level of pain, worst level of pain, average mood, pain interference, pain relief over past month. Addiction Behavior Checklist, Opioid Medication Discontinuation for non-compliance, Oswestry, ADEs	Effectiveness: Mixed model analysis for usual pain showed a small but significant time effect ($p < .002$). No significant main effect or interactions between groups. Using LOCF, 29% of ED and 15% of SD subjects reported greater than 1.5-point increase in amount of relief from medications ($p < 0.06$). 29% of ED and 23% of SD reported greater than 10-point decline in ODI scores ($p = .50$) ADEs/Safety/Risks: No serious ADEs reported. Substance misuse or noncompliance discontinuations were due to alcohol or illicit substance abuse (10%), noncompliance with medications (15%), noncompliance with clinic procedures (4%).	Small sample size. No control groups. Demographics skewed to men.
4.								
Burgess et al. (2016) (40) Association between pain outcomes and race and opioid treatment: Retrospective cohort study of Veterans	Retrospective cohort study using survey data VA National Patient Care Database (NPCD) and SHEP scores.	Black = 3,505 Non-Hispanic White = 46,203	Type of CNCP = Chronic Back, Neck, and Joint Pain Type of Opioid = NR	Age: White = 68 (SD 12.31) Black = 58 (SD 12.80) Gender: White = 95.4% Black = 90% Married:	Single year (2007)	Data from 2007 VA Survey of Healthcare Experience of Patients (SHEP) and (NPCD). Pain interference was measured using SHEP item "During the past 4 weeks, how much did pain interfere with your normal work? "If you have been treated by	Effectiveness: Opioid use did not moderate the association between race and perceived effectiveness of pain treatment. The main effect of opioid prescription was not significant, except for the mild pain intensity group. (Pain scores 0, $p = 0.13$;	No control groups.

				White = 68.6% Black = 48.9%		VA provider for chronic pain, please rate the effectiveness of your pain treatment?" Receipt of opioid was defined as an outpatient prescription of any opioid for any duration issued by a VA pharmacy between the Pain Diagnosis and the SHEP index visit attained from the NPCD.	1-3, p = 0.003; 4-6, p = 0.77; 7-10, p = 0.37). ADEs/Safety/Risks: Pain interference was significantly higher for veterans who received an opioid.	
Author/Year/Title	Design & Setting	Sample (Veterans)	Type of CNCP and Opioid	Demographics	Follow up period	Data Collection/ Measurements	Outcome: Effectiveness/ adverse side effects, safety, and risks associated with LTOT	Comments
5.								
Krebs et al. (2018) (43) Effect of Opioid vs Non-opioid Medications on Pain-Related Function in Patients with Chronic Back Pain or Hip or Knee Osteoarthritis Pain: The SPACE Randomized Clinical Trial	RCT Minneapolis VA Healthcare System, Primary Care	N = 240 Opioid = 120 Non-Opioid = 120 Follow up rate = 92% at 3 months 97% at 6 months 90% at 9 months 98% at 12 months	Back = 156 Hip/knee = 84 Opioid Protocol (morphine immediate release (IR), hydrocodone, oxycodone (IR), morphine sustained action (SA) or Oxycodone SA, Fentanyl patches versus Non-Opioid Protocol	Mean age 58.3 (range 21-80) Female = 72 Males = 168 White = 207 Black = 18 Other = 13	Monthly to every 3 months after stable.	Adherence measures by patient report and checking prescription monitoring program. Brief Pain Inventory (BPI) (Interference Scale, Severity Scale, 12-Item) Health Survey (VR-12) quality of life measure, Roland-Morris Disability Questionnaire Patient Health Questionnaire (depression), Generalize Anxiety Disorder (GAD-7), Patient Reported Outcomes Measurement Information System (PROMIS), Migraine Disability Assessment (MIDAS), Arizona Sexual Experience Scale (ASEX), Multidimensional Fatigue Inventory,	Effectiveness: No significant difference in pain related function between groups after 12 months (overall P = .58). Mean BPI interference was 3.4 for opioid group, vs. 3.3 for non-opioid group (0.1 difference) (95% CI, -0.5 to 0.7). Pain Intensity was better for non-opioid group compared to opioid group (P = 0.03). Mean BPI severity was 4.0 in opioid group vs. 3.5 in non-opioid group (difference 0.5) (95% CI, 0.0 to 1.0). Functional (>30% improvement in BPI interference) and Pain intensity (>30% improvement in BPI severity) response was greater in non-opioid group compared to opioid group. Health related quality of life and mental health did not differ between groups. Anxiety	Non-pharmacological treatments were allowed outside of the study (confounding) No follow-up after 12 months. Opioid group received low or moderate dosage therapy. 15% or less received mean opioid 50 morphine equivalent (ME) mg/day. Tramadol prescribed to non-opioid group.

							symptoms were less in the opioid group vs non-opioid group (mean 2.5 vs. 2.8) (P = 0.2). ADEs/Safety/Risks: Opioid group had more medication-related symptoms over 12 months compared to non-opioid group (P = .03). no difference in adverse outcomes or potential misuse measures. 23 patients in opioid group discontinued meds, vs 10 patients in non-opioid group.	
Author/Year/Title	Design & Setting	Sample (Veterans)	Type of CNCP and Opioid	Demographics	Follow up period	Data Collection/ Measurements	Outcome: Effectiveness/ adverse side effects, safety, and risks associated with LTOT	Comments
6.								
Macey et al. (2013) (13) Patterns of care and side effects for patients prescribed methadone for treatment of chronic pain	Retrospective cohort study Setting: VA Medical Center in the Pacific Northwest	Methadone = 92 Morphine = 90 Total: 182 LTOT (90 days consecutive prescription) Methadone = 42 Morphine SR = 46	Chronic Pain of moderate to severe (Numeric Pain Rating >4 at least 3 months in 2008). Not stratified Type of Opioid: Methadone and Morphine SR. Opioid dosages were converted into morphine equivalent dosages	Methadone (92) Average Age = 54.8 (11.5) Male = 92.4%) Single = 13% Married = 52% Morphine (90) Average Age 55.1 (12.5) Male = 87.8% Single = 13.3% Married = 48.9%	Veterans prescribed morphine and methadone for CNCP at least 3 different months in 2018 Average duration: Methadone= 5.6 months Morphine = 7.2 months	Data warehouse from Veterans Integrated Service Network (VISN 20) and national VA database. Age, sex, marital status, ethnicity, VA service connection, ICD-9-CM codes Measurements: Electrocardiograms pre and post opioid initiation, medication related ADEs, liver function tests, and electrolytes	Effectiveness: NR ADEs/Safety/Risks: No difference in QTc prolongation between methadone versus morphine SR. 26% in the methadone and 34% in the morphine group reported ADEs (i.e., cognitive, mental health, gastrointestinal, cardiopulmonary). Reported inadequate pain relief as reason for stopping medication: 25% in the methadone group 10 % in the morphine group Non-adherence: 9% in the methadone group	Small sample size. No control groups. Demographics skewed to men.

							4% in the morphine group	
Author/Year/Title	Design & Setting	Sample (Veterans)	Type of CNCP and Opioid	Demographics	Follow up period	Data Collection/ Measurements	Outcome: Effectiveness/ adverse side effects, safety, and risks associated with LTOT	Comments
7.								
Sekhon et al., (2013) (44) Compliance with opioid treatment guidelines for chronic non-cancer pain (CNCP) in primary care at a Veterans Affairs Medical Center (VAMC)	Retrospective Cohort Study Setting: W.G (Bill) Hefner Veterans Affairs Medical Center North Carolina	N = 797 Ages 18 to 87 years old who received schedule II opioids for 3 or more consecutive months during 1-year period	CNCP: Back/neck: 83.1% Osteoarthritis: 34.7% Neuropathy: 16.9% Headaches/ migraines: 14.5% Other: 23.3% Type of Opioid: Oxycodone, oxycodone-acetaminophen, hydromorphone, morphine, methadone	Age: median 58 (22-87) Gender: male: 752 (94%)	1-year period (July 2009-August 2010)	Data Collection Medical and pharmacy records obtained from CPRS. Measurements: Type of pain, number of comorbidities, and psychiatric comorbidities, presence of opioid pain care agreement (OPCA), morphine equivalent dosage, past non-opioid drug abuse, aberrant drug-related behaviors (ADRB), urine drug testing (UDT).	Effectiveness = NR ADEs/Safety/Risks: UDT positive for illicit drugs/unreported opioids (19.5%) UDT negative for prescribed opioids (25.2%) ADRB identified in 183 patients (22.9%) ADRB higher risk factor: bipolar disorder (odds ratio [OR] 2.39, p<0.003), < 40 years of age (OR 2.04, p <0.006), past history or current non-opioid substance abuse (OR 2.17, OR 5.78, p<0.001), morphine equivalent dose > 200mg/day (OR 1.69, p<0.002)	No control groups. Demographics skewed to men.
8.								
Morasco et al., (2010) (25) Clinical characteristics of veterans prescribed high doses of opioid medications for chronic non-cancer pain	Retrospective cohort study Setting: VA in Pacific Northwest (Washington, Oregon, Idaho, Alaska).	Three groups: High dose opioid (>180mg morphine equivalent/day, N = 478) Traditional dose (5-179mg/day, N = 500), No opioid CNCP veterans (N = 500).	CNCP score >4 or greater recorded in at least 3 different months Opioids: Codeine, Fentanyl Transdermal, Hydrocodone, Hydromorphone, Methadone, Morphine, Oxycodone, Propoxyphene	Age (mean age 55.1, SD 12.6), Gender (male 90.7%), Marital Status (married 49.3%, divorced 32.5 %), Race (white 70.8%), VA service connection (64.3%)	Veterans who receive care anytime during 2008 calendar year	Data Warehouse for Veteran Integrated Service Network). Charlson Comorbidity Score, Pharmacy database for opioid and non-opioid medications, Pain diagnosis, medical and psychiatric diagnosis in the past 5 years.	Effectiveness = NR ADEs/Safety/Risks: Veterans on high dose opioids had a greater number of documented pain diagnoses compared to traditional and no-opioid groups. They also had higher scores on the Charlson Comorbidity Index (indicating more severe illness) compared to the no-opioid group. Diagnoses of neuropathy, low back pain, or nicotine	No control groups. Demographics skewed to men.

							disorder were associated with increased likelihood of being prescribed high dose opioids.	
Author/Year/Title	Design & Setting	Sample (Veterans)	Type of CNCP and Opioid	Demographics	Follow up period	Data Collection/ Measurements	Outcome: Effectiveness/ adverse side effects, safety, and risks associated with LTOT	Comments
9.								
Dobscha et al., (2013) (12) Correlates of prescription opioid initiation and long-term opioid use in veterans with persistent pain.	Retrospective cohort study VISN-20 (VA facilities in the Pacific Northwest (Washington, Oregon, Idaho, & Alaska)	N = 5961 No opioid = 3921, Short-term opioid (SOT) = 1767 (30%), Chronic opioid therapy (COT) = 273 (4.6%) over 12 months.	Type of CNCP = Fibromyalgia, inflammatory bowel disease, low back pain (49.5%), migraine headaches (9.5%), neck or joint pain (55.7%), neuropathy (7.3%), and arthritis (45.4%) Type of opioid = Converted to morphine equivalent dosages	Age, sex, race, marital status, VA service connection disability status.	Calendar year 2008	VISN-20 Data Warehouse for 2008. Pain numeric rating scores > 4 recorded in at least 2 different months. Veterans prescribed opioid during the 12-month study period. Diagnosis of common psychiatric and substance use disorders. ICD-9 diagnoses, Charlson Comorbidity score, BMI, VA pharmacy data collected 12 months after the index date (2008) including opioid and non-opioid prescriptions. Opioid converted to a morphine equivalent dose.	Effectiveness: NR ADEs/Safety/Risks: Compared to the other groups, the rates of nicotine use disorder, major depressive disorder, PTSD, and substance use disorder were higher in the COT group.	Smaller group of Veterans prescribed chronic opioid therapy compared to No opioid and Short-term opioid group. Most commonly prescribed opioid was hydrocodone followed by oxycodone. COT was more likely to be prescribed a combination of opioids.
10.								
Edlund et al., (2014) (3) Patterns of opioid use for chronic noncancer pain in the Veterans Health Administration from 2009 to 2011	Retrospective cohort study Setting: VHA National Database	2009 = 1,332,810 2011 = 1,405,563 2012 = 1,437,392	Neck pain (8.9%), Back pain (42.1%), Arthritis pain (65.1%), Headache (7.9%), Neuropathic (13.5%). Type of opioid = NR. Morphine equivalent dosages.	Age, race, gender, marital status, OIF/OEF status	Data from 2009 to 2011	Data from the Pharmacy Benefit Management, The Corporate Data Warehouse, and the Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) roster. CNCP diagnosis, opioid prescriptions, morphine equivalent dosages, ICD-9 revision diagnoses	Effectiveness = NR ADEs/Safety/Risks: Both depression and PTSD were positively associated with receipt of high-volume opioids (OR = 1.52, 95% CI 1.49, 1.56) and (OR 1.10, 95% CI = 1.07,1.13) respectively.	Among veterans with CNCP 57% were prescribed chronic opioid therapy. 60% had daily dose < 30mg morphine. 4.5% received daily dose of > 120mg morphine.

Author/Year/Title	Design & Setting	Sample (Veterans)	Type of CNCP and Opioid	Demographics	Follow up period	Data Collection/ Measurements	Outcome: Effectiveness/ adverse side effects, safety, and risks associated with LTOT	Comments
Salas et al., (2017) (63) Gender and the Association between Long-Term Prescription Opioid Use and New Onset Depression	Retrospective cohort study Setting: VHA National Database	VHA N = 70,997 Female = 4,300 Male = 66,697	Arthritis, back pain, headaches, musculoskeletal pain, neuropathic pain Type of opioid: codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, morphine, oxycodone, oxymorphone, and pentazocine.	Age, race, gender, marital status	Follow-up time was defined as months January 1, 2002–2012	VHA Data Warehouse: Data included ICD-9-CM diagnostic codes, inpatient and outpatient visits, prescription fill records, vital signs, and demographic information from January 1, 2000 to December 31, 2012 for the VHA NDE was defined by a primary ICD-9-CM in follow-up. OAU duration as the outcome (1–30 days vs 31–90 days vs >90 day).	Effectiveness: NR ADEs/Safety/Risks: Compared to 1-30 days of OAU, greater than 90 days of OAU among female veterans was associated with a 79% increased risk of NDE. This was significantly larger than the 25% increase seen in male veterans with greater than 90 days of OAU.	Male veterans more likely than women to use opioids for greater than 90 days, and a higher proportion of men than women had a daily MED greater than 50 mg.
12.								
Lovejoy et al., (2017) (46) Reasons for discontinuation of long-term opioid therapy in patients with and without substance use disorder	Retrospective cohort study Setting: All VHA facility	Cohort = 7247 patients on long-term opioid therapy who discontinued opioid therapy in 2012 N = 300 patients with SUD diagnosis N = 300 patients without SUD diagnosis, matched as controls	N = 600 CNCP diagnosis: Musculoskeletal (86%), Neuropathy (5.8%), Migraine headache (10.5%). Type of opioid: codeine, fentanyl, hydrocodone, hydromorphone, propoxyphene, morphine, oxycodone, methadone, tapentadol	Age, race/ethnicity, gender, period of military service. Mean age of 55 years old, male (95%), non-Hispanic white (72%), resided in urban location (73%)	2011 to 2012	VHA Data Warehouse: national cohort of patients prescribed opioid therapy for 2011. Variables: medical comorbidities assessed with Elixhauser Comorbidity Measure, service connection status, type of opioids, average daily dosage in morphine equivalent, number of opioid prescribers, patients prescribed benzodiazepines.	Effectiveness: NR ADEs/Safety/Risks: Clinician-initiated discontinuation reason included suspected substance abuse (44%), aberrant urine drug test results (37%), opioid misuse behaviors (15%), non-adherence to pain clinic plan of care (11%), concerns about opioid diversion (4%). Patients with SUD diagnosis was more likely than those without to be discontinued for aberrant behaviors, specifically substance abuse.	No control groups. Demographics skewed to men.

TABLE 3.2: STRENGTH OF EVIDENCE FOR EFFECTIVE LONG-TERM OPIOID THERAPY FOR CHRONIC NON-CANCER PAIN

Author/Year/Title	Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence
Mahowald et al. (2005) (41)	High	Unknown	Direct	Precise	Undetected	Low
Wu et al. (2010) (14)	High	Unknown	Direct	Imprecise	Undetected	Insufficient
Naliboff et al. (2011) (42)	Moderate	Unknown	Direct	Imprecise	Undetected	Low
Burgess et al. (2016) (40)	Moderate	Unknown	Direct	Imprecise	Undetected	Insufficient
Krebs et al. (2018) (43)	Moderate	Unknown	Direct	Imprecise	Undetected	Moderate

TABLE 3.3 STRENGTH OF EVIDENCE FOR SAFETY LONG-TERM OPIOID THERAPY FOR CHRONIC NON-CANCER PAIN

Author/Year/Title	Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence
Macey et al. (2013) (13)	Moderate	Unknown	Direct	Precise	Undetected	Low
Sekhon et al., (2013) (44)	Moderate	Unknown	Direct	Precise	Undetected	Low
Morasco et al., (2010) (25)	Moderate	Unknown	Direct	Precise	Undetected	Insufficient
Dobscha et al., (2013) (12)	Moderate	Unknown	Direct	Precise	Undetected	Insufficient
Edlund et al., (2014) (3)	Moderate	Unknown	Direct	Precise	Undetected	Low
Salas et al., (2017) (63)	Moderate	Unknown	Direct	Precise	Undetected	Low
Lovejoy et al., (2017) (46)	Moderate	Unknown	Direct	Precise	Undetected	Low

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CHAPTER 4

TRAJECTORIES OF PAIN INTENSITY AND OPIOID USE IN VETERANS PRESCRIBED LONG-TERM OPIOID THERAPY FOR CHRONIC NON-CANCER PAIN

ABSTRACT

Background: The effectiveness of LTOT for improving pain intensity over 12 months is limited in veterans with CNCP. Given the numerous adverse side effects associated with this treatment and potential risk for opioid abuse and addiction contributing to the "opioid epidemic", the effectiveness of LTOT should be closely scrutinized. **Purpose:** This study examined the trajectories of pain intensity and opioid use among veterans with CNCP and whether these trajectories differed by age, marital status, living situation, employment, and mood (anxiety and depression). **Methods:** The study analyzed data from a previously described randomized clinical trial (RCT) that compared opioid prescribing practices (escalating dose versus stable dosing) in 134 veterans for 12 months in an outpatient VA pain clinic. An additional 24-month data on pain intensity and opioid dosage (but not on sociodemographic characteristics and mood) were collected retrospectively on veterans who remained on LTOT when they had return to standard prescribing practice. Regression models were used to test change over time in the later 24 months of follow-up for pain intensity and opioid use (log-transformed). Second, the effects of sociodemographic characteristics were tested in the first 12 months only, since these characteristics were not collected in the later years after the original RCT analysis. **Results:** First, in the 2 years following the RCT and veterans with CNCP returned to standard prescribing practices, pain intensity and prescribed opioid dosage did not change significantly over time. The median (IQR) pain scores were 6.0 (95% CI= 4.2-7.7) for the escalating dose group and 6.2 (95% CI=5.1-7.5) for the stable dose group. Median opioid dosage was 27.0 (95% CI=20.0 - 40.0) for the escalating dose group and 30.0 (95% CI=15.0 - 63.8) for the stable dose group. Second, in the first year while on the original RCT, increased pain was significantly associated with increased depression scores (β=0.06, P=0.003) and decreased opioid dosage was nominally

associated with increased pain intensity (β=-0.03, P=0.04). Socio-demographic characteristics, anxiety, and depression were not associated with opioid dosage. **Conclusion:** In veterans prescribed LTOT for CNCP, there was no significant effect of time on pain intensity and opioid dosage showing only small fluctuations in pain intensity while morphine equivalent opioid dosages remained relatively unchanged. However, increased pain intensity was associated with increased depression. These findings may suggest a pragmatic view on effectiveness of LTOT for CNCP and offer a more realistic clinical expectation and rationale for treatment. In addition, the concurrent and optimal management of depression and CNCP is an important consideration in this vulnerable patient population.

INTRODUCTION

Chronic non-cancer pain (CNCP) is a prevalent health problem (1), affecting over 1.44 million veterans (2). Based on the 2010-2014 National Health Interview Survey (NHIS) (3, 4), CNCP was more prevalent in veterans (65.5%) than non-veterans (56.4%), and veterans (9.1%) were more likely to report severe pain than non-veterans (6.3%). As illustrated in Figure 4.1, CNCP in veterans is complex and requires a heuristic model that identifies the biopsychosocial factors and the central and peripheral processes contributing to this pain experience. The most common causes of CNCP in this population include musculoskeletal disorders, polytrauma, neuropathy, amputation, and traumatic brain injury. CNCP in veterans is often associated with mental health disorder such as post-traumatic stress disorder, depression, anxiety, other mood disorders, and substance use disorder, and social dysfunctions (i.e., homelessness, social isolation, financial problems, poverty) (5, 6).

Over the past three decades, the use of long-term opioid therapy (LTOT) for management of CNCP has steadily increased (7, 8). Among veterans enrolled in the Veterans Health Administration (VHA), 50% had CNCP and 57% of these veterans were prescribed at least one opioid medication (5). This trend in LTOT for CNCP has decreased in light of recent evidence suggesting that opioids can cause adverse effects such as arrhythmia, thyroid disease, hypogonadism, falls, fractures, and hyperalgesia (9-11). In addition, the “opioid epidemic” and strict opioid prescribing guidelines have questioned the utility and effectiveness of LTOT especially among veterans because of the high risk for abuse, overdose, deaths (12, 13).

A number of reviews have investigated the effectiveness of LTOT for CNCP (9, 10, 14). Two systematic reviews reported weak or no evidence to suggest LTOT effectiveness among individuals with CNCP greater than 12 months (9, 10). However, a more recent meta-analysis

that evaluated 51 high quality randomized clinical trials (RCT) found LTOT was associated with a small improvement in pain intensity compared to placebo, non-steroidal anti-inflammatory medications, tricyclic antidepressants and synthetic cannabinoids for less than 12 months (14). In addition, two RCTs on LTOT in veterans with CNCP showed no significant difference in pain intensity and physical functioning when opioid was compared to non-opioid therapy (15) or when opioids are prescribed in a conservatively stable manner compared to a more escalated titration for 12 months (16).

Given the increased risks for opioid side effects and the mixed evidence on opioid effectiveness, the utility of LTOT for CNCP should be closely scrutinized (17). Moreover, studies that examined the effectiveness of LTOT longer than 12 months are limited both in the general and veteran population. This study aimed to examine the trajectories of pain intensity and opioid use among veterans with CNCP and whether these trajectories differed by sociodemographic characteristics and mood. Examining the effectiveness and utility of LTOT can provide more clinically relevant and useful information on opioid treatment outcomes for CNCP.

METHODS

This study was a secondary data analysis of 134 veterans who were prescribed LTOT in a single blind randomized clinical trial (16) for 12 months in an outpatient pain clinic. The original study compared the effectiveness of different opioid prescribing practices (i.e., liberal escalating dose versus conservative stable dose prescribing) in veterans with CNCP and found no group difference in pain intensity. This current study collected an additional 24 months of information retrospectively on pain intensity (N=72) and opioid dose (N=73) on individuals through electronic medical records (EMR) for study participants who remained on opioids, but the

majority of sociodemographic and mood variables were only present in the first 12 months of data. Approvals of the current study were obtained from the Institutional Review Boards (IRBs) at the VA Greater Los Angeles Healthcare and University of California San Francisco.

Study Sample

The original study was conducted at an outpatient pain management clinic in the Greater Los Angeles Veterans Affairs Healthcare System. Participants were recruited from sequential referral consultations from various providers in primary care, orthopedic, neurosurgery and other subspecialty clinics. The pain clinic is staffed by a multidiscplinary team of board certified pain providers from physiatry, anesthesiology, psychiatry, psychology, neurology, and nursing and provides consultation, treatment, and follow-up care for veterans with complex chronic pain conditions.

Inclusion criteria included (1) a diagnosis of CNCP at least 6 months prior to enrollment, (2) a determination by the pain research team that opioid was indicated for management of CNCP, and (3) participants eligible for LTOT for 12 months. The determination for study participants to initiate or resume LTOT was based on review of medical records, clinical history and physical examination, assessment for active or recent substance abuse, and a willingness to participate in clinic procedures for medication monitoring.

Figure 4.2 presents a schematic overview of the study sample. In the original study, among 140 veterans recruited, stable dose group included 73 participants and the escalating dose group had 67 participants. The study excluded five subjects who dropped out after randomization and one subject with outlier for opioid dosage >300mg at the time of recruitment. The sample for the current study included 134 veterans. Of these, 75 participants remained at the end of the 12-month original study.

Data Collection

Initial pain clinic interviews included demographic information, opioid and adjuvant pain medication histories, other pain management treatments, and psychosocial information. Monthly follow-up visits were scheduled and clinical decision to titrate or discontinue opioid use was made by the pain clinic team. Study participants were instructed to closely follow the clinic standard of care procedures for opioid prescription, which included completion of pain medication agreement, random urine toxicology screening and opioid confirmation testing, pill counts, and a review of Prescription Drug Monitoring Program (PDMP). Data were collected monthly to every three months for 12 months in the original study. At the end of the study, most veterans were referred back to their primary care provider to resume stable LTOT recommendations. After the original study, additional information was collected retrospectively from the EMR every 3-4 months up to 24 months on veterans who remained on LTOT.

Variables and Measures

Prescription groups

In the original study, participants were randomly assigned to the stable dose or escalating dose group using a random number generator. Participants were blinded to the group assignment. Based on group assignment, opioids were prescribed in a conservative manner for the stable dose group versus a more liberal prescribing practice for the escalating dose group over 12 months. After the end of 12-month study, participants resumed standard opioid prescribing practices and completed follow-up in the pain clinic or their primary care provider to resume LTOT treatment.

Sociodemographic information

Sociodemographic variables included age, gender, marital status, employment status (fulltime, parttime, retired, disabled), and current living situation (i.e., alone, with spouse or equivalent, with children, relatives, or roommates, homeless or in transition, or other).

Pain intensity

Pain intensity was measured by "usual or average pain intensity" over the past month, using a 10-cm visual analog scale (VAS) that ranged from 0 (no pain) to 10 (most intense pain imaginable). The VAS pain rating scale has been used extensively in previous studies and found to be valid and reliable in both the veteran and general population with CNCP (18). These data were collected every 3-4 months for a total of 36 months.

Opioid dosage in morphine equivalence

Participants were questioned on current opioid use prescribed in the VA and from other non-VA providers. From computerized pharmacy EMR, opioid medication prescribed per day was calculated in morphine equivalent daily dosing (MEDD) to standardize unit dosages across different opioid formulations (i.e., codeine, hydrocodone, oxycodone, methadone, and fentanyl). The use of MEDD to quantify a standardized unit of opioid intake for each study participants has been used in various studies (16, 19, 20). MEDD was calculated for opioid use every 3-4 months for a total of 36 months.

Mood

Mood was measured using the Hospital Anxiety and Depression Scale (HADS) every 4 months, for up to 12 months. The HADS is a sensitive screening tool that measures changes in anxiety (7 items) and depression (7 items) related to the course of disease and in response to psychotherapeutic and psychopharmacological intervention (21). Each item is scored from 0-3

based on statements that assessed depression and anxiety symptoms (e.g., “I feel tense or wound up”, 3= “most of the time”, 2= “a lot of the time”, 1= “from time to time, occasionally”, 0= “not at all”). Each depression and anxiety scale score ranges from 0 to 21 (22). The total score indicates the degree of severity: a score above 11 indicates probable anxiety/depression, and a score above 15 indicates severe anxiety/depression. The HADS has been shown to have good validity and reliability indices to assess depression and anxiety in somatic, psychiatric, and other patient populations (22). The HADS demonstrated acceptable to excellent reliability with Cronbach’s alpha for HADS-anxiety ranging from 0.68 to 0.93 and HADS-depression 0.67 to 0.90. Correlation coefficients between HADS and other similar instruments (i.e., Beck Depression Index, General Health Questionnaire, Clinical Anxiety Scale, and Spielberger’s State-Trait Anxiety Inventory) ranged from 0.49 to 0.83 (22).

Opioid misuse and clinic follow-up status

Through EMR review, information on whether participants exhibited any evidence of opioid misuse were identified and recorded as none, minor (i.e., early refill request, missed follow-up appointments), or major (i.e., inconsistent urine toxicology, the presence of illicit drugs or nonprescribed opioids, aberrant drug behavior, opioid diversion) as well as whether participants where followed in mental health clinics (MHC) and/or pain clinic after the original study ended.

Analysis

Descriptive statistics were calculated with SPSS (version 25, 2017): for continuous variables as means and standard deviations or medians and interquartile ranges (IQR) if skewed, and for categorical variables as percentages and frequencies. Data distributions were evaluated for skewness and kurtosis. Opioid dosage was log transformed. Gender was not included in the

analysis because of the small number of female veterans enrolled in the study, consistent in the original study (16).

The effects of pain intensity and opioid use over time were each modeled under a longitudinal model for the outcome along with time to study drop-out models with the package JM (23) in R v3.6.0 (24), The first analyses on individuals looked at the effect of pain intensity (N=72) and opioid dose (N=73) from 15 months to 36 months (results from the first 12 months were done in an RCT with a different dosing strategy, and has been previously reported on) (16).

The second analysis assessed the effects of sociodemographic/mood variables that were recorded in the 0-12 months (as many were not recorded in the 15-36-month timeframe), which included 134 individuals, using the same joint modelling method described for the association with time. For each of the two outcomes, the effect of each sociodemographic/ mood variable was tested first (covariates that did not change with time: age, living with partner, living alone, employment; and covariates that did: anxiety, depression, and log (opioid dosage) [only for pain intensity], as described above), while also adjusting for important covariates of time, group (escalating vs. not), and the interaction between time and group (for the opioid dose outcome only). Sociodemographic/mood variables that met $p<0.0056$, a Bonferroni correction for the 9 covariates tested, were considered significant and variables that met $p<0.05$ were also reported as suggestive or nominal associations. Finally, a stepwise regression was conducted to assess independent contributors to the two outcomes (pain and opioid dose), including covariates as long as they contributed to the model with $p<0.05$, as well as important variables for opioid misuse.

Sensitivity analysis was performed to address the high attrition rate and missing data up to 36 months (See Table 4.6 & Table 4.7). The joint modeling approach, present in the main

analysis (described above), is the most flexible approach explored, and is valid under a missing not at random (MNAR) mechanism (23). This analysis also fit a standard linear mixed effect model LMM using lme4 (25), valid under a missing at random (MAR) missingness mechanism, which was used in the original RCT analysis (16), and that with the strongest missing data assumption of listwise complete valid under a missing completely at random (MCAR).

RESULTS

Sample Characteristics

Table 4.1 displays sociodemographic characteristics of 134 veterans prescribed LTOT for CNCP at the start of the original study. Of the participants, 95% were male and 66% were 55 years and younger, the mean age was 52.5 years (SD 7.4). Among the study participants, 30% lived alone, 37% were unemployed because of pain, 41% were divorced or separate, and 78% complained of chronic pain from musculoskeletal diagnosis. Mean HADS scores were 8.14 (SD 4.7) for anxiety and 8.84 (SD 4.4) for depression at baseline. Table 4.2 displays veterans with a positive anxiety and depression score at baseline, 4^{th}, 8^{th}, and 12^{th} month follow-up. At baseline, 32% of veterans screened positive for anxiety and 38% for depression.

Table 4.3 shows the number of participants who continued to follow-up in the pain clinic and mental health clinic. At 36 months, 17% of participants continued some of their follow-up visits in the pain clinic and 22% continued with the mental health clinicians. The majority of veterans continued LTOT through their primary care provider.

Table 4.4 displays mean pain intensity and median opioid dosage for both escalating and stable dose groups on which data were available up to 36 months. During the first 0-12 months, mean pain score was 6.1 out of 10 (SD 0.57) which decreased to 5.3 out of 10 (SD 0.29) at 36 months for escalating dose group. For stable dose group, mean pain intensity was 6.6 out of 10

(SD 0.25) at 0-12 months which decreased to 5.7 out of 10 at 36 months. Median (IQR) dosage among both groups were relatively similar at 31.9mg (22.5-47.5) for escalating dose group and 30.0mg (19.6-40.7) for stable dose group at 0-12 months. At 36th months, those participants remaining in the stable dose group had a median (IQR) dose of 34mg (18.0-71.3). However, the group median (IQR) of the remaining participants in the escalating dose group decreased to 23mg (20-40) (see Table 4.5).

Pain Intensity

Figure 4.3 illustrates the trajectory for pain intensity up to 36 months in veterans prescribed LTOT for CNCP. In the first 12 months, the overall pain intensity trajectory showed a downward trend as discussed in the original study (16). However, in 15-36-month range, in the 72 veterans remaining in the study, the pain intensity trajectories appear to plateau, and no effect of time was seen (P=0.82). Pain intensity scores remained at moderate levels for a majority of the participants.

The impact of sociodemographic characteristics was assessed on pain intensity, using only the 0-12-month range, as these covariates were not included after 12 months. When testing each sociodemographic characteristic separately, both depression (β=0.062, p=.003) and anxiety (β=0.055, p=0.009) were significantly and suggestively associated with increased pain intensity (Table 4.7), with the stepwise model suggested depression was the driver of this (β=.061, p=0.003). Other sociodemographic characteristics such as age, employment, living with a partner or other social support, and marital status showed no association with pain intensity (P>0.05, Table 4.7).

Opioid Dose

Figure 4.5 illustrates opioid dosage trajectories in the participants. During the first 12 months, as previously discussed, the dosage over time was significantly different based on prescription groups (month x treatment group interaction, $\beta = -1.44$, $p<0.001$) (16). After 12 months, those remaining in the escalating dose group had opioid dosage lowered similar to the stable dose group (no group main effect, P=0.1) while an increase in opioid dosage was seen in the stable dosage group. There was no significant interaction between the prescription groups and time (P=0.17) and the overall opioid dosage did not change significantly over time (P=0.1) (See Figure 4.5). Figure 4.6 displays the trajectories of opioid dosage by the prescription group and by sociodemographic characteristics and mood. As displayed in Table 4.7, when testing each of the sociodemographic characteristics separately, only pain was nominally associated with a higher opioid dosage (β=-0.03, P=0.04). The stepwise model was the same model.

DISCUSSION

To the best of our knowledge, this is the first study that investigated pain intensity and opioid dosage trajectories for 24 months in veterans prescribed LTOT for CNCP. Pain at moderate levels and opioid dosage remained relatively stable with some fluctuations for 24 months and no statistically significant changes over time were observed. However, this study found a significant association between depression and pain intensity, illustrating the importance of managing both conditions in this population.

Trajectories in Pain Intensity

In veterans prescribed LTOT for 36 months, no significant improvement in pain intensity was seen over time. This finding is consistent with a study by Wu et al. (26) who reported that LTOT was not associated with improvement in pain scores after initiation of long-acting opioids

at 3 and 6 months in Operation Enduring Freedom/ Operation Iraqi Freedom veterans with CNCP. Similarly, Krebs et al. (15) compared LTOT with non-opioid medication therapy in veterans with CNCP and found no significant difference in pain intensity over a 12-month period. Moreover, the non-opioid medication group reported significantly better pain scores compared to the opioid group.

While the overall evidence for the effectiveness of LTOT remains limited and unclear, evidence in this present study may provide pertinent clinical information on utility of LTOT in veterans with CNCP. In this study, overall pain intensity was at moderate levels and remained relatively unchanged for 36 months. Whether this reduction only to moderate pain levels is clinically meaningful is an important consideration in the overall management of CNCP in veterans. Optimal management of CNCP requires the use of multimodal approaches that utilize both pharmacological and non-pharmacological treatments to target pain nociception (i.e., transduction, conduction, transmission, modulation, and perception) (6). Opioids are one treatment that can reduce pain by inhibiting and modulating pain symptoms via the central nervous system and nociceptive neural circuitry (27, 28). An individual's analgesic response to opioids varies significantly and may depend on several factors that include genetic characteristics, molecular mechanisms of opioid receptor signaling, and other factors that contribute to pharmacological and behavioral effects (e.g., analgesia, reward, depression, anxiety, and addiction) (28). Treatments should also incorporate a biopsychosocial approach to address the multitude of factors associated with CNCP (6). Veterans are particularly a vulnerable population whose complex military experience can result in difficult to manage CNCP conditions because of multiple injuries and trauma, mental health disorders, and social dysfunctions (6). The effectiveness of LTOT in these individuals may vary significantly and, for

some, a moderate pain level may be the most that can be achieved with this therapy, without causing adverse side effects.

Trajectories in Opioid Dosage

After the original randomized clinical trial comparing escalating and stable dose prescribing practices, this study observed a sharp decrease in opioid dosage among participants in the escalating dose group, while the dosage among the stable dose group participants increased. This finding suggests that both groups required modification to their opioid dosages (i.e., opioid rotation) because of the gradual loss of efficacy or tolerance. Such constant fluctuations in opioid dosage are common in LTOT and may represent the clinical challenges associated with opioid tolerance, opioid-induced hyperalgesia, and/or disease progression (29, 30). Moreover, a gradual plateau in pain intensity after 12 months coincided with these dosage changes and may provide additional evidence that highlights the unique pharmacokinetics and pharmacodynamics properties of opioid for CNCP. These properties include the effects of different opioid formulations that produce either short and long-acting mechanism of actions, affinity to different opioid receptors (i.e., methadone and N-methyl-D-aspartate receptors), and/or an individual's ability to metabolize these drugs.

Current opioid guidelines (31) suggest the need to modify treatment and consider opioid rotation for individuals whose opioid dosage exceeds 50mg-90mg MEDD (32) to achieve more effective pain control and minimize adverse effects. In this study, the median dosage was 30mg MEDD (IQR 20mg-45mg), which may reflect the specific pain management clinic's dosing threshold to rotate opioids when participants report inadequate or suboptimal pain relief or adverse effects. In most pain management settings, opioid rotation is common and is described as switching from one opioid to another "equianalgesic" opioid (33). Opioid rotation involves the

calculation of an equal opioid analgesia taken into account incomplete cross-tolerance dosing to reduce the risk of overdose or side effects. Incomplete cross-tolerance requires a reduction in the new alternative opioid dose at least 50% or more. These changes in opioid and dosages may explain the decrease in morphine equivalent dosing and a steep increase in pain intensity in some participants in the escalating dose group after 12 months. Similarly, the stable dose group showed an increase opioid dosage in response to higher pain scores after 12 months. However, despite these fluctuations, overall pain intensity and opioid dosages remained relatively stable or unchanged over time.

Sociodemographic Characteristics and Mood

In this study, sociodemographic characteristics were not associated with pain and opioid dosage. However, a number of studies (34-41) have investigated sociodemographic disparities including age, gender, race, and ethnicity related to analgesic and pain treatment utilization, pain outcomes, and prescription opioid misuse in both the veterans and general population. These disparities remain a central factor in the undertreatment of pain and serve as barriers to appropriate pain care (42). In addition, veterans with CNCP are a vulnerable population who may experience a multitude of social problems as they transition from active military duty to civilian status (6). These problems include financial problems, unemployment, disability, homelessness, social isolation, and/or limited access to pain care that can contribute to poor pain outcomes.

This study found a significant association between pain intensity and depression in veterans prescribed LTOT for CNCP. Whether an increase in depression scores is associated with worsening pain intensity or an increase in pain intensity worsened depression symptoms, this bi-direction association highlighted the need for concurrent assessment and treatment of both

conditions (23). In veterans, the prevalence of CNCP and depression comorbidity ranges from 15% to 57% (16, 43-47). These rates varied depending on coexisting comorbidities including hepatitis C (48), spinal disorders (49), musculoskeletal disease (44) and different veteran subgroups (i.e., OIF/OEF veterans (43, 47, 50)). In this study sample, the comorbidity prevalence was 24% for current depressive disorder and 43% for past depressive disorder. This finding underscored the importance of managing depression for optimal pain treatment outcomes (16).

Depression was not associated with opioid dosage in this study; however, several studies reported the risk of a new or recurrent depression diagnosis among veterans prescribed opioid therapy (20, 51, 52). According to Scherrer et al. (52), longer duration of opioid use is associated with an increased risk of major depression. In addition, veterans with a history of depression who are prescribed opioids were 77%-110% more likely to have a recurrence of their depression compared to those who were not prescribed opioids (51). For type of opioids, codeine was associated with a 30% greater risk of a new depression diagnosis compared to hydrocodone (52). Furthermore, opioid use of 90 days or greater was strongly associated with a new depression diagnosis among female veterans compared to men but this gender association was not seen in the general population (20).

Among the study participants, 21%-38% continued some follow-up visits in the outpatient pain clinic during 36 months. In the VA system, not many primary care clinicians or subspecialists outside of pain medicine are adequately trained to modify opioid dosing, conduct opioid rotation, or use equianalgesic conversion charts to maximize LTOT use. In the current healthcare system, these providers may have limited time to address the complex physical, psychological, and social factors that contribute to the CNCP experience in veterans (53). Therefore, these clinicians may refer patients to pain medicine colleagues or continue to increase

existing opioid dosage until high dose thresholds are met or patients experience severe adverse effects. This study highlights the pragmatic use of LTOT and pain care seen in major urban centers where a multidisciplinary team are readily available to provide comprehensive treatments.

Limitations

A number of limitations are noted in this study. First, as a retrospective cohort study, the ability to control for confounding variables that can affect pain intensity and opioid dosage was limited. Potential residual confounders include unknown treatments (i.e., surgeries, interventional pain procedures, other pharmacological and non-pharmacological treatments) that can increase or decrease pain intensity or alter LTOT over time. Second, even though sensitivity analysis were performed with multiple assumptions on missingness, lost to follow-up and missing data might have biased the study results. In this study, only 42% (n=56) remained on LTOT for 36 months. When LTOT is prescribed, opioid misuse, abuse or other adverse side effects are important clinical outcomes in treatment. Patients might have discontinued LTOT because of misuse or other reasons, and/or transferred their care outside of the VA system. Unfortunately, this study did not have the information on adverse effects, except for possible misuse from the medical records. Lastly, the study sample was small and homogenous, primarily comprising of men, ages of 52-65, and retired or not employed. Comparison of gender was not possible because of the small female sample size. These factors limit the generalizability of the findings.

CONCLUSION

CNCP is prevalent and an extremely challenging disease. Veterans with CNCP are difficult to manage because of the multitude of biopsychosocial factors that contribute to their

experience. In addition, clinical treatments may be limited for some individuals whose pain condition continue to deteriorate, have failed interventional procedures, surgical interventions, and/or have contraindications to medications. The appropriate use of LTOT for the management of CNCP requires more scrutiny due in part because of the "opioid epidemic" and the need for more robust evidence on effectiveness over time. This study found that pain intensity and prescribed opioid dosage did not significantly changed over time for 36 months among veterans prescribed LTOT for CNCP. Minimal fluctuations in opioid dosing, plateau in pain intensity, and a significant association with depression underscore the importance of routine assessments and psychological evaluation to achieve overall stability of treatment.

The findings in this study underscore the challenges for investigating the utility and effectiveness of LTOT in veterans with CNCP. More studies are needed to explore general stability of pain intensity and opioid dosage in LTOT including prospective longitudinal studies greater than 36 months with larger sample sizes. These studies should investigate pain and dosage fluctuations and the interventions (i.e., opioid rotation, drug holiday) to reduce higher dose escalation, optimize opioid use, and reduce adverse effects. Opioids remain one of the most potent treatments available to modulate pain symptoms however, additional studies are needed to help validate and/or clarify this role for veterans with CNCP.

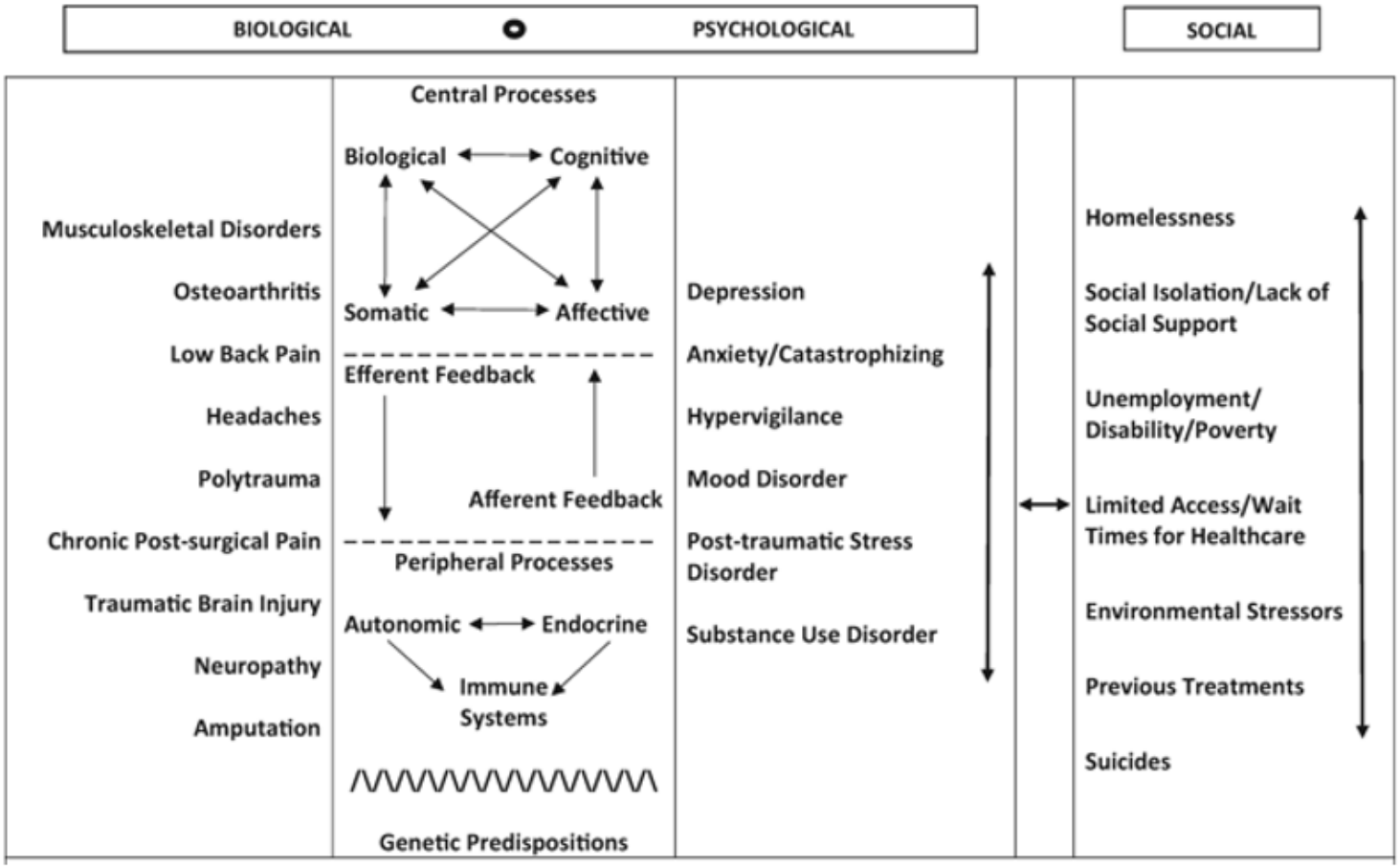

FIGURE 4.1: THE BIOPSYCHOSOCIAL MODEL OF CHRONIC NON-CANCER PAIN IN VETERANS

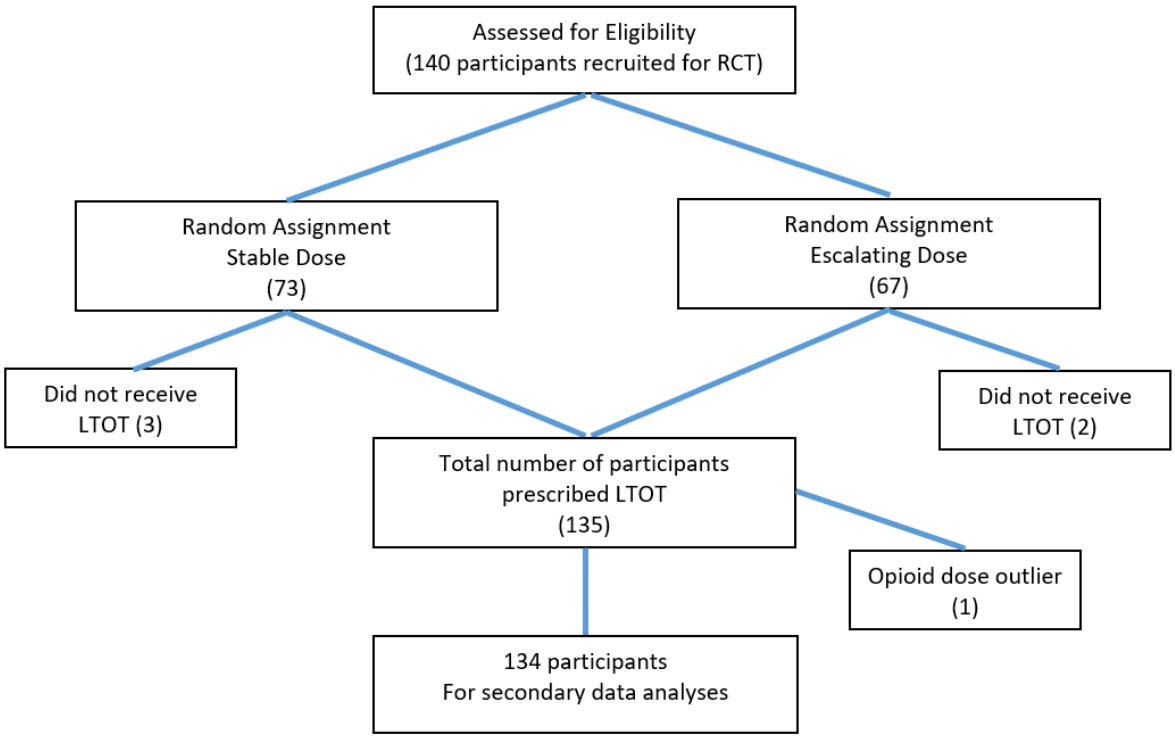

FIGURE 4.2: SCHEMATIC OVERVIEW OF STUDY PARTICIPANTS

TABLE 4.1 STUDY SAMPLE CHARACTERISTICS (n=134)

Characteristic	**N (%)**
Age	
25 to 55 years old	89 (66)
56 to 65 years old	45 (44)
Mean (SD), years	52.6 (7.45)
Gender	
Women	7 (5)
Men	127 (95)
Marital status	
Married	42 (32)
Never married	18 (13)
Living with spouse equivalent	11 (8)
Divorced/separated	54 (41)
Widowed	8 (6)
Living situation	
Alone	38 (30)
With spouse or equivalent only	26 (20)
With children	4 (3)
With spouse and children	24 (19)
With other relatives	14 (11)
With friends or roommates	11 (8)
Homeless or in transition	6 (4)
Other	8 (5)
Employment status	
Full-time	17 (13)
Part-time	8 (6)
Unemployed but not because of pain	2 (1)
Unemployed or unable to work due to pain	47 (37)
Retired	10 (7)
On VA Service connection disability	21 (16)
On Non-VA disability	25 (20)
Chronic Pain Diagnosis	
Musculoskeletal	104 (78)
Neuropathic	25 (19)
Complex	5 (3)
Anxiety (baseline), Mean (SD)	8.14 (4.7)
Depression (baseline) Mean (SD)	8.84 (4.4)
Attrition N (%)	
1-12 months	57 (42)
13-24 months	14 (19)
25-36 months	5 (8)

TABLE 4.2 VETERANS WITH CHRONIC NON-CANCER PAIN WHO SCREENED FOR ANXIETY AND DEPRESSION

(Score ≥11) (%)	Baseline	4th month	8th month	12th month
HADS Anxiety	43 (32)	22 (20)	15 (18)	13 (20)
HADS Depression	51 (38)	30 (28)	25 (30)	21 (33)

TABLE 4.3 VETERANS WHO CONTINUE TO FOLLOW-UP IN THE PAIN CLINIC AND MENTAL HEALTH CLINIC

	Follow-up visit		
Variable	>12 months	24 months	36 months
Follow-up, N (%)			
Pain Clinic	78 (53)	25 (18)	24 (17)
Mental health clinician	43 (31)	33 (24)	30 (22)

TABLE 4.4: MEAN AND MEDIAN OPIOID DOSAGE AND PAIN SCORES IN VETERANS PRESCRIBED LONG-TERM OPIOID THERAPY FOR CHRONIC NON-CANCER PAIN

Opioid Use Dosage (morphine equivalent daily dosing in milligrams)		
	12 months follow-up	36 months follow-up
log(Dose), Escalating Dose Group	3.53 (0.22)	3.41 (0.18)
log(Dose), Stable Dose Group	3.33 (0.08)	3.48 (0.18)
Median[a] (IQR) Escalating Dose Group	31.9 (22.5 - 47.5)	27.0 (20.0 - 40.0)
Median[a] (IQR) Stable Dose Group	30.0 (19.6 - 40.7)	30.0 (15.0 - 63.8)
[a]The median of each individual median opioid use between escalating opioid group and stable opioid group during 12 months and 13-36 months follow-up.		
Pain Intensity (numeric rating scale 0-10)		
Mean Escalating Dose Group	6.1 (0.57)	5.3 (0.29)
Mean Stable Dose Group	6.6 (0.25)	5.7 (0.37)
Median[b] (IQR) Escalating Dose Group	6.6 (5.5 - 7.6)	6.0 (4.2 - 7.7)
Median[a] (IQR) Stable Dose Group	6.8 (5.9 - 7.8)	6.2 (5.1 - 7.5)
[b]The median of each individual median pain intensity between escalating opioid group and stable opioid group during 12 month and over13- 36-month follow-up		

TABLE 4.5 MEDIAN OPIOID DOSAGE IN MORPHINE EQUIVALENCE 1-36 MONTHS

Opioid Dosage (morphine equivalent daily dosing in milligrams), Median [IQR]			
	1-12 months	13-24 months	25-36 months
Escalating Dose Group	31.9 [22.5 - 47.5]	28.0 [20.0 - 41.3]	23.0 [20.0 - 40.0]
Stable Dose Group	30.0 [19.6 - 40.7]	30.0 [20.8 - 63.0]	34.0 [18.0 - 71.3]

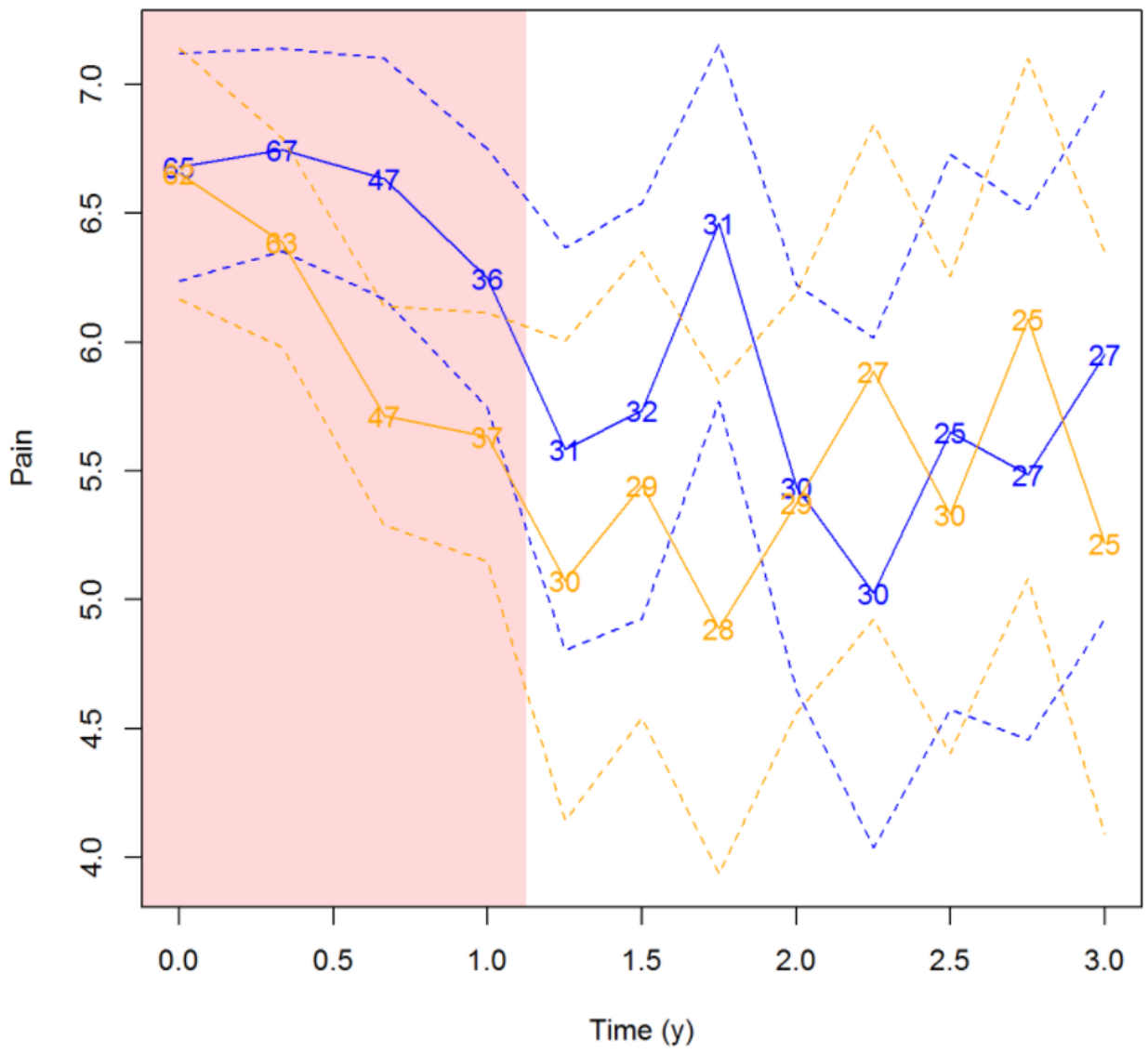

FIGURE 4.3: PAIN INTENSITY TRAJECTORIES FOR VETERANS PRESCRIBED LONG-TERM OPIOID THERAPY FOR CHRONIC NON-CANCER PAIN 0-36 MONTHS

= Escalating Dosage Group
= 95% Confidence Intervals
= Stable Dosage Group
= 95% Confidence Intervals

TABLE 4.6 Associations of **Pain Intensity** Over 12 Months with Opioid Dosage (Log), Sociodemographic Characteristics, Anxiety, Depression in Veterans Prescribed Long-term Opioid Therapy for Chronic Non-cancer Pain

Association with pain intensity at baseline	Association with pain intensity, adjusting for time, prescription group, and interaction between time and group (MCAR)	Association with pain intensity, adjusting for time, prescription group, and interaction between time and group (MAR)	Association with pain intensity, adjusting for time, prescription group, and interaction between time and group (MNAR)
Estimate Std..Error t.value Pr...t.. n betaci	Estimate Std..Error df t.value Pr...t.. n betaci	Estimate Std..Error df t.value Pr...t.. n betaci	Value Std.Err z.value p.value n betaci
age 0.0004114 0.0228486 0.0180069 0.9856618 128 0.000 (-0.044, 0.045)	-0.0249744 0.0215404 67.00016 -1.1594238 0.2503988 70 -0.025 (-0.067, 0.017)	-0.0180676 0.0177486 116.3043 -1.0179729 0.3108038 129 -0.018 (-0.053, 0.017)	-0.0178091 0.0177154 -1.0052904 0.3147570 129 -0.018 (-0.053, 0.017)
livepartner -0.4600103 0.3402971 -1.3517903 0.1788834 127 -0.460 (-1.127, 0.207)	-0.4475029 0.3186900 65.99987 -1.4041949 0.1649492 70 -0.448 (-1.072, 0.177)	-0.4139256 0.2666722 118.2338 -1.5521891 0.1232897 128 -0.414 (-0.937, 0.109)	-0.4217037 0.2661261 -1.5846013 0.1130569 128 -0.422 (-0.943, 0.100)
alone 0.2582707 0.3599982 0.7174221 0.4745559 118 0.258 (-0.447, 0.964)	0.1422503 0.3526360 63.99994 0.4033913 0.6880049 70 0.142 (-0.549, 0.833)	0.1695847 0.2752854 111.9914 0.6160324 0.5391232 118 0.170 (-0.370, 0.709)	0.1871533 0.2746494 0.6814264 0.4956017 118 0.187 (-0.351, 0.725)
hadanx1 0.0690368 0.0353968 1.9503673 0.0533527 128 0.069 (-0.000, 0.138)	0.0708707 0.0251418 216.62645 2.8188363 0.0052663 70 0.071 (0.022, 0.120)	0.0537762 0.0210991 316.9904 2.5487460 0.0112822 130 0.054 (0.012, 0.095)	0.0547434 0.0211888 2.5835995 0.0097775 130 0.055 (0.013, 0.096)
haddep1 0.0860289 0.0370398 2.3226094 0.0218037 128 0.086 (0.013, 0.159)	0.0862277 0.0241103 178.67841 3.5763798 0.0004483 70 0.086 (0.039, 0.133)	0.0623166 0.0212555 280.4030 2.9317796 0.0036481 130 0.062 (0.021, 0.104)	0.0619068 0.0211792 2.9229940 0.0034668 130 0.062 (0.020, 0.103)
tsopa601 -0.0975724 0.2915507 -0.3346672 0.7384326 128 -0.098 (-0.669, 0.474)	0.2060081 0.1239380 209.99185 1.6621871 0.0979672 70 0.206 (-0.037, 0.449)	0.1152286 0.1085208 287.7013 1.0618109 0.2892120 130 0.115 (-0.097, 0.328)	0.1015008 0.1087006 0.9337649 0.3504252 130 0.102 (-0.112, 0.315)
logmm -0.0523144 0.2534033 -0.2064471 0.8367723 129 -0.052 (-0.549, 0.444)	-0.0649526 0.2119578 146.88417 -0.3064412 0.7597027 70 -0.065 (-0.480, 0.350)	-0.2692583 0.1450807 338.9759 -1.8559209 0.0643325 130 -0.269 (-0.554, 0.015)	-0.2408106 0.1452849 -1.6575060 0.0974172 130 -0.241 (-0.526, 0.044)
employcf_yn -0.4119242 0.4351432 -0.9466406 0.3456932 124 -0.412 (-1.265, 0.441)	-0.3046647 0.3923345 148.60732 -0.7765434 0.4386624 70 -0.305 (-1.074, 0.464)	0.0432981 0.3063957 279.3520 0.1413144 0.8877235 125 0.043 (-0.557, 0.644)	0.0672242 0.3079740 0.2182787 0.8272120 125 0.067 (-0.536, 0.671)
p1misuse_bin 1.3608772 0.5021499 2.7101014 0.0076561 129 1.361 (0.377, 2.345)	0.1371283 0.1501866 188.80868 0.9130527 0.3623793 70 0.137 (-0.157, 0.431)	0.1778000 0.1324281 270.7353 1.3426146 0.1805214 130 0.178 (-0.082, 0.437)	0.1541357 0.1316944 1.1704042 0.2418383 130 0.154 (-0.104, 0.412)

Multivariable Model (Joint Model)

Variable	Value	Standard Error	P-Value
Time	6.310	0.270	0.018
Escalating	-0.469	0.240	0.050
Misuse	0.209	0.140	0.136
Depression	0.061	0.021	0.003

*With a Bonferroni correction for the 9 covariates, results with p<0.0056 were stated as significant. Results with p<0.05 were reported as suggestive nominal associations
(MCAR) Missing completely at random, (LMM) Linear Mixed Model, (MAR) Missing at random

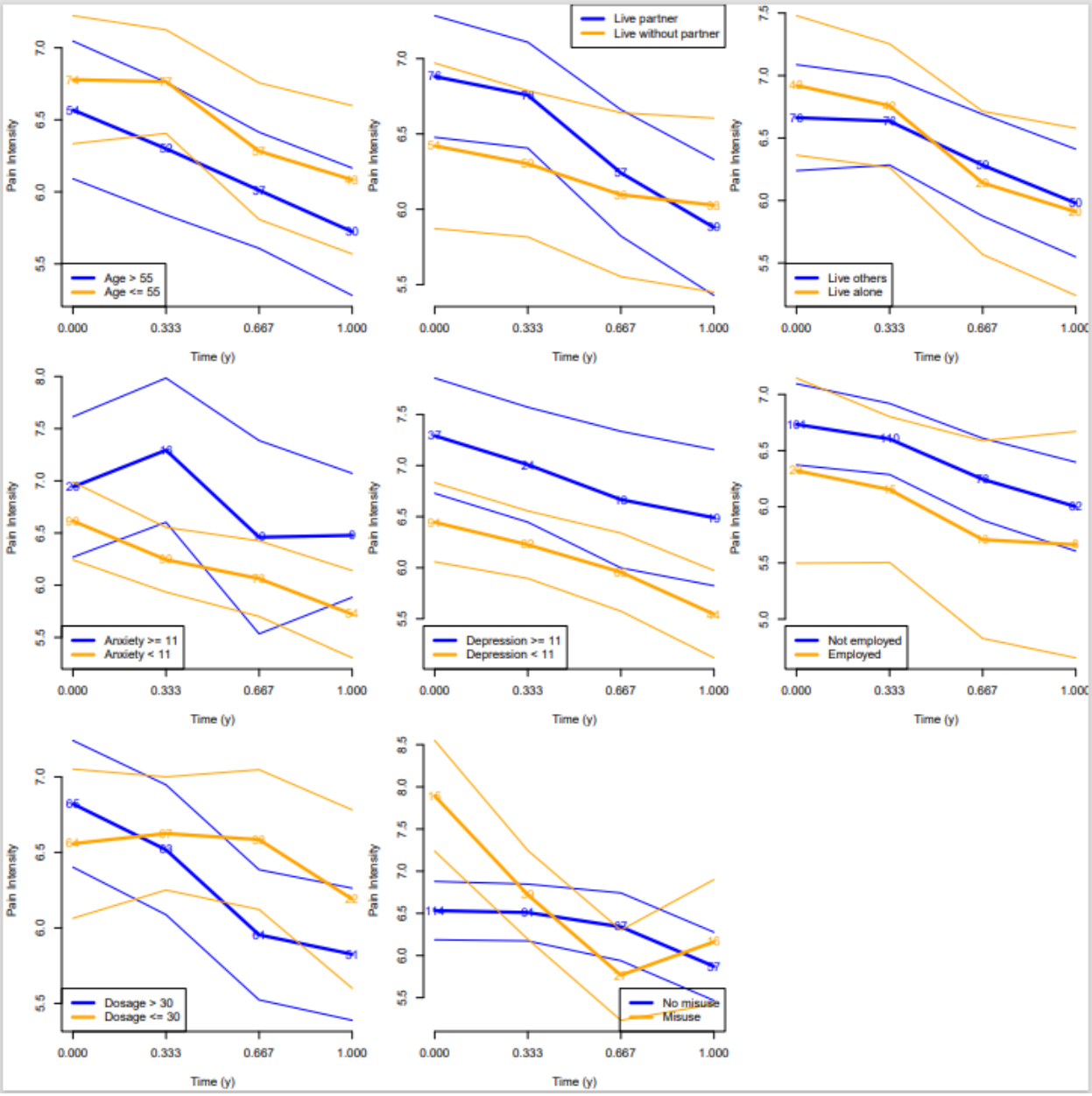

FIGURE 4.4 TRAJECTORIES OF SOCIODEMOGRAPHICS CHARACTERISTICS, DEPRESSION, & ANXIETY WITH PAIN INTENSITY (MEDIAN AND 95% CI)) IN VETERANS PRESCRIBED LONG-TERM OPIOID THERAPY FOR CHRONIC NON-CANCER PAIN

Y-axis= Pain intensity (scale 0-10)
X-axis= Time 0= baseline, 0.333= 4th months, 0.667= 8th months, 1.000= 12th months

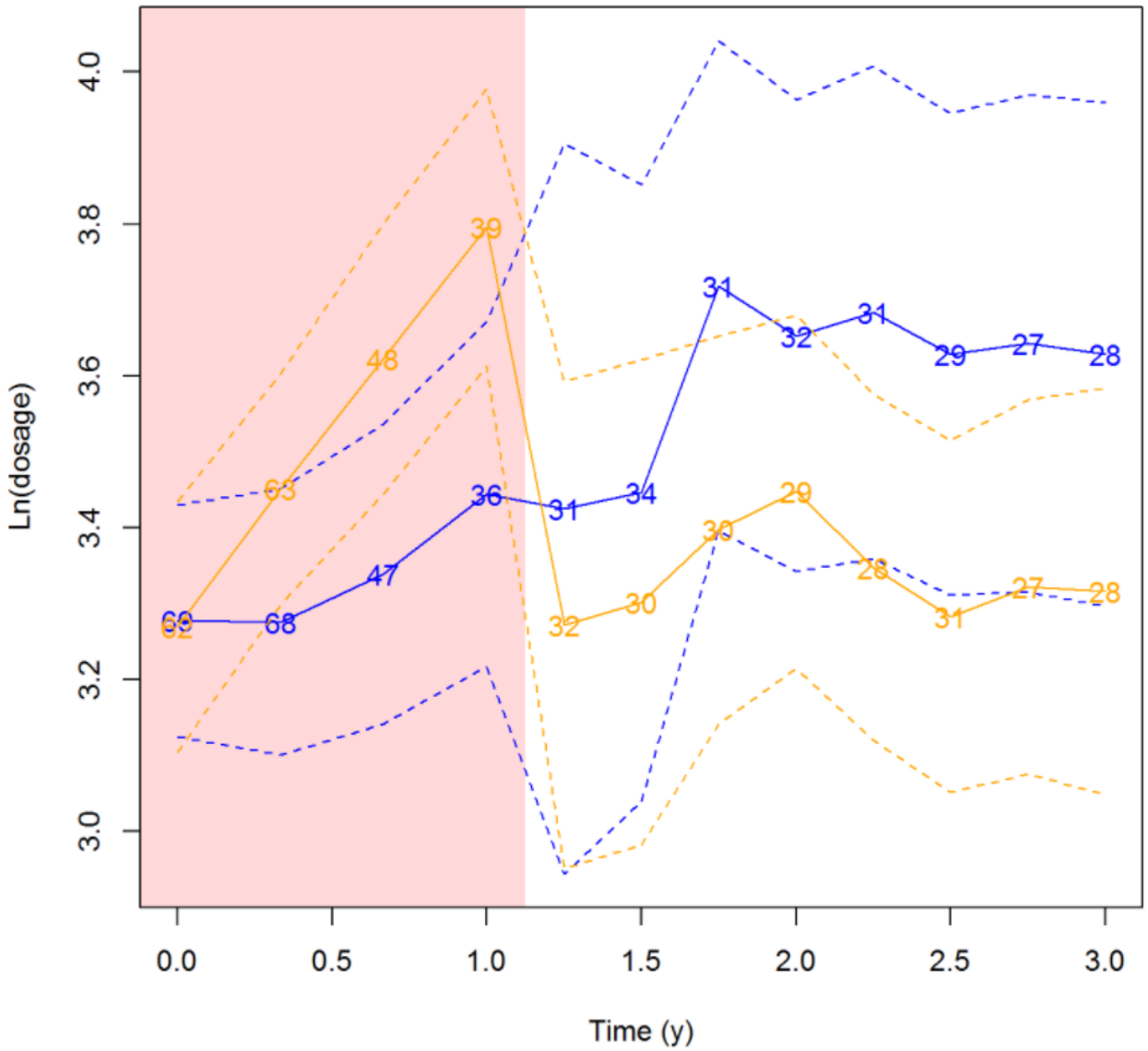

FIGURE 4.5 OPIOID DOSAGE TRAJECTORIES FOR VETERANS PRESCRIBED LONG-TERM OPIOID THERAPY FOR CHRONIC NON-CANCER PAIN 0-36 MONTHS

= Escalating Dosage Group
= 95% Confidence Interval
= Stable Dosage Group
= 95% Confidence Interval

TABLE 4.7 Associations of **Opioid Dosage** (Log) Over 12 Months with Pain Intensity, Sociodemographic Characteristics, Anxiety, Depression in Veterans Prescribed Long-term Opioid Therapy for Chronic Non-cancer Pain

Association with opioid dosage at baseline	Association with opioid dosage, adjusting for time, prescription group, and interaction between time and group (MCAR)	Association with opioid dosage, adjusting for time, prescription group, and interaction between time and group (MAR)	Association with opioid dosage, adjusting for time, prescription group, and interaction between time and group (MNAR)

Covariate association at baseline.

	Estimate	Std..Error	t.value	Pr...t..	n	betaci
age	-0.0130100	0.0076440	-1.7019983	0.0911644	131	-0.013 (-0.028, 0.002)
livepartner	-0.0197946	0.1175962	-0.1683270	0.8665917	130	-0.020 (-0.250, 0.211)
alone	0.0408112	0.1277982	0.3193408	0.7500327	120	0.041 (-0.210, 0.291)
hadanx1	-0.0180801	0.0121376	-1.4895933	0.1387721	131	-0.018 (-0.042, 0.006)
haddep1	-0.0002303	0.0130623	-0.0176314	0.9859601	131	-0.000 (-0.026, 0.025)
tsopa601	0.0283751	0.1010677	0.2807530	0.7793497	131	0.028 (-0.170, 0.226)
pain1	-0.0064128	0.0310626	-0.2064471	0.8367723	129	-0.006 (-0.067, 0.054)
employcf_yn	0.0226090	0.1455169	0.1553705	0.8767798	127	0.023 (-0.263, 0.308)
p1misuse_bin	0.0001881	0.1802712	0.0010437	0.9991689	131	0.000 (-0.353, 0.354)

	Estimate	Std..Error	df	t.value	Pr...t..	n	betaci
age	-0.0092126	0.0099176	68.99993	-0.9289151	0.3561714	72	-0.009 (-0.029, 0.010)
livepartner	0.1437567	0.1479841	68.00006	0.9714335	0.3347753	72	0.144 (-0.146, 0.434)
alone	-0.0460941	0.1618568	66.00012	-0.2847830	0.7767021	72	-0.046 (-0.363, 0.271)
hadanx1	0.0009375	0.0056655	206.12262	0.1654673	0.8687384	72	0.001 (-0.010, 0.012)
haddep1	-0.0017422	0.0058396	197.48440	-0.2983429	0.7657551	72	-0.002 (-0.013, 0.010)
tsopa601	-0.0038661	0.0238003	166.40712	-0.1624409	0.8711558	72	-0.004 (-0.051, 0.043)
pain1	-0.0201120	0.0122395	225.84758	-1.6432106	0.1017308	72	-0.020 (-0.044, 0.004)
employcf_yn	0.1007511	0.1045979	263.03674	0.9632235	0.3363201	72	0.101 (-0.104, 0.306)
p1misuse_bin	-0.0088421	0.0276175	167.27705	-0.3201617	0.7492453	72	-0.009 (-0.063, 0.045)

	Estimate	Std..Error	df	t.value	Pr...t..	n	betaci
age	-0.0133790	0.0075366	126.1250	-1.7752096	0.0782753	130	-0.013 (-0.028, 0.001)
livepartner	0.0967822	0.1153568	125.1236	0.8389818	0.4030796	129	0.097 (-0.129, 0.323)
alone	-0.0596904	0.1236198	115.7933	-0.4828552	0.6301102	119	-0.060 (-0.302, 0.183)
hadanx1	-0.0013366	0.0052704	268.7038	-0.2536078	0.7999925	131	-0.001 (-0.012, 0.009)
haddep1	-0.0003001	0.0052850	258.4345	-0.0567773	0.9547665	131	-0.000 (-0.011, 0.010)
tsopa601	-0.0096331	0.0225109	202.9033	-0.4279319	0.6691546	131	-0.010 (-0.054, 0.034)
pain1	-0.0308793	0.0148119	369.4555	-2.0847627	0.0377771	131	-0.031 (-0.060, -0.002)
employcf_yn	-0.0586422	0.0906085	402.4102	-0.6472040	0.5178690	126	-0.059 (-0.236, 0.119)
p1misuse_bin	-0.0174050	0.0381758	193.1787	-0.4559181	0.6489609	131	-0.017 (-0.092, 0.057)

	Value	Std.Err	z.value	p.value	n	betaci
age	-0.0134942	0.0074748	-1.8053010	0.0710276	130	-0.013 (-0.028, 0.001)
livepartner	0.0957507	0.1158405	0.8265736	0.4084788	129	0.096 (-0.131, 0.323)
alone	-0.0595284	0.1226786	-0.4852385	0.6275072	119	-0.060 (-0.300, 0.181)
hadanx1	-0.0012081	0.0053488	-0.2258586	0.8213114	131	-0.001 (-0.012, 0.009)
haddep1	-0.0002008	0.0053221	-0.0377341	0.9698997	131	-0.000 (-0.011, 0.010)
tsopa601	-0.0090361	0.0225362	-0.4009616	0.6884484	131	-0.009 (-0.053, 0.035)
pain1	-0.0302387	0.0148213	-2.0402209	0.0413283	131	-0.030 (-0.059, -0.001)
employcf_yn	-0.0612439	0.0906848	-0.6753494	0.4994538	126	-0.061 (-0.239, 0.116)
p1misuse_bin	-0.0173619	0.0382171	-0.4542967	0.6496153	131	-0.017 (-0.092, 0.058)

Multivariable Model (Joint Model)

Variable	Value	Standard Error	P-Value
Time	0.128	0.079	0.104
Escalating	0.014	0.114	0.897
Misuse	-0.011	0.038	0.761
Pain	-0.030	0.014	0.041
TimeXGroup	0.358	0.108	0.001

*With a Bonferroni correction for the 9 covariates, results with $p<0.0056$ were stated as significant. Results with $p<0.05$ were reported as suggestive nominal associations
(MCAR) Missing completely at random, (LMM) Linear Mixed Model, (MAR) Missing at random

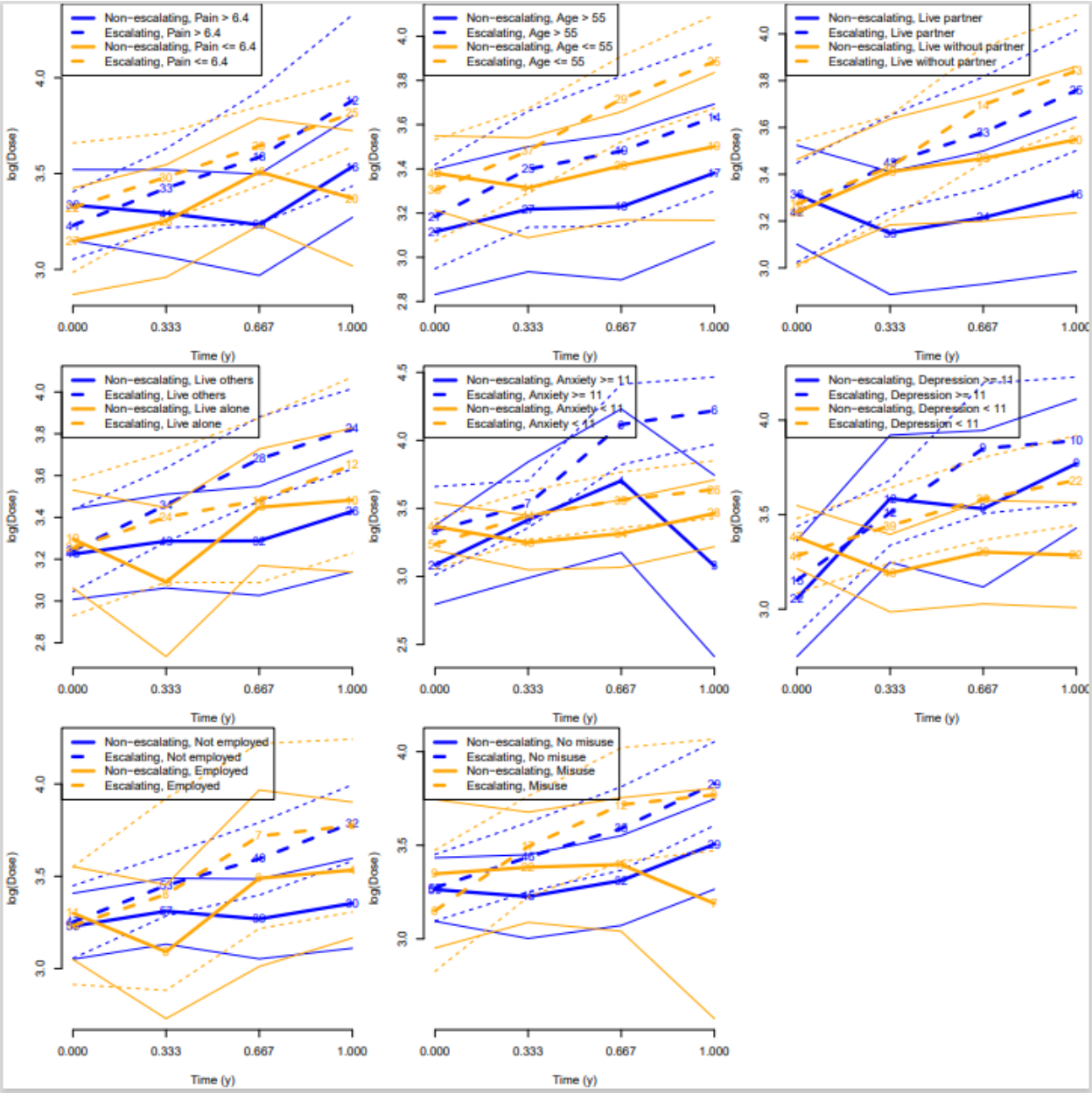

FIGURE 4.6 TRAJECTORIES OF SOCIODEMOGRAPHICS CHARACTERISTICS, DEPRESSION, ANXIETY, & PAIN WITH OPIOID DOSAGE (LOG) BETWEEN ESCALATING DOSE GROUP VERSUS STABLE DOSE GROUP

Y-axis= Opioid Dosage (log) morphine equivalent daily dosing in milligrams
X-axis= Time 0= baseline, 0.333= 4th months, 0.667= 8th months, 1.000= 12th months

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CHAPTER 5

TRAJECTORIES OF PHYSICAL FUNCTION AND DISABILITY IN VETERANS PRESCRIBED LONG-TERM OPIOID THERAPY FOR CHRONIC NON-CANCER PAIN

ABSTRACT

Background: Physical functioning is an important clinical outcome used to assess the effectiveness of long-term opioid therapy (LTOT) in patients with chronic non-cancer pain (CNCP). Little is known about the physical functioning among veterans in LTOT for CNCP. **Purpose:** The aims of this study were to describe the trajectories of physical functioning among veterans prescribed LTOT for CNCP and examine whether these trajectories differ by sociodemographic characteristics (i.e., age, sex, living situation), pain intensity, and mood (anxiety and depression). **Methods:** The study analyzed data from a single blind randomized clinical trial that compared opioid prescribing practices (liberal versus conservative dosing) in 134 veterans for 12 months in an outpatient VA pain clinic but did not previously assess physical functioning. Physical functioning was measured by the Oswestry Disability Index (ODI). Regression models were used to test change over time. **Results:** In veterans with CNCP, LTOT was nominally associated with improving physical functioning for 12 months (β=-0.84, p= 0.03). Lower physical functioning was associated with increased pain intensity (β=1.30, p=0.002), anxiety (β=0.81, p<.0001) and depression (β=1.48, p<0.0001). Physical functioning did not differ by other sociodemographic characteristics (p>0.05). **Conclusion:** The study findings suggest that physical functioning can increase over time with appropriate management of pain and depression among veterans prescribed LTOT for CNCP.

INTRODUCTION

Chronic non-cancer pain (CNCP) is prevalent among veterans and can have a negative impact on their physical functioning (1-3). Over 1.44 million veterans in the U.S. have CNCP from musculoskeletal disorders and traumatic blast injuries with impaired physical functioning a significant concern (3-5). In addition, about 3.95 million veterans have a service-connected disability that affects their physical functioning. Approximately 1.52 million of these veterans have their disability rated 70% or higher which can result in severe functional impairments and poor quality of life (4). The most common service-connected disabilities include: musculoskeletal/joint injuries (66%), post-traumatic stress disorder (60%), tinnitus (59%), anxiety (56%), depression (53%), hearing loss (50%), traumatic brain injury (25%), and other causes (29%) (4-6). These disabilities are often associated with medical and psychiatric comorbidities along with social problems (i.e., social isolation, lack of social support, financial problems, unemployment, homelessness, and poor access to medical care and resources) that result in increased morbidity and mortality among veterans (1-3, 7, 8).

For veterans with CNCP, function and physical activity are important assessments that evaluate the effectiveness of pain management treatments including long-term opioid therapy (LTOT) (9-13). Many veterans with CNCP may rely on LTOT to maintain or improve their level of physical functioning especially when multiple treatments have failed. Since 2016, however, the use of LTOT for CNCP has decreased in response to the "opioid epidemic", more stringent opioid prescribing guidelines, and the lack of empirical evidence for the long-term effectiveness of opioid treatment (14). Given the high prevalence of CNCP and disability among veterans often resulting in opioid use, LTOT needs to be examined comprehensively. The purpose of this study was to describe trajectories of physical functioning among veterans prescribed LTOT for

CNCP and examine whether these trajectories differ depending on sociodemographic characteristics, pain intensity, and mood (depression and anxiety). This information may provide a better understanding of the key factors contributing to the effectiveness of LTOT for CNCP and identify strategies to improve physical functioning and disability among veterans.

METHODS

The study conducted a secondary data analysis from a single-blinded randomized clinical trial that compared the effectiveness of two opioid prescribing practices (i.e., liberal escalating dose versus stable conservative prescribing) in veterans with CNCP (13). The data included 134 veterans who were prescribed LTOT for 12 months in an outpatient pain clinic. Institutional Review Board (IRB) approvals were obtained from the VA Greater Los Angeles Healthcare System and University of California San Francisco.

Sample/Setting/Recruitment

The original study recruited participants from a multidisciplinary outpatient pain management clinic (13). The pain management team included board certified clinicians in physiatry, anesthesiology, psychiatry, psychology, neurology, and nursing. After a thorough pain specific history and physical exam, review of pharmacological and non-pharmacological treatments, mental health comorbidities, and substance use histories, participants were recruited based on the study inclusion and exclusion criteria. These inclusion criteria included: 1) a diagnosis of CNCP for at least 6 months, 2) pain team's determination that LTOT was indicated for study participant's pain condition, and 3) eligiblility for opioid treatment. Participants were excluded if they met any of the following: 1) any planned surgery during the one year follow-up, 2) unclear CNCP diagnosis or participants undergoing work-up to determine pain etiology, 3) participants with acute or post-operative pain, 4) participants with severe comorbid disease,

active substance use disorder, and/or acute psychiatry admission within the past 2 years. After completion of the initial pain clinic interviews, study participants were followed monthly for 12 months based on study protocols.

Figure 5.1 outlines a schematic overview of the 140 veterans recruited in the study. A total of 73 participants were included randomly assigned to the opioid escalating dose group while 67 participants were assigned to the conservative stable dose arm. The study sample included 134 veterans after five participants dropped out after randomization and one was an outlier (i.e., participant's opioid dosage >300mg at the time of recruitment).

Variables

Sociodemographic Characteristics

Study participants completed an initial interview for sociodemographic information that included age, gender, marital status, employment status, and current living situation. This information was collected every 4 months until study completion.

Pain Intensity

Pain intensity was assessed at baseline and every four months until the conclusion of the 12-month study. A 10-cm visual analog scale (VAS) that ranged from 0 (no pain) to 10 (most intense pain imaginable) was used to measure "usual or average pain intensity" over the past month. The VAS pain rating scale has been used extensively in previous pain studies in veterans and the general population and been found to be valid and reliable (15).

Opioid Dosage in Morphine Equivalence

Opioid prescriptions from both VA and non-VA clinicians were assessed at baseline and then every four months. Oral morphine equivalent (OME) daily dosing was calculated to standardize opioid dosage across different formulations (i.e., codeine, hydrocodone, oxycodone,

methadone, and fentanyl). Various studies (13, 16, 17) have used OME dosing to quantify and standardize opioid intake among participants with chronic pain.

Mood

Participants completed the Hospital Anxiety and Depression Scale (HADS) at baseline and every 4 months. The HADS is used to measure change in anxiety (7 items) and depression (7 items) related to the course of disease and in response to psychotherapeutic and psychopharmacological intervention (18). Each item is scored from 0-3 based on 14 statements on how participants have felt in the past week. An example of an anxiety statement includes "I feel tense or wound up" and proceeding answers include: "most of the time" = 3, "a lot of the time" = 2, "from time to time, occasionally" = 1, and "not at all" = 0. An example of a depression statement is "I feel as if I am slowed down" with the following answer choices: "nearly all of the time" = 3, "very often" = 2, "sometimes" = 1, and "not at all" = 0. Scoring for the depression and anxiety scale can range from 0 to 21 with a score above 11 indicating anxiety/depression, and a score above 15 indicating severe anxiety/depression (19). The HADS has demonstrated acceptable to excellent validity and reliability. Cronbach's alpha coefficients ranged from 0.0.68 to 0.93 for the HADS-anxiety scale and from 0.67 to 0.90 for the HADS-depression scale. Correlation coefficients between HADS and other similar instruments (i.e., Beck Depression Index, General Health Questionnaire, Clinical Anxiety Scale, and Spielberger's State-Trait Anxiety Inventory) ranged from 0.49 to 0.83 (19).

Physical Functioning

Physical functioning was measured by the Oswestry Disability Index (ODI) at baseline, and at the 4^{th}, 8^{th}, and 12^{th} months. Validated by the Medical Research Council, the 10-item ODI can identify disturbances in activities of daily living due to pain and illness (10). These items

include pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex activities, social life, and travelling. Each item contains 6 statements that are scored from 0 to 5 corresponding to the degree of severity. For example, an assessment of sleep on ODI include: "my sleep is never disturbed by pain" = 0, "my sleep is occasionally disturbed by pain" = 1, "because of pain I have less than 6 hours sleep" = 2, "because of pain I have less than 4 hours sleep" = 3, "because of pain I have less than 2 hours sleep" = 4, and "pain prevents me from sleeping at all" = 5. The sum of the ten items is multiplied by 2 to yield an ODI score. This ODI score is interpreted as the percentage of disability (0-100%). As an example, if a total score on the 10-item questionnaire is 23, this number is multiplied by 2 to yield 46, or 46% ODI score. ODI scores that range from 0% to 20% indicate minimal disability, 21% to 40% as moderate disability, 41% to 60% as severe disability, 61% to 80% as crippled, and 81% to 100% as bed-bound or exaggerating symptoms. A 10% change in the score has been defined as being clinically meaningful (20).

The ODI demonstrated acceptable to excellent reliability with Cronbach's alpha ranging from 0.79 to 0.96 and test-retest correlation coefficient ranging from 0.71 to 0.96 (10, 20-22). Validation studies also showed good to excellent criterion validities when the ODI was compared to VAS (r = 0.73) and Roland-Morris Disability Questionnaire (RMDQ) (r = 0.819) (21).

During the initial interview, the average number of hours performing activities over a 24-hour period was collected to assess baseline physical function. These activities include: walking, working, exercising, sitting, and lying. No reliability or validity study was performed on these specific measures; however, this clinical information is pertinent to the overall level of physical functioning of participants.

Analysis

IBM SPSS Statistics (Version 26) (23) and R v3.6.0 (24) statistical programs were used for data analysis. Continuous variables were described using means, medians, and standard deviations and categorical variables were described by frequencies and percentages. Data distributions were evaluated for skewness and kurtosis, and log transformations were conducted for opioid dosage variable. Physical functioning variables (ODI scores and hours of daily activities) were compared by sociodemographic characteristics using independent sample t-tests.

Physical functioning over time was modeled under a joint longitudinal model for the outcome along with time to study drop-out model with the package JM (25) in R v3.6.0 (24). The effect of each sociodemographic/mood variable (covariates that did not change with time: age, living with partner, living alone, employment; and covariates that did: anxiety, depression, and log (opioid dosage) [only for pain intensity], as described above) were tested first, while also adjusting for important covariates of time, group (escalating vs. not), and the interaction between time and group (for the opioid dose outcome only. Sociodemographic variables were considered significant if they met a $p<0.0056$, a Bonferroni correction for the 9 covariates tested, and suggestive or nominal associations if ($p<0.05$). Finally, a stepwise regression was conducted to assess independent contributors to pain intensity, including covariates as long as they contributed to the model with $p<0.05$, and including important covariates such as group and opioid misuse.

Sensitivity analysis was performed to address the high attrition rate and missing data (Tables 5.4). The joint modeling approach present in the main analysis is the most flexible approach and is valid under a missing not at random (MNAR) mechanism (25). The analysis fit a standard linear mixed effect model LMM using lme4 (26), valid under a missing at random (MAR) missingness mechanism, which was used in the original RCT analysis (13), and that with

the strongest missing data assumption of listwise complete valid under a missing completely at random (MCAR).

RESULTS

Sample Characteristics

Table 5.1 displays sociodemographic characteristics of 134 veterans prescribed LTOT for CNCP. The study participants included 127 males and 7 females with mean age of 52.6 years (SD 7.49). Approximately 44% (n=45) of the veterans were between the ages of 56 to 65 years old. At baseline, 61% (n=82) of veterans did not have a partner (i.e., spouse or significant other) but 68% (n=91) lived with someone. A majority of the veterans (81%) reported that they were either unemployed, retired, or collecting disability through the Veterans Health Administration or from other sources. Of the 47 veterans who reported they were unable to work because of pain, 29 (62%) were 55 years old or younger, 46 (97%) were male, 31 (66%) lived with someone, and 29 (62%) were never married, divorced, or widowed. The percentage of employed veterans was higher among female veterans (71%) than male veterans (16%) ($p < 0.003$). The majority of veterans (78%) reported chronic pain from musculoskeletal injuries. At baseline, 53 (39%) veterans reported scores of 11 or greater (i.e., positive screen) on the HADs depression scale and 45 (33%) veterans on the anxiety scale.

Table 5.2 displays the average number of hours per day spent sitting, lying, walking, working, and exercising. At baseline, employed veterans reported significantly higher numbers of hours walking (2.6 versus 1.5, $p= 0.04$) and working (4.4 versus 1.8, $p= 0.003$) and a lower number of hours lying down (2.5 versus 4.5, $p= 0.001$) than unemployed, retired, or disabled veterans. There were no differences in activities of daily living by gender, living situation, and presence of a partner ($p>0.05$).

Table 5.3 displays mean ODI scores of study participants at baseline, and at the 4th, 8th and 12th months of follow-up. At baseline, the mean ODI score for the sample was 48.2 (SD 13.3), which indicated severe disability and decreased to 45.5 (SD 16.9) at the 12th-month follow-up. During enrollment, ODI scores were significantly different between veterans who were employed and those unemployed (40.0 vs. 49.8, p=0.001). ODI scores were not different by age, gender, living situation, or the presence of a partner (p>0.05). In addition, no difference in ODI scores was seen between the escalating versus stable dose groups as reported in the original study (13).

Trajectories in Physical Functioning

Figure 5.2.1 illustrates the 12-month trajectory of physical functioning in both escalating and stable dose groups of veterans prescribed LTOT for CNCP. In the12-months study timeframe, ODI scores slightly fluctuated within 3-5% for both groups. The escalating dose group showed a steady decline from baseline until 8th-month and then a slight upward trend at the 12th-month. The stable dose group showed a decline in ODI scores from baseline to 4th-month, an upward increase on the 8th-month, and then a downward trend on the 12th-month. Figure 5.2.2 illustrates overall ODI scores combining escalating and stable groups. This figure displays a decrease in ODI scores from the baseline to 4 month and then a plateau from 8th to 12th months which suggest improvements in physical functioning over time (β=-0.84, p<0.03).

Figure 5.3 shows changes in ODI scores over 12 months by sociodemographic characteristics, anxiety, depression, pain and opioid dosage. Table 5.4 presents the analysis of each sociodemographic/mood characteristic separately, as well as the stepwise regression model. When assessing each sociodemographic/mood characteristic separately, physical functioning showed significant associations with anxiety (β=0.81, p<.0001), depression (β=1.48, p<.0001),

and pain (β=1.30, p=0.002). The final stepwise regression model included only depression (β=1.48, p<.0001).

DISCUSSION

To the best of our knowledge, this is the first study that investigated physical functioning trajectories in veterans prescribed LTOT for CNCP. In this sample of veterans with high prevalence of severe disability and low levels of physical functioning, LTOT was nominally associated with improved physical functioning for up to 12 months. In addition, pain intensity and depression were shown as important factors associated with physical functioning in veterans prescribed LTOT.

Trajectories in Veterans with CNCP

Physical Functioning

This study identified only a slight improvement in physical functioning associated with LTOT among individuals with CNCP for 12 months. This finding is consistent with a recent meta-analysis of 51 high quality RCTs that found LTOT was associated with a small improvement in physical functioning compared to placebo, non-steroidal anti-inflammatory medications, tricyclic antidepressants, and synthetic cannabinoids during 1 to 6 months duration (27). In addition, in a head-to-head RCT that compared LTOT versus non-opioid treatment (12), moderate improvements in physical functioning were reported among veterans prescribed LTOT for chronic knee, hip, back pain from osteoarthritis. However, the improvements were not significantly different when compared to the non-opioid treatment group.

The clinical relevance of these findings is an important consideration especially when starting or continuing opioids in patients with severe functional disabilities refractory to multiple treatments and/or worsening disease progression (12, 28-31). LTOT may provide a number of

benefits by improving an individual's ability to function physically and engage in regular physical exercise. In this sample of veterans who reported a high degree of sedentary activities (lying and sitting) including less than 1 hour per day engaged in physical exercise, the importance of exercises for improving physical functioning and disability cannot be understated (32). The benefits of physical exercise/activities extend beyond physical functioning (i.e., physical endurance and strength) and may include improvements in pain intensity, fatigue, sleep, depression, anxiety, and quality of life in individuals with CNCP (32-34). Moreover, physical exercise and training have been shown to release serum concentrations of endogenous opioids (i.e., β-endorphins and β-lipotropins), linked to several physiological and psychological changes (34). These changes include altered pain perception, exercise-induced euphoria, and the release of stress hormones (i.e., cortisol, catecholamines, growth hormones).

The release of endogenous opioids through regular physical exercise may have a potential effect on opioid dependence and tolerance in individuals with CNCP. Ballantyne et al., (28) described the natural progression of opioid dependence and tolerance in individuals prescribed LTOT for CNCP. The continuous use of opioids and increasing dosage requirements over time (associated with tolerance) may be an attempt to avoid dysphoria and restore hedonic homeostasis. Exogenous opioids can produce pain relief and euphoria in individuals with CNCP, but with continued use, could result in hyperalgesia and an increase in dosing to avoid a perpetual state of withdrawal. Physical exercise may help counter this state of altered homeostasis by release of endogenous opioids to provide analgesic effects. The release of endogenous opioids may also lead to improved function and reduced reliance on exogenous opioids, allowing patients to taper off opioids and/or avoid dose titration.

Physical Functioning and Pain Intensity

This study found an association with pain when analyzing each sociodemographic/mood variable separately, although the association for pain was no longer significant when adjusting for depression. Nevertheless, as we showed previously (Chapter 4), pain is also associated with depression. Previous work has reported on the seriousness of uncontrolled pain and the effects on an individual's physical functioning and disability (3, 35, 36). Physical response to pain leads to guarding and cessation of physical activities as a result of an acute or chronic injury and neurophysiological signaling (i.e., pain mechanism of transduction, transmission, modulation, and perception) (32). In addition, individuals who are severely disabled and more physically deconditioned have lower tolerance for activities that can result in increased pain intensity. This bi-directional association between pain intensity and physical functioning serves as a strong rationale for utilizing a biopsychosocial model for assessment and treatment of these individuals within an interdisciplinary team setting.

In this sample of severely disabled veterans prescribed LTOT for CNCP, a multimodal approach to treatment must optimize other adjuvant pain medications, interventional pain procedures, psychological and social interventions, and physical rehabilitation with the goals of improving both pain and function (3, 35). Merely focusing on decreasing pain intensity could cause unintended consequences that include reducing individual's active participation, engagement, responsibility in their pain care, and minimizing other factors that contribute to individual's suffering (i.e., depression, anxiety, social problems) (28). In addition, escalating opioid dosage to reduce pain intensity scores may cause adverse side effects (e.g., sedation, respiration depression, falls, overdose, reducing an individual's ability to function, exercise, or perform activities of daily living). Assessing both pain intensity and physical functioning to

measure the effectiveness of LTOT may reinforce goals of treatment and clarify realistic expectations in individuals with CNCP.

Physical Functioning and Depression and Anxiety

In this sample of veterans prescribed LTOT for CNCP, the study showed physical functioning and disability is associated with depression and anxiety. This finding is consistent with numerous studies that reported on the effects of mental health, physical disability, and the overall influence on an individual's pain experience (3, 33, 37-46). Depression and anxiety are highly prevalent comorbid psychological conditions in CNCP and contribute to the significant burden on pain-related disability and its associated consequences on unemployment, loss of productivity, poverty, and increased utilization of healthcare (3, 35). Moreover, anxiety, fear, and avoidance play an important role on an individual's cognitive and affective experience and disability (3). In order to cope with CNCP, individuals with depression and anxiety may exhibit maladaptive or avoidance behaviors associated with helplessness, vulnerability, and hopelessness (47). These maladaptive behaviors may lead to increased pain and more severe functional disabilities resulting in perpetuation of the chronic pain cycle or the chronification of pain (3, 35, 39).

In this study, 39% and 33% of the sample screened positive at baseline for depression and anxiety, respectively. For many individuals living with CNCP, a link between physical activities and mood may be explained by the endomorphin system and its neurophysiological role (48). Based on the effects of β-endorphins, endogenous μ-opioid receptor-selective ligands produced in the pituitary gland and hypothalamus have been associated with producing analgesia and a sense of well-being similar to antidepressants (33). During physical activities, the release of these endogenous opioid peptides in the brain can cause a sense of general euphoria. When

individuals with CNCP experience an increase in disability or limitations in physical activities, the release of these endogenous opioid peptides are reduced which may further contribute to the psychological and affective well-being of these patients. This bi-directional association between physical disability and psychological dysfunctions may be more severe among veterans with CNCP because of multiple physical injuries and trauma and high prevalence of psychiatric disorders (i.e., depression, anxiety, post-traumatic stress order (PTSD), catastrophizing) and social dysfunction (i.e., disability, financial problems, social isolation, and homelessness) associated with military experience (35, 45, 49-51).

Physical Functioning and Sociodemographic Characteristics

In veterans prescribed LTOT for CNCP, sociodemographic characteristics were not associated with physical functioning. However, veterans who were unemployed, retired, or disabled reported significantly higher ODI scores and lower physical activities compared to those who are employed. This finding is expected but important since 66% of the study sample were between 25-55 years old, typically their most productive age. Whether LTOT contributes to a veteran's ability to resume employment is another important clinical outcome that requires further investigation. The benefits of being employed extend beyond financial benefits. For many individuals with CNCP, employment may provide additional opportunities for social interaction, a sense of accomplishment and contribution to society at large, reduced feelings of being a burden to society, and a tremendous boost to self-esteem and self-efficacy (3).

Limitations

Several limitations are noted in this study. One primary limitation is the small sample size which may affect the robustness of the findings and limits generalizability to a larger population of veterans with CNCP. While majority of the study participants were not prescribed

opioids during the start of the study, some participants who enrolled were already prescribed LTOT prior to their random assignments. For these non-opioid naïve individuals, their level of physical functioning improvements may be less apparent over time because they were already taking opioid medications prior. It is also important to report limitations associated with sample attrition including individuals lost to follow-up and/or early study termination because of opioid non-compliance (27% of sample discontinued because of misused). Other confounding variables include pain treatments not reported by participants during enrollment in the study. These treatments may affect physical functioning outcomes not associated with the use of LTOT. Lastly, the sample demographics represented more male than female, ages 25 to 55 years old, and retired or not employed which may limit the generalizability of the findings.

CONCLUSIONS

The effectiveness of LTOT in improving physical functioning is an important clinical assessment in veterans with CNCP. This study investigated the trajectory of physical functioning among veterans enrolled in a pragmatic study on opioid use. The study findings suggest that physical functioning can improve in veterans with severe disability and that depression and pain intensity are important factors associated with physical functioning. Further research using a larger sample is needed to investigate the effectiveness of LTOT for a longer term for improving physical functioning and how clinicians can maximize physical activities in these individuals with severe disability. Studies that investigate physical functioning greater than 12 months may provide a better understanding on the effectiveness of this treatment over time. Future studies should also assess physical functioning with various measurements including patient-reported, objective performance-based, and other physical measures of activity in order to evaluate actual functional disability (52). Utilizing a combination of these measurements could provide a

comprehensive assessment of the true physical limitations among these individuals especially when physical limitations are caused by a variety of conditions that affect different anatomical regions (i.e., lower extremity, upper extremity, spine, headaches or facial pain).

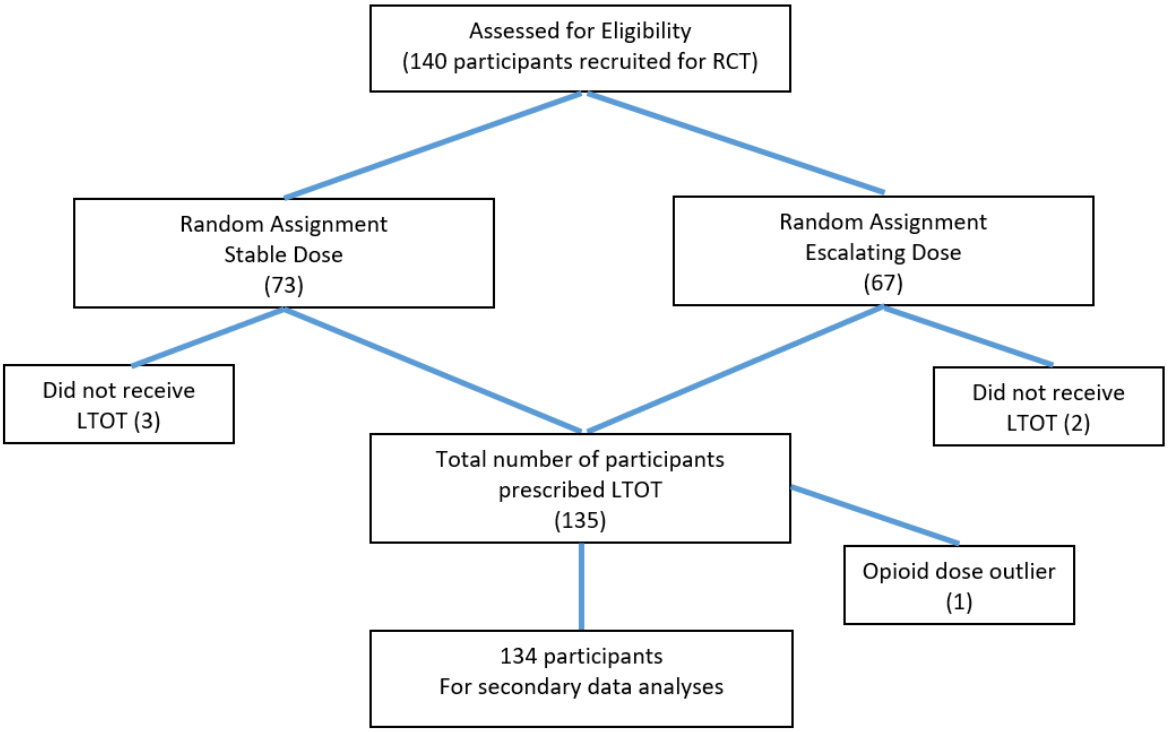

FIGURE 5.1 SCHEMATIC OVERVIEW OF STUDY PARTICIPANTS

TABLE 5.1: Study Sample Characteristics (n=134)

Characteristic	**N (%)**
Age	
25 to 55 years old	89 (66)
56 to 65 years old	45 (44)
Mean (SD), years	52.6 (7.5)
Gender	
Women	7 (5)
Men	127 (95)
Partnered versus non-partnered	
Partnered	52 (39)
Non-partnered	82 (61)
Living situation	
Lives alone or homeless	43 (32)
Living with someone	91 (68)
Employment status	
Full-time	17 (13)
Part-time	8 (6)
Unemployed but not because of pain	2 (1)
Unemployed or unable to work due to pain	47 (37)
Retired	10 (7)
On VA Service connection disability	21 (16)
On Non-VA disability	25 (20)
Chronic Pain Diagnosis	
Musculoskeletal	104 (78)
Neuropathic	25 (19)
Complex	5 (3)
Depression HADS > 11 score	53 (39)
Anxiety HADS >11 Score	45 (33)
Follow-up completion	
4^{th}-month	105 (78)
8^{th}-month	84 (62)
12^{th}-month	65 (48)

TABLE 5.2 AVERAGE NUMBER OF HOURS/DAY OF ACTIVITIES FOR VETERANS WITH CHRONIC NON-CANCER PAIN

Hours of activities per day, Mean (SD)										
Variable	Working	P	Walking	P	Exercising	P	Lying	P	Sitting	P
All	2.2 (2.8)	-	1.6 (1.5)	-	0.7 (1.0)	-	4.3 (4.1)	-	5.9 (4.1)	-
Age										
55 ≥ years old	2.2 (2.8)	.56	1.7 (1.5)	.87	0.8 (1.2)	.43	4.2 (4.1)	.55	6.0 (4.2)	.91
56 ≤ years old	2.5 (2.9)		1.7 (1.8)		0.6 (0.8)		4.7 (4.4)		5.9 (3.9)	
Gender										
Women	1.7 (2.4)	.61	2.0 (2.7)	.54	0.9 (2.0)	.55	3.6 (3.4)	.63	8.0 (6.6)	.22
Men	2.3 (2.9)		1.7 (1.5)		0.7 (1.0)		4.4 (4.1)		5.9 (3.5)	
Living situation										
Lives alone or homeless	2.3 (2.9)	.95	1.4 (1.5)	.23	0.5 (1.0)	.07	5.0 (4.7)	.31	5.3 (3.8)	.21
Living with someone	2.3 (2.8)		1.8 (1.6)		0.9 (1.1)		4.1 (3.8)		6.3 (4.2)	
Partner										
Partnered	2.6 (3.0	.31	1.9 (1.7)	.33	0.9 (1.2)	.11	3.7 (4.2)	.61	6.3 (4.2)	.43
Non-partnered	2.1 (2.7)		1.6 (1.5)		0.6 (1.0)		4.7 (4.1)		5.7 (4.1)	
Employment status										
Employed (full-time or part-time)	4.4 (3.5)	**.003**	2.6 (2.5)	**.04**	0.7 (1.2)	.99	2.5 (2.4)	**.001**	5.9 (3.9)	.78
Unemployed, retired, or disabled	1.8 (2.4)		1.5 (1.2)		0.7 (1.1)		4.8 (4.4)		6.1 (4.2)	
Prescription assignment										
Escalating Dose	2.33	0.90	1.64	0.70	0.67	0.58	4.56	0.65	4.67	0.43
Stable Dose	2.26		1.75		0.78		4.22		3.50	

TABLE 5.3 OSWESTRY DISABILITY INDEX (ODI) SCORES OF VETERANS WITH CHRONIC NON-CANCER PAIN

Variable Mean (SD)	Baseline	P	4th month follow-up	P	8th month follow-up	P	12th month follow-up	P
All	48.2 (13.3)	-	45.6 (15.3)	-	45.2 (14.9)	-	45.5 (16.9)	-
Age								
55 ≥ years old	48.0 (13.5)	0.76	45.8 (15.5)	0.76	43.7 (15.8)	0.23	45.3 (16.9)	0.88
56 ≤ years old	49 (13.0)		44.8 (15.1)		47.8 (12.7)		46.0 (17.5)	
Gender								
Women	50.0 (12.4)	0.71	51.8 (15.5)	0.29	52.0 (11.3)	0.21	56.6 (16.6)	0.13
Men	48.1 (13.3)		45.1 (15.3)		44.6 (15.0)		44.6 (16.5)	
Living situation								
Lives alone or homeless	48.3 (14.0)	0.91	43.3 (16.8)	0.28	44.1 (14.6)	0.65	41.3 (20.5)	0.29
Living with someone	48.1 (13.0)		46.8 (14.5)		45.7 (15.0)		47.1 (15.2)	
Partner								
Partnered	47.5 (13.3)	0.66	47.4 (14.2)	0.38	45.8 (15.7)	0.75	46.4 (13.6)	0.70
Non-partnered	48.6 (13.3)		44.6 (16.0)		44.8 (14.4)		44.8 (19.2)	
Employment status								
Employed (full-time/ part-time)	40.0 (11.0)	**0.001**	40.6 (11.6)	0.11	41.2 (13.6)	0.19	42.2 (16.8)	0.41
Unemployed, retired, or disabled	49.8 (13.0)		46.8 (15.8)		46.5 (15.0)		46.9 (16.9)	
Prescription assignment								
Escalating Dose	48.6	0.74	45.8	0.89	43.5	0.28	45.8	0.89
Stable Dose	47.8		45.4		47.2		45.2	

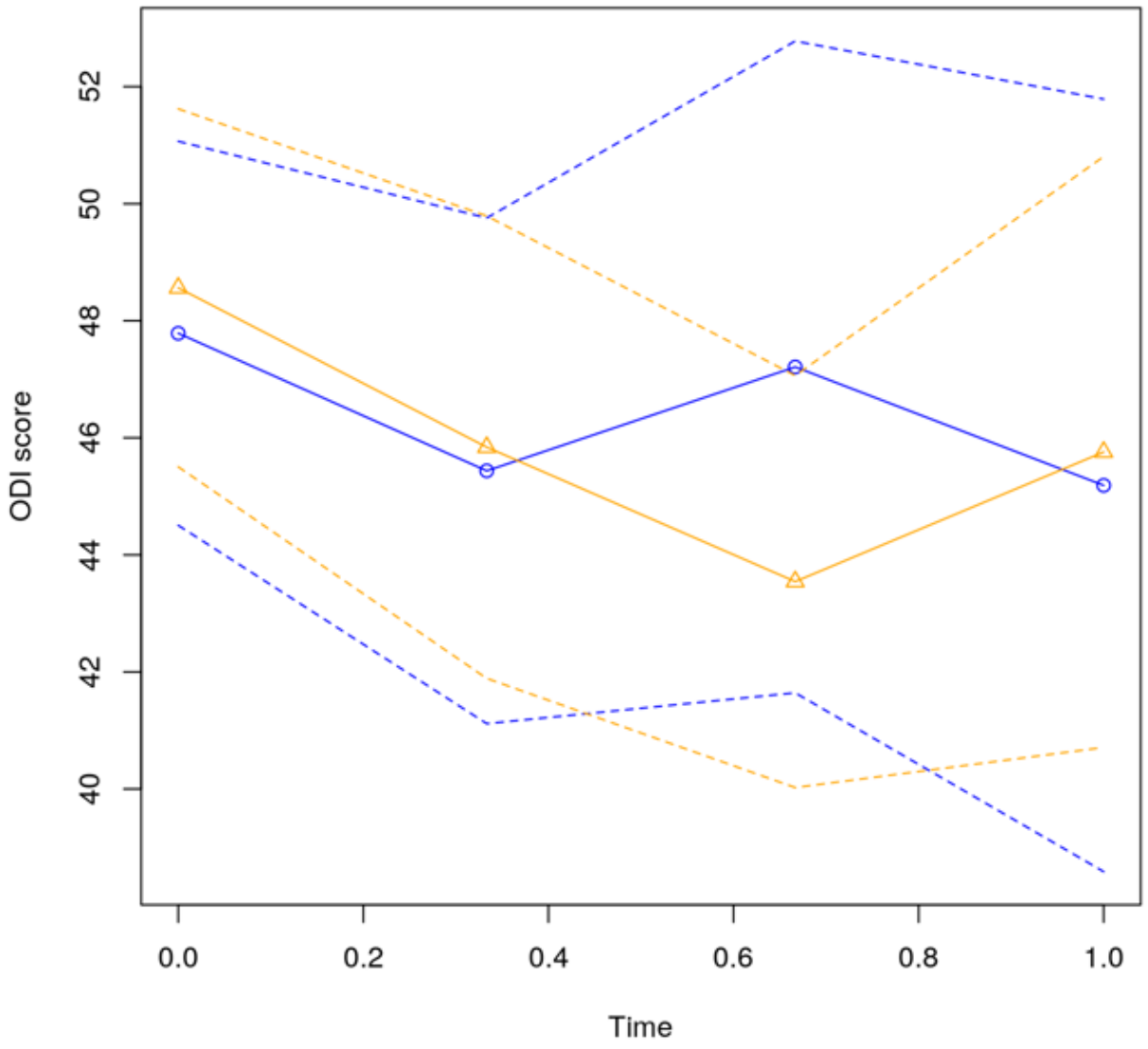

FIGURE 5.2.1 PHYSICAL FUNCTIONING TRAJECTORIES FOR ESCALATING DOSAGE GROUP VERSUS STABLE DOSAGE GROUP

Y-axis = Oswestry Disability Index Score
X-axis = Time in year. The four measurement points are baseline, 4th months, 8th months, & 12th months

= Escalating Dosage Group
= 95% Confidence Interval
= Stable Dosage Group
= 95% Confidence Interval

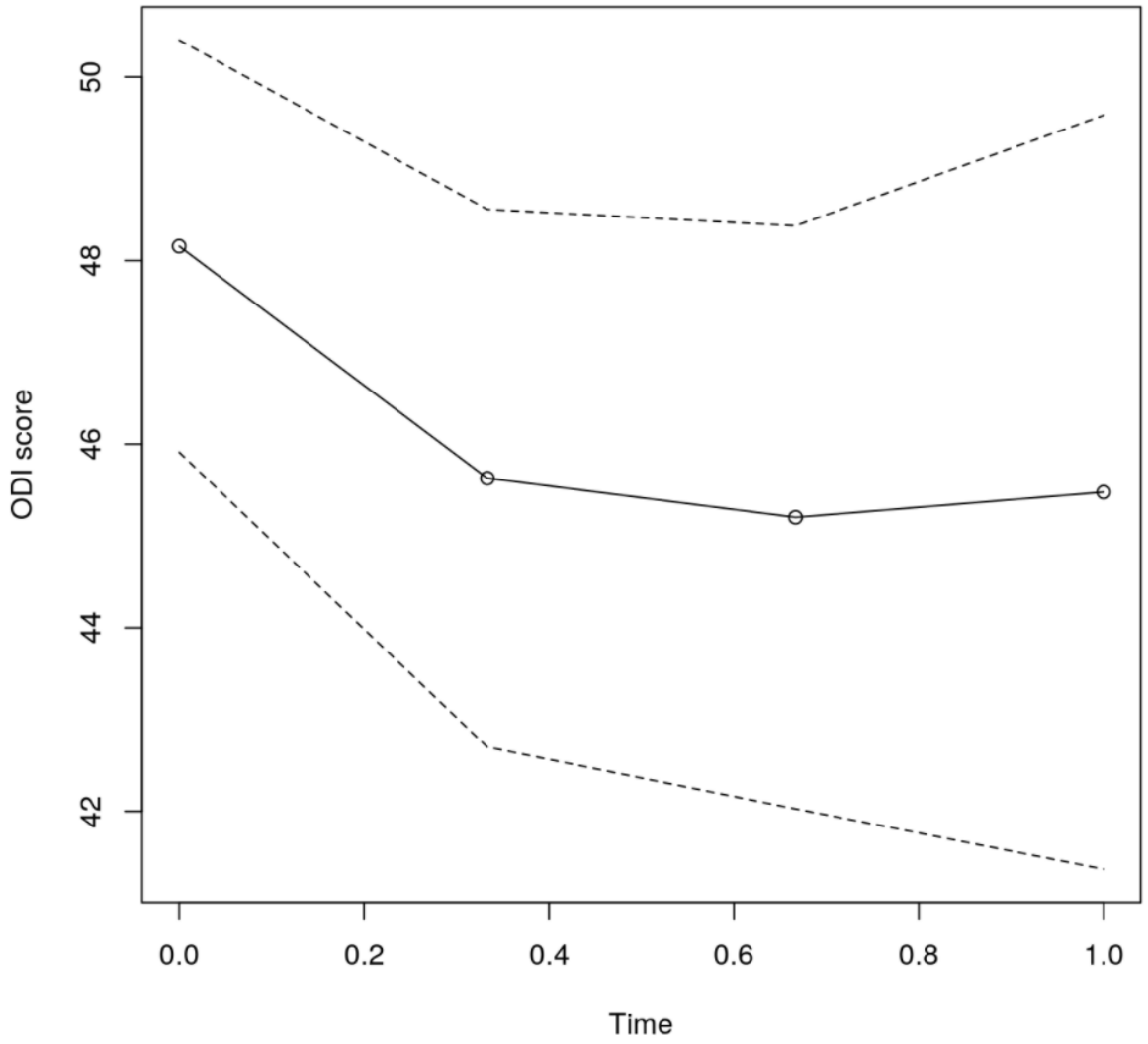

FIGURE 5.2.2 PHYSICAL FUNCTIONING TRAJECTORIES FOR COMBINE GROUPS OF VETERANS PRESCRIBED LONG-TERM OPIOID THERAPY FOR CHRONIC NON-CANCER PAIN

Y-axis = Oswestry Disability Index Score
X-axis = Time 0= baseline, 0.333= 4th months, 0.667= 8th months, 1.000= 12th months
—O— = All participants
-------- = 95% Confidence Interval

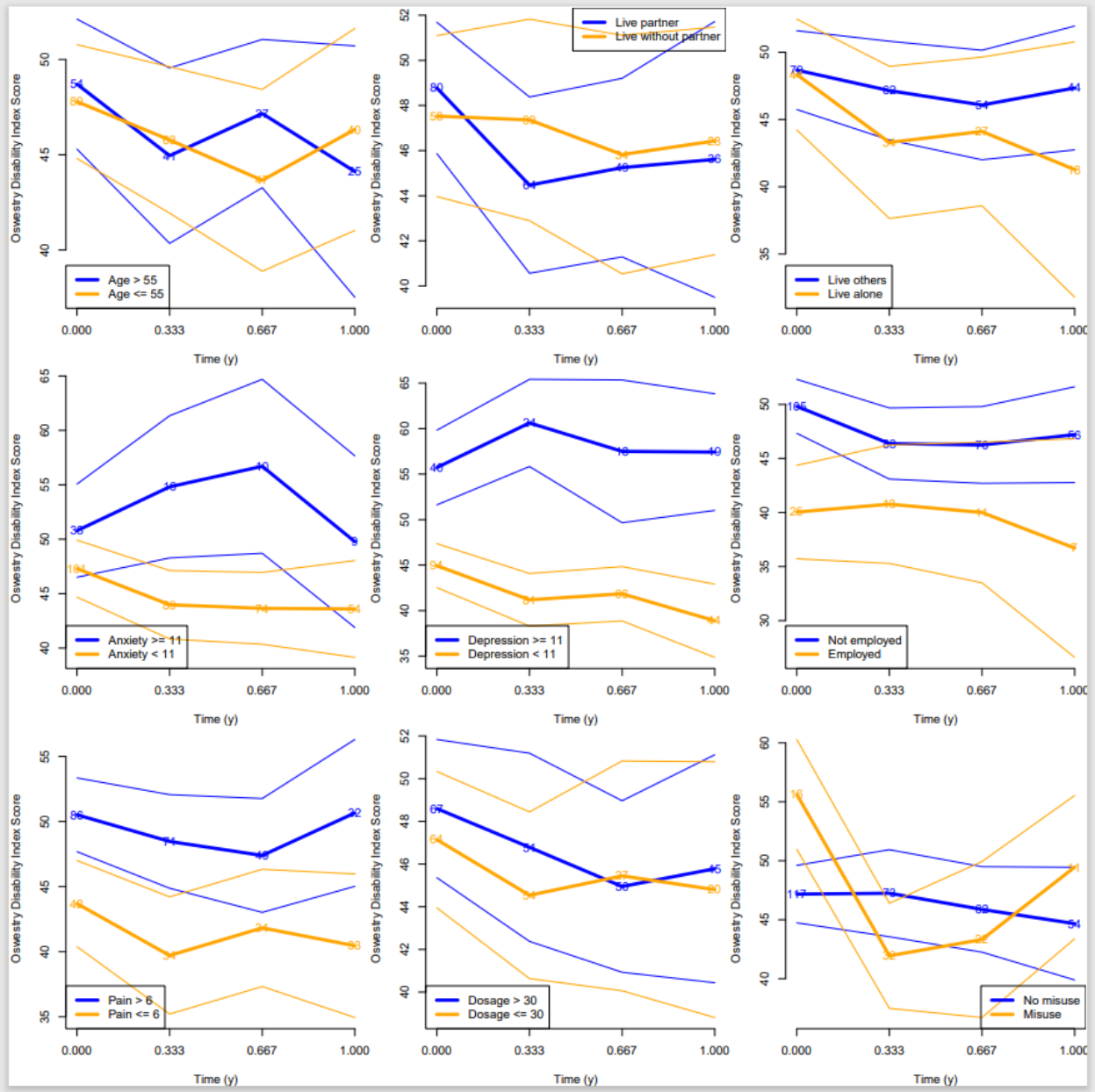

FIGURE 5.3 TRAJECTORIES OF SOCIODEMOGRAPHICS CHARACTERISTICS, DEPRESSION, ANXIETY, PAIN, & DOSAGE WITH PHYSICAL FUNCTIONING (MEAN, 95% CI) IN VETERANS PRESCRIBED LONG-TERM OPIOID THERAPY FOR CHRONIC NON-CANCER PAIN

Y-axis= Oswestry Disability Index Score
X-axis= Time 0= baseline, 0.333= 4th months, 0.667= 8th months, 1.000= 12th months

TABLE 5.4 Associations of **Physical Functioning** Over 12 Months with Pain Intensity, Opioid Dosage (Log), Sociodemographic Characteristics, Anxiety, Depression in Veterans Prescribed Long-term Opioid Therapy for Chronic Non-cancer Pain

Association with physical functioning at baseline

	Estimate	Std..Error	t.value	Pr...t..	n	betaci
escalating	0.7767857	2.3004953	0.3376602	0.7361556	134	0.777 (-3.732, 5.286)
age	0.0844057	0.1539490	0.5482703	0.5844324	134	0.084 (-0.217, 0.386)
livepartner	-1.2466981	2.3499933	-0.5305113	0.5966556	133	-1.247 (-5.853, 3.359)
alone	-0.3299770	2.5431191	-0.1297529	0.8969774	123	-0.330 (-5.314, 4.654)
hadanx1	0.3505424	0.2419269	1.4489597	0.1497203	134	0.351 (-0.124, 0.825)
haddep1	1.3577679	0.2317720	5.8582054	0.0000000	134	1.358 (0.904, 1.812)
tsopa601	6.3330217	1.9484253	3.2503282	0.0014627	134	6.333 (2.514, 10.152)
logmm	1.8768602	1.7822532	1.0530828	0.2942716	131	1.877 (-1.616, 5.370)
pain1	1.7605583	0.5964146	2.9519033	0.0037678	128	1.761 (0.592, 2.930)
employcf_yn	-9.7790476	2.8230597	-3.4639889	0.0007245	130	-9.779 (-15.312, -4.246)
p1misuse_bin	8.4540598	3.4817586	2.4281005	0.0165360	133	8.454 (1.630, 15.278)

Association with physical functioning, adjusting for time, prescription group, and interaction between time and group (MCAR)

	Estimate	Std..Error	df	t.value	Pr...t..	n	betaci
ytime	-2.6156250	1.4862049	62.99940	-1.7599356	0.0832731	64	-2.616 (-5.529, 0.297)
escalating	-0.1658956	3.5879175	62.00046	-0.0462373	0.9632697	64	-0.166 (-7.198, 6.866)
age	-0.0302822	0.2450996	61.00018	-0.1235504	0.9020774	64	-0.030 (-0.511, 0.450)
livepartner	-0.3384323	3.7394157	59.99999	-0.0905041	0.9281881	64	-0.338 (-7.668, 6.991)
alone	-4.2232808	4.0969699	58.00155	-1.0308303	0.3068998	64	-4.223 (-12.253, 3.807)
hadanx1	1.2871380	0.2284182	242.19308	5.6350062	0.0000000	64	1.287 (0.839, 1.735)
haddep1	1.8939531	0.1836407	171.70100	10.3133619	0.0000000	64	1.894 (1.534, 2.254)
tsopa601	3.6288997	1.0312269	202.69845	3.5190118	0.0005347	64	3.629 (1.608, 5.650)
logmm	3.7595527	2.0129864	180.45872	1.8676403	0.0634324	64	3.760 (-0.186, 7.705)
pain1	0.9833381	0.4809135	194.44859	2.0447297	0.0422290	64	0.983 (0.041, 1.926)
employcf_yn	-7.6141938	3.2813775	190.77388	-2.3204260	0.0213753	64	-7.614 (-14.046, -1.183)
p1misuse_bin	1.1931710	1.2657644	178.70570	0.9426485	0.3471333	64	1.193 (-1.288, 3.674)

Association with physical functioning, adjusting for time, prescription group, and interaction between time and group (MAR)

	Estimate	Std..Error	df	t.value	Pr...t..	n	betaci
ytime	-2.2757907	1.3577421	80.35107	-1.6761583	0.0975943	105	-2.276 (-4.937, 0.385)
escalating	-0.2839038	2.5494539	103.41945	-0.1113587	0.9115478	105	-0.284 (-5.281, 4.713)
age	0.0022201	0.1756087	102.34166	0.0126423	0.9899378	105	0.002 (-0.342, 0.346)
livepartner	0.8145575	2.6866536	101.43964	0.3031867	0.7623685	104	0.815 (-4.451, 6.080)
alone	-1.7843648	2.8287783	94.56972	-0.6307899	0.5296994	97	-1.784 (-7.329, 3.760)
hadanx1	0.8084696	0.1835083	341.13498	4.4056305	0.0000141	105	0.808 (0.449, 1.168)
haddep1	1.4883342	0.1668974	295.36292	8.9176575	0.0000000	105	1.488 (1.161, 1.815)
tsopa601	4.1194192	0.8967829	293.26001	4.5935524	0.0000065	105	4.119 (2.362, 5.877)
logmm	2.5259266	1.5270093	257.78540	1.6541659	0.0993109	105	2.526 (-0.467, 5.519)
pain1	1.2715692	0.4144359	276.92594	3.0681929	0.0023670	105	1.272 (0.459, 2.084)
employcf_yn	-5.9310673	2.5361223	264.25360	-2.3367933	0.0201974	102	-5.931 (-10.906, -0.956)
p1misuse_bin	0.7265984	1.1601052	255.49604	0.6263211	0.5316635	105	0.727 (-1.547, 3.000)

Association with physical functioning, adjusting for time, prescription group, and interaction between time and group (MNAR)

	Value	Std.Err	z.value	p.value	n	betaci
ytime	-2.2690072	1.3586303	-1.6700697	0.0949056	105	-2.269 (-4.932, 0.394)
escalating	-0.2864103	2.5327303	-0.1130836	0.9099643	105	-0.286 (-5.250, 4.678)
age	0.0020522	0.1747564	0.0117433	0.9906305	105	0.002 (-0.340, 0.345)
livepartner	0.8129429	2.6614272	0.3054538	0.7600206	104	0.813 (-4.403, 6.029)
alone	-1.7754996	2.8101864	-0.6318085	0.5275120	97	-1.775 (-7.283, 3.732)
hadanx1	0.8063867	0.1917272	4.2059077	0.0000260	105	0.806 (0.431, 1.182)
haddep1	1.4814715	0.1703682	8.6957063	0.0000000	105	1.481 (1.148, 1.815)
tsopa601	4.1226985	0.9217335	4.4727662	0.0000077	105	4.123 (2.316, 5.929)
logmm	2.5312690	1.5259974	1.6587636	0.0971634	105	2.531 (-0.460, 5.522)
pain1	1.3006957	0.4214873	3.0859668	0.0020289	105	1.301 (0.475, 2.127)
employcf_yn	-5.9506767	2.5443710	-2.3387614	0.0193478	102	-5.951 (-10.938, -0.964)
p1misuse_bin	0.7309058	1.1589938	0.6306382	0.5282771	105	0.731 (-1.541, 3.002)

Multivariable Model (Joint Model)

Variable	Value	Standard Error	P-Value
Time	-0.919	1.351	0.496
Escalating	0.553	2.031	0.785
Misuse	0.444	1.101	0.686
Depression	1.483	0.170	<0.0001

*With a Bonferroni correction for the 9 covariates, results with p<0.0056 were stated as significant. Results with p<0.05 were reported as suggestive nominal associations

(MCAR) Missing completely at random, (LMM) Linear Mixed Model, (MAR) Missing at random

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CHAPTER 6

CONCLUSION

CONCLUSION:

The “opioid epidemic” has revealed gaps in our healthcare system and limitations in our national policies that has contributed to the clinical challenges of ensuring appropriate and safe use of LTOT in patients with chronic non-cancer pain (CNCP). In hindsight, these challenges have provided an opportunity to re-examine the utility of LTOT for CNCP and emphasize the importance of evidence-based patient care. Not all veterans will be a candidate for LTOT, however, all patients should receive a thorough evaluation of their pain experience in order to obtain optimal management of their pain symptoms. Veterans with CNCP are a vulnerable population whose pain experience requires and deserves further investigation (1, 2). To fully understand this pain experience, a conceptual framework such as BPS model of CNCP is needed to identify and describe the key components and influencing factors commonly seen in veterans. The BPS model is particularly useful when evaluating the utility and effectiveness of long-term opioid therapy (LTOT) for CNCP among veterans.

The use of LTOT for CNCP has garnered national attention in recent years due to the increasing prevalence of opioid abuse, misuse, overdose, suicide, and death associated with the “opioid epidemic”. In addition, numerous literature reviews have reported on the paucity of evidence for LTOT clinical effectiveness and an abundance of evidence on the risks and adverse side effects for individuals with CNCP. Based on the conclusions and recommendations of these literature reviews, more studies are needed to investigate LTOT effectiveness in order to improve clinical outcomes and predict those individuals who may benefit from treatments from those for whom opioids should be avoided.

The study investigated the trajectories of pain intensity, opioid dosage, and physical functioning in veterans prescribed LTOT for CNCP and examine whether sociodemographic

characteristics and mood (i.e., depression and anxiety) can influence these trajectories. In veterans prescribed LTOT for CNCP, pain intensity and opioid dosage did not change for 36 months while improvements in physical functioning were nominally associated for 12 months. However, a significant association among depression, pain intensity, and physical functioning provided additional evidence on the importance of concurrent pain and psychological evaluation and management of veterans prescribed LTOT for CNCP. A multidisciplinary team composed of clinicians with pain expertise, psychologists, psychiatrists, rehabilitation therapists, nurses, addiction specialists and other ancillary staff is essential to address the psychological and rehabilitation needs of veterans with CNCP. Routine screening of depression and suicidal ideation should be part of the treatment plan especially for veterans prescribed LTOT.

As with many complex medical conditions, more studies are needed to examine LTOT and CNCP in veterans including the assessment, treatments, and the multitude of biological, psychological, social factors associated with their pain experience. These studies should include longitudinal prospective studies greater than 12 months on large diverse population (i.e., female, racially and ethnically diverse participants, and subgroups of veterans (i.e., geriatric, homeless veterans, Operation Enduring Freedom/Operation Iraqi Freedom, polytrauma and traumatic brain injury veterans). Studies that examine LTOT effectiveness as well as adverse side effects, misuse, abuse, and opioid risk mitigation strategies will help promote evidence-base practices and curtail the devastating consequences of the “opioid epidemic”. Furthermore, not only do these treatments (i.e., LTOT, acupuncture, ketamine infusion, interventional pain procedures) need more investigations, the outcome measurements should undergo appropriate scrutiny.

A number of clinical opioid guidelines have been developed to improve the safety of individuals prescribed LTOT, however, more studies are needed to examine the implications of

these guidelines across clinical settings (i.e., inpatient, outpatient, emergency room) and various patient populations including veterans with substance use disorders and addiction. With the national trend to decrease the prescribing of LTOT for CNCP, this study is a reminder that LTOT is an important and potentially effective treatment option for stabilizing pain intensity and improving physical functioning in carefully selected individuals. Veterans with CNCP deserve an unwavering effort to improve their clinical care and treatment outcomes. These efforts require careful investigation of the important factors that contribute to the overall pain experience including the effectiveness of LTOT on pain intensity, physical functioning, and mood.

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