Health-Related Quality of Life among Chronic Opioid Users, Nonchronic Opioid Users, and Nonopioid Users with Chronic Noncancer Pain

Corey J. Hayes , Xiaocong Li, Chenghui Li, Anuj Shah, Niranjan Kathe, Naleen Raj Bhandari, and Nalin Payakachat

Objective. Evaluate the association between opioid therapy and health-related quality of life (HRQoL) in participants with chronic, noncancer pain (CNCP).

Data Sources. Medical Expenditure Panel Survey Longitudinal, Medical Conditions, and Prescription Files.

Study Design. Using a retrospective cohort study design, the Mental Health Component (MCS12) and Physical Health Component (PCS12) scores of the Short Form-12 Version 2 were assessed to measure mental and physical HRQoL.

Data Collection. Chronic, noncancer pain participants were classified as chronic, nonchronic, and nonopioid users. One-to-one propensity score matching was employed to match chronic opioid users to nonchronic opioid users plus nonchronic opioid users and chronic opioid users to nonopioid users.

Principal Findings. A total of 5,876 participants were identified. After matching, PCS12 was not significantly different between nonchronic versus nonopioid users (LSM Diff = -0.98 , 95% CI: $-2.07, 0.10$), chronic versus nonopioid users (LSM Diff = -2.24 , 95% CI: $-4.58, 0.10$), or chronic versus nonchronic opioid users (LSM Diff = -2.23 , 95% CI: $-4.53, 0.05$). Similarly, MCS12 was not significantly different between nonchronic versus nonopioid users (LSM Diff = 0.76 , 95% CI: $-0.46, 1.98$), chronic versus nonopioid users (LSM Diff = 1.08 , 95% CI: $-1.26, 3.42$), or chronic versus nonchronic opioid users (LSM Diff = -0.57 , 95% CI: $-2.90, 1.77$).

Conclusions. Clinicians should evaluate opioid use in participants with CNCP as opioid use is not correlated with better HRQoL.

Key Words. Health-related quality of life, opioids, pain

Chronic noncancer pain (CNCP) is a prevalent condition with around 20 percent of the U.S. population experiencing pain for a minimum of 6 months (Verhaak et al. 1998; Edlund et al. 2010a). Unfortunately, it is also a condition

with a growing incidence rate (Zondervan et al. 1999; Gran 2003; Freburger et al. 2009) and a costly burden to society. The cost of treating chronic back pain, one of the most common CNCP conditions, has risen by almost 130 percent from 2000 to 2007 with the cost being \$35.7 billion in 2007 (Smith et al. 2013). Most patients with CNCP report self-perceived burden to be clinically elevated (Kowal et al. 2012), and approximately 30 percent of patients with chronic pain have moderate-to-severe work role disability (Gureje et al. 1998).

For decades, clinicians have struggled with the balance of treating pain without incurring addiction (Meldrum 2003). During the 1980s, opioid use became prominent in treating pain associated with cancer, which led some to later conclude that opioids should also be used in CNCP (Portenoy and Foley 1986). Opioid use for CNCP rose drastically from the 1980s until around 2012 (Guy et al. 2017). A study looking at data from the Medical Expenditure Panel Survey (MEPS) from 2000 to 2010 found that prescriptions for opioid analgesics increased from 43.8 to 89.2 million (Sites, Beach, and Davis 2014). Currently, opioid analgesics are among the top commonly prescribed medications in the United States.

This rise in opioid use has been paralleled by rising opioid dependence and addiction (Edlund et al. 2010b; Sullivan et al. 2010; Ronan and Herzig 2016). It is essential to determine whether the benefits of opioid use outweigh the risks. Due to the lack of objective clinical markers of pain, pain intensity scores and health-related quality of life (HRQoL) are two of the best indicators for evaluating the benefits of opioids. HRQoL will not only measure improvements due to decreased pain interference but will also incorporate the impact of opioid side effects such as constipation, drowsiness, itching, and hyperalgesia.

Address correspondence to Nalin Payakachat, B.Pharm., M.Sc., Ph.D., Division of Pharmaceutical Evaluation and Policy, Department of Pharmacy Practice, University of Arkansas for Medical Sciences College of Pharmacy, 4301 W. Markham St., # 522, Little Rock, AR 72205; e-mail: npayakachat@uams.edu. Corey J. Hayes, Pharm.D., M.P.H., is with the Division of Pharmaceutical Evaluation and Policy, Department of Pharmacy Practice, University of Arkansas for Medical Sciences College of Pharmacy, Little Rock, AR, and NIDA T32 Addiction Research Training Program, Psychiatric Research Institute, University of Arkansas for Medical Sciences College of Medicine, Little Rock, AR. Xiacong Li, M.H.A., is with the Department of Health Policy and Management, University of Arkansas for Medical Sciences College of Public Health, Little Rock, AR. Chenghui Li, Ph.D., Anuj Shah, B.Pharm., Niranjana Kathe, M.S., and Naleen Raj Bhandari, M.S., are with the Division of Pharmaceutical Evaluation and Policy, Department of Pharmacy Practice, University of Arkansas for Medical Sciences College of Pharmacy, Little Rock, AR.

Currently, limited evidence exists on the efficacy of long-term opioid use for CNCP (Abdel Shaheed et al. 2016). One systematic review and meta-analysis found that patients who stayed on oral opioids for at least 6 months had statistically significant reductions in long-term pain scores, but this conclusion is based on weak evidence with a standard mean difference just under 2 on the pain intensity scale (Noble et al. 2008). Another systematic review evaluated the effect of long-term opioid use on HRQoL, which found long-term HRQoL was improved by long-term opioid use (Devulder, Richarz, and Nataraja 2005), but this conclusion was based mostly on pre- and postassessment without comparison to other treatment options (Chou et al. 2009). Head-to-head, multicenter, trials of opioid use in chronic back pain and pancreatitis have found no differences in HRQoL between the two groups (Niemann et al. 2000; Allan et al. 2005). This study adds to the literature by comparing long-term HRQoL among chronic opioid users, nonchronic opioid users, and nonopioid users with CNCP using MEPS, one of the rare sources of nationally representative data on HRQoL in the United States.

METHODS

Data Sources

This study used a retrospective cohort study design employing data obtained from MEPS. MEPS collects information on the health of the noninstitutionalized, civilian population of the United States. Data in MEPS are obtained through five rounds of self-administered questionnaires (SAQs) and/or interviews over a two-year period with each two-year period being considered a panel (Agency for Healthcare Research and Quality n.d.b.). MEPS obtains health-related data from families and individuals from around 15,000 households in each panel. In order to create national estimates, these health-related data obtained by MEPS are weighted.

The Longitudinal, Medical Conditions, and Prescribed Medicines (PM) Files within MEPS were used for this analysis. The Longitudinal Files contain information collected for households of each panel, including demographics, self-reported disease states, measures of mental and physical health, medical and prescription insurance coverage, employment status, level of income, and other information related to health care (Agency for Healthcare Research and Quality n.d.b.) The Longitudinal Files have two years' worth of data for each participant in the panel. The PM Files contain over 300,000 observations with each observation being one prescription for a person in the household during

a certain calendar year. Data within the PM files are gathered initially from participant interviews. For verification of medication exposure, the participants' pharmacy or pharmacies are contacted to obtain printouts of all prescriptions filled by the participants (Agency for Healthcare Research and Quality n.d.b.). For this study, files were obtained spanning from 2010 to 2013 as it was not until 2010 that MEPS began to obtain information on days' supply which was essential to this study. This study was reviewed and approved by the University of Arkansas for Medical Sciences Institutional Review Board.

Study Sample

A cohort of participants with CNCP derived from MEPS was based on the following question, asked in both rounds 2 and 4, within the Medical Outcomes Study Short Form-12 Version 2 (SF-12v2) instrument: "*During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?*" (Stockbridge, Suzuki, and Pagán 2015) The response options for this item include the following: "not at all," "a little bit," "moderately," "quite a bit," and "extremely." Participants who report "a little bit" of pain in the first year of the panel and at least "a little bit" of pain in the second year of the panel were classified as having "a little bit" of chronic pain. Participants who mark "moderately" or at least "quite a bit" of pain to this item in the first year of the panel and at least "a little bit" of pain in the second year of the panel were classified as having either moderate or severe chronic pain, respectively. This approach of collapsing the final two pain response options in coming up with severe chronic pain has previously been done (Institute of Medicine [US] Committee on Advancing Pain Research, Care, and Education 2011). Participants who were categorized as having either "a little bit," moderate, or severe pain based on the above definition were included in the analysis. Further inclusion criteria were (1) in-scope and information obtained from all five rounds of interviews, and (2) eligible for the self-administered questionnaire from both rounds 2 and 4. Exclusion criteria included (1) self-reported diagnosis of cancer within either year of the panel, (2) missing responses in regard to Mental Component Summary (MCS12) or Physical Component Summary (PCS12) from the SF-12v2 in either round 2 or 4, (3) missing National Drug Codes (NDC) for any prescription medication, and (4) opioid use in round 1, which provides a new user approach as a round is approximately 8 weeks long.

Opioid Exposure

Using the PM files, Multum Lexicon Drug Classes and NDC were used to identify opioid exposure within MEPS. Multum Lexicon Drug Classes provide a means for classifying medications based on therapeutic drug classes. NDCs are specific, universal identifiers of medications that characterize the drug, strength, and formulation and are required for each medication per Food and Drug Administration guidelines. As with the Lemke study, Multum classes 60 (“Narcotic Analgesics”) and 191 (“Narcotic Analgesic Combinations”) were used for this study (Lemke 2015). Multum classes 59 (“Miscellaneous Analgesics”) and 63 (“Analgesic Combinations”) were also evaluated for opioid exposure; however, these categories are not specific to opioids. Hence, NDCs were used to cross-reference with these categories for validation of opioid exposure.

Chronic versus Nonchronic Opioid Use versus No Opioid Use

Opioid days’ supply and average daily dose were determined for each participant from rounds 2 through 4, which represents a 12-month period. No opioid use was defined as having received no opioid prescription over rounds 2 through 4. Nonchronic opioid use was defined as having received at least one prescription for an opioid but less than 90 days’ supply over rounds 2 through 4. Similar to Lemke’s definition of an intensive user, a chronic opioid user, therefore, was defined as one who received at least 90 days’ supply of opioids over this time frame (Lemke 2015). For intensive users, Lemke restricted the sample to those with 90 days’ supply of Schedule II opioids; however, for this analysis, the focus was on chronicity of opioid use, and therefore, the definition was relaxed to include all opioids. The dates of prescription fills are not captured within MEPS. Therefore, average daily dose was calculated by converting all opioids to morphine equivalents, summing morphine equivalents for all opioid fills per participant, and then dividing by the participant’s total opioid days’ supply (Hayes et al. 2015).

Imputation of Missing Days’ Supply

Around 30 percent of opioid prescriptions had a missing value for days’ supply. To overcome missing days’ supply, average quantity per day was calculated for each type of opioid and each dosage form by pain severity among those prescriptions that had days’ supply recorded. If a certain opioid type

and dosage form did not have greater than 10 prescriptions within those in a certain pain severity category, the average quantity per day was calculated for that specific opioid and dosage form from the Pharmetrics LifeLink Plus database (IMS Health 2012). With the newly imputed quantity per day for those opioid prescriptions with a missing days' supply, the total quantity of the prescription was divided by the imputed quantity per day to obtain an imputed days' supply for a particular opioid prescription. If the days' supply was greater than 30 for a Schedule II opioid, then the days' supply was capped at 30 days. Similarly, if days' supply for a non-Schedule II opioid was greater than 90 days, then the days' supply was capped at 90 days. These rules were put in place to mimic federal laws regulating the days' supply of controlled prescriptions (Aetna 2014; U.S. Department of Justice Drug Enforcement Administration Office of Diversion Control 2014).

Primary Outcome Measure

The SF-12v2 contains the MCS12 and the PCS12, which, respectively, measure the latent concepts of mental and physical health (Ware 2005). For each component, the score ranges between 0 and 100, where better mental and physical health is demonstrated by higher scores. The PCS12 is composed of four domains, which include physical pain and functioning, role restrictions, and general overall health (Cheak-Zamora, Wyrwich, and McBride 2009). The MCS12 also is composed of four domains, which include social and vitality functioning, role emotional, and overall mental health (Cheak-Zamora, Wyrwich, and McBride 2009). The SF-12v2 has recently been validated in a noncancer pain cohort in MEPS (Hayes et al. 2017). PCS12 and MCS12 are collected in round 2 and round 4. PCS12 and MCS12 scores from round 4 were used as the primary outcome measures, while PCS12 and MCS12 scores from round 2 were used as baseline covariate measures.

Covariates

General demographics (age, gender, race, marital status, and education level), income level, insurance status (health and prescription), and geographic location (South, West, Midwest, Northeast) were obtained. The Charlson comorbidity index was also calculated, and participants were grouped into three categories of the comorbidity score (0, 1, ≥ 2 ; Deyo, Cherkin, and Ciol 1992). Diagnoses for rheumatoid arthritis and osteoarthritis/other joint disorders were obtained from the medical conditions files. Using the PM files, exposure

to other pain-related medications were obtained from rounds 2 through 4 (Antidepressants [Multum Therapeutic Subclasses: 76, 208, 209, 250, 306, 307, 308], COX-2 Inhibitors [278], Nonsteroidal Anti-inflammatory Drugs (NSAIDs) [61], Skeletal Muscle Relaxants [178, 179], and Anti-Anxiety Medications [68, 69, 70]).

Propensity Score Matching and Statistical Analysis

For the analysis of differences in MCS12 and PCS12 by opioid use among participants with CNCP, a 1:1 greedy match without replacement was employed to match participants on propensity scores (Austin 2008; Garrido et al. 2014). Separate logistic regression models were used to obtain the propensity scores for nonchronic opioid use and chronic opioid use as compared to nonopioid use, derived from age categories, gender, race, marital status, education level, Charlson comorbidity index categories, medical and prescription insurance status, region of the country, income level, MCS12 and PCS12 in round 2, whether or not rheumatoid arthritis or osteoarthritis/ other joint disorders, and exposure to other pain-related medications. C statistics ≥ 0.7 for the logistic regressions will be considered acceptable (LaValley 2008). Next, three sets of greedy matches were performed as follows: (1) nonchronic opioid users matched to nonopioid users, (2) chronic opioid users matched to nonopioid users, and (3) chronic opioid users matched to nonchronic opioid users. To verify that propensity score matching alleviated observed biases, the pre- and postmatch p values were obtained. Additionally, differences between covariates can be nonsignificant between matches due to the decreased sample size. This potential imbalance was evaluated by assessing the standardized differences of greater than 10 percent between matched groups (Austin 2011) and by graphing the distribution of the propensity scores between the two groups before and after matching (Garrido et al. 2014). If standardized differences remained greater than 10 percent for some variables even after matching, these variables were controlled for in the final regression models. Among participants that matched, PROC SURVEYREG was used to model PCS12 and MCS12 in round 4 as the dependent variables with opioid use as the primary independent variable; average daily dose in morphine equivalents was also incorporated. In order to incorporate sampling stratum for the matched pairs, adjusted least square means (LSM) and least square mean differences (LSM Diff) were reported. All the analyses were conducted using SAS v9.3 (SAS Institute Inc., Cary, NC) with a significance level of .05.

Sensitivity Analysis

To test whether imputed days' supply created misclassification for the level of opioid use (chronic vs. nonchronic), only participants who had days' supply documented for all of their opioid prescriptions were analyzed. As with the primary analyses, participants were again classified into nonopioid users, nonchronic, and chronic opioid users and matched based on propensity score (nonchronic opioid users to nonopioid users, chronic opioid users to nonchronic opioid users, and chronic opioid users to nonopioid users). PCS12 and MCS12 were evaluated in Round 4 among these matched pairs similarly to the primary analysis.

RESULTS

Participant Characteristics

A total of 5,876 participants were identified who had CNCP, no opioid use in round 1, and no missing NDC values for their reported prescription medications (Figure 1). Of these, 4,200 had no opioid use in rounds 2 through 4, 1,359 used opioids nonchronically, and 317 used opioids chronically. Table 1 shows the characteristics of each of these participants categorized by their opioid use. Across all categories of opioid users, most are Caucasian, female and have high school or less education. The most prevalent age range and region are 50–65 years and the South, respectively. Most participants do not have prescription medication insurance by all categories of opioid use. As opioid use increases, a higher percentage of those participants are poor or near poor, have rheumatoid arthritis or osteoarthritis/other joint disorders, are not married, have public insurance, have no prescription insurance, have high school or less education, and have severe pain.

Propensity Score Matching

Measures of validation for the propensity score matching and the distribution of the propensity scores before and after matching for the three sets of matches can be found in Tables S1–S3 and Figures S1–S3.

Nonchronic Opioid Use versus No Opioid Use

Of the 1,359 nonchronic opioid users with CNCP, 1,147 matched in a 1:1 greedy match propensity score analysis (84.4 percent). Logistic regression

Figure 1: Derivation of Study Sample

Note. CNCP, chronic, non-cancer pain; MCS, mental component score; PCS, physical component score; SAQ, self-administered questionnaire.

modeling was used to model nonchronic opioid use versus nonopioid use with the characteristics defined in Table 1 as the independent variables. The c statistic from the logistic regression was at the prespecified threshold of 0.7 (0.702). PCS12 in round 4 was found to not significantly differ between those that use opioids nonchronically as compared to those that do not use opioids as shown in Table 2 (PCS 12: LSM Diff = -0.98 , 95% CI: -2.07 to 0.10 , $p = .075$).

Table 1: Demographic Characteristics of Participants with Chronic, Noncancer Pain

	Unweighted Number of Participants (%)			Weighted Row % (Standard Error)		
	No Opioid Use (N = 4,200)	Nonchronic Opioid Use (N = 1,359)	Chronic Opioid Use (N = 317)	No Opioid Use	Nonchronic Opioid Use	Chronic Opioid Use
N = 5,876						
Race						
White	2,902 (69.1)	925 (68.1)	204 (64.4)	71.8 (0.96)	22.9 (0.88)	5.3 (0.46)
Black	853 (20.3)	324 (23.8)	94 (29.7)	68.0 (1.54)	25.2 (1.44)	6.8 (0.78)
Other	445 (10.6)	110 (8.1)	19 (6.0)	73.4 (2.61)	22.0 (2.44)	4.7 (1.17)
Age						
18–34	722 (17.2)	290 (21.3)	27 (8.5)	70.9 (1.95)	25.8 (1.74)	3.3 (0.77)
35–49	1,017 (24.2)	408 (30.0)	80 (25.2)	66.5 (1.58)	27.9 (1.35)	5.6 (0.80)
50–65	1,488 (35.4)	484 (35.6)	146 (46.1)	69.9 (1.33)	23.8 (1.22)	6.3 (0.71)
66–85	973 (23.2)	177 (13.0)	64 (20.2)	80.0 (1.63)	14.5 (1.35)	5.5 (0.90)
Gender						
Male	1,661 (39.6)	475 (35.0)	119 (37.5)	72.6 (1.26)	21.9 (1.16)	5.5 (0.62)
Female	2,539 (60.5)	884 (65.1)	198 (62.5)	70.7 (1.05)	24.0 (1.00)	5.4 (0.51)
Marital status						
Married	2,179 (51.9)	632 (46.5)	132 (41.6)	73.0 (1.15)	22.1 (1.00)	4.9 (0.56)
Not married	1,156 (27.5)	422 (31.1)	124 (39.1)	69.6 (1.42)	23.5 (1.33)	6.9 (0.73)
Never married	865 (20.6)	305 (22.4)	61 (19.2)	69.6 (1.84)	25.4 (1.71)	5.0 (0.88)
Education level						
High school or less	2,304 (54.9)	728 (53.6)	205 (64.7)	71.5 (1.02)	21.7 (0.88)	6.8 (0.61)
More than high school	1,848 (44.0)	624 (45.9)	109 (34.4)	71.3 (1.19)	24.5 (1.10)	4.2 (0.46)
Missing	48 (1.1)	7 (0.5)	3 (1.0)	79.3 (7.88)	12.6 (5.24)	8.2 (5.10)
Health insurance						
Public	1,310 (31.2)	412 (30.3)	147 (46.4)	70.8 (1.34)	20.5 (1.18)	8.8 (0.82)
Private	2,178 (51.9)	749 (55.1)	133 (42.0)	71.6 (1.09)	24.1 (1.00)	4.4 (0.49)
Uninsured	712 (17.0)	198 (14.6)	37 (11.7)	72.2 (1.87)	23.5 (1.77)	4.2 (0.77)

continued

Table 1: Continued

	Unweighted Number of Participants (%)			Weighted Row % (Standard Error)		
	No Opioid Use (N = 4,200)	Nonchronic Opioid Use (N = 1,359)	Chronic Opioid Use (N = 317)	No Opioid Use	Nonchronic Opioid Use	Chronic Opioid Use
N = 5,876						
Prescription insurance						
Insured	1,702 (40.5)	605 (44.5)	96 (30.3)	71.4 (1.13)	24.6 (1.08)	4.0 (0.52)
Uninsured	2,498 (59.5)	754 (55.5)	221 (69.7)	71.5 (1.17)	21.6 (1.00)	6.8 (0.60)
Region						
Northeast	694 (16.5)	206 (15.2)	36 (11.4)	74.7 (2.12)	22.1 (2.13)	3.2 (0.59)
Midwest	842 (20.1)	299 (22.0)	72 (22.7)	70.0 (1.55)	23.6 (1.59)	6.4 (0.99)
South	1,596 (38.0)	526 (38.7)	147 (46.4)	71.0 (1.52)	22.5 (1.22)	6.5 (0.68)
West	1,068 (25.4)	328 (24.1)	62 (19.6)	71.1 (1.48)	24.3 (1.33)	4.6 (0.77)
Income level						
Poor/near poor	1,238 (29.5)	432 (31.8)	126 (39.8)	68.2 (1.42)	24.1 (1.28)	7.7 (0.90)
Low income	745 (17.7)	234 (17.2)	62 (19.6)	70.8 (1.87)	22.6 (1.74)	6.5 (1.25)
Middle income	1,200 (28.6)	372 (27.4)	86 (27.1)	73.0 (1.38)	21.8 (1.28)	5.2 (0.54)
High income	1,017 (24.2)	321 (23.6)	43 (13.6)	72.6 (1.48)	23.9 (1.42)	3.5 (0.55)
Osteoarthritis/joint disorders	2,009 (47.8)	767 (56.4)	249 (78.6)	66.9 (1.15)	25.0 (1.05)	8.1 (0.65)
Rheumatoid arthritis	236 (5.6)	93 (6.8)	55 (17.4)	64.3 (2.77)	22.8 (2.45)	12.9 (2.07)
Charlson comorbidity index						
0	2,448 (58.3)	837 (61.6)	124 (39.1)	71.2 (1.00)	25.1 (0.97)	3.8 (0.40)
1	627 (14.9)	211 (15.5)	65 (20.5)	71.4 (1.90)	20.7 (1.63)	7.9 (1.09)
≥2	1,125 (26.8)	311 (22.9)	128 (40.4)	72.2 (1.66)	19.8 (1.37)	8.0 (0.93)
Antidepressant medication use	715 (17.0)	317 (23.3)	113 (35.7)	65.6 (1.71)	25.0 (1.64)	9.4 (0.97)
Anti-anxiety medication use	320 (7.6)	160 (11.8)	75 (23.7)	57.1 (2.85)	30.0 (2.52)	12.9 (1.82)
COX-2 inhibitor medication use	74 (1.8)	29 (2.1)	20 (6.3)	58.3 (5.44)	24.1 (5.10)	17.6 (4.20)
Skeletal muscle relaxant medication use	240 (5.7)	247 (18.2)	88 (27.8)	39.6 (2.57)	44.2 (2.52)	16.2 (1.96)
NSAID medication use	760 (18.1)	443 (32.6)	113 (35.7)	56.8 (1.86)	34.1 (1.74)	9.1 (1.02)

continued

Table 1: Continued

	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SEM)	Mean (SEM)	Mean (SEM)
MCS12 in round 2	46.98 (11.12)	45.98 (11.78)	42.59 (11.99)	48.06 (0.26)	46.89 (0.41)	43.24 (0.60)	
PCS12 in round 2	41.68 (10.33)	39.99 (10.97)	31.45 (9.72)	42.35 (0.21)	40.93 (0.38)	31.77 (0.62)	
Average daily dose (MME/day)		36.89 (34.68)	40.25 (52.92)		38.03 (1.21)	39.64 (2.08)	

Note. In the final regression models, only adjustment for strata among matched pairs was used. LONGWT, the longitudinal weight variable; MME, morphine milligram equivalent; SD, standard deviation; VARPSU, variance estimation PSU variable; VARSTR, variance stratum variable. Variables were used for strata, cluster, and weight to provide weighted national estimates.

Similarly, MCS12 was not significantly different between the two groups (MCS12: LSM Diff = 0.76, 95% CI: -0.46 to 1.98, $p = .223$; Table 3).

Chronic Opioid Use versus Nonchronic Opioid Use

Of the 317 chronic opioid users with CNCP, 178 matched in a 1:1 greedy match propensity score analysis (56.2 percent). Logistic regression modeling was used to model chronic opioid use versus nonchronic opioid use with the covariates defined in Table 1 as the independent variables. The c statistic from the logistic regression was adequate (0.814). PCS12 was not found to be significantly different between the two groups as shown in Table 2 (PCS 12: LSM Diff = -2.24, 95% CI: -4.52 to 0.05, $p = .055$). MCS12 was also not found to be significantly different between chronic opioid users as compared to non-chronic opioid users (MCS12: LSM Diff = -0.57, 95% CI: -2.90 to 1.77, $p = .634$; Table 3).

Chronic Opioid Use versus No Opioid Use

Of the 317 chronic opioid users with CNCP, 213 matched in a 1:1 greedy match propensity score analysis (67.2 percent). Logistic regression modeling was used to model chronic opioid use versus no opioid use with the covariates defined in Table 1 as the independent variables. The c statistic from the

Table 2: PCS12 Values for Each Propensity Score Matching

PCS12					
Propensity Score Match	LS Means (SE)	95% Confidence Interval		LSM Difference	
				Estimate, (CI)	SE, p-Value
Match #1					
Nonchronic opioid use*	39.89 (0.36)	39.19	40.58	−0.98, (−2.07, 0.10)	0.55, .0747
No opioid use	40.87 (0.36)	40.16	41.58		
Match #2					
Chronic opioid use†	32.79 (0.81)	31.19	34.38	−2.24, (−4.53, 0.05)	1.16, .0554
Nonchronic opioid use	35.02 (0.80)	33.44	36.61		
Match #3					
Chronic opioid use*	32.71 (0.79)	31.16	34.26	−2.25, (−4.58, 0.10)	1.19, .0603
No opioid use	34.95 (0.78)	33.43	36.48		

*Matched to no opioid use.

[†]Matched to nonchronic opioid use.

SE, standard error.

Table 3: MCS12 Values for Each Propensity Score Matching

MCS12					
Propensity Score Match	LS Means (SE)	95% Confidence Interval		LSM Difference	
				Estimate, (CI)	SE, p-Value
Match #1					
Nonchronic opioid use*	47.26 (0.39)	46.48	48.03	0.76, (−0.46, 1.98)	0.62, .2232
No opioid use	46.50 (0.39)	45.73	47.26		
Match #2					
Chronic opioid use†	44.69 (0.86)	42.99	46.38	−0.57, (−2.90, 1.77)	1.18, .6335
Nonchronic opioid use	45.25 (0.81)	43.66	46.85		
Match #3					
Chronic opioid use*	45.46 (0.76)	43.97	46.95	1.08, (−1.26, 3.42)	1.19, .3663
No opioid use	44.38 (0.85)	42.71	46.06		

*Matched to no opioid use.
†Matched to nonchronic opioid use.
SE, standard error.

logistic regression was adequate (0.888). PCS12 was not found to be significantly different between those that use opioids chronically as compared to those that do not use opioids as shown in Table 3 (PCS 12: LSM Diff = −2.25, 95% CI: −4.58 to 0.10, $p = .0603$). MCS12 was also not significantly different between the two groups (MCS12: LSM Diff = 1.08, 95% CI: −1.26, 3.42, $p = .3663$; Table 3).

Sensitivity Analyses

Among matches without an imputed days’ supply for one of their opioid prescriptions, the results were similar as to the main analysis. Both MCS12 and PCS12 in Round 4 were not significantly different between matched pairs of nonchronic opioid users to nonopioid users, chronic opioid users to nonopioid users, or chronic opioid users to nonopioid users.

DISCUSSION

Chronic, noncancer pain and opioid use for CNCP (Guy et al. 2017) have been on the rise since the 1980s with the liberalization of opioid use outside of cancer pain until it reached a plateau and started to decline in the past 5 years (Nelson and Perrone 2012). The ultimate goal of using opioids for the

treatment of CNCP is to ease the burden of pain and hopefully improve HRQoL. With opioid overdoses now reaching epidemic proportions and prescription drug addiction rising exponentially, it is important that clinicians and researchers evaluate the benefit of opioid use on HRQoL among individuals with CNCP. However, studies are limited on whether or not chronic opioid use for CNCP is associated with significantly better HRQoL.

This study showed that PCS12 was not significantly different among those with CNCP who use opioids chronically or nonchronically as compared to those with CNCP that did not use opioids at all. This relationship was demonstrated after matching on many covariates that would be associated with lower PCS12 scores, including joint pain, arthritis, and pain severity level. Many of these covariates have previously been shown to be associated with opioid use (Bartoli et al. 2015; Lemke 2015; Teunis et al. 2015; Kea et al. 2016).

Several previous studies have reported similar findings. Also using MEPS data, one study found that despite the rise in opioid use, disability and health status metrics have not improved among opioid users (Sites, Beach, and Davis 2014). A cross-sectional study in a nationally representative Danish population found opioid use to be associated with higher pain severity and lower HRQoL; however, causation is difficult to ascertain (Eriksen et al. 2006). In a 3-year cohort study of postmenopausal women with chronic pain, baseline prescription opioid use was associated with worse physical functioning and a lack of improvement in pain (Braden et al. 2012). Another cohort study of back pain patients found baseline opioid use to be associated with higher disability 6 months after baseline, even after substantial covariate adjustment (Ashworth et al. 2013). Another cohort study of veterans found that opioid use was associated with a lower likelihood of improvements in pain intensity scores over a year timespan (Dobscha et al. 2016). In those with neuropathic pain, PCS12 was found to be higher among those who used opioids; however, it was deemed to not likely be a clinically significant improvement (Bostick et al. 2015). Our study found that PCS12 trended lower with opioid use among those who used opioids chronically, although the difference did not reach statistical or minimal clinically important difference (MCID) for general populations (Warkentin et al. 2014) or for two specific pain conditions (Parker et al. 2012a, b; MCID range of 4–8).

MCS12 was also not significantly different between chronic, nonchronic, and nonopioid users. Differences in MCS12 among opioid users have not been extensively evaluated in the literature. One study found that MCS12 was significantly higher among those who experienced 50 percent or more pain relief as compared to those who experienced less than 50 percent pain relief

when oxycodone was given for nonmalignant pain (Anastassopoulos et al. 2011). Another study found that use of opioids was associated with poorer pain-related mental health even after controlling for duration of pain and physical functioning related to pain (Skinner, Lewis, and Trafton 2012). Validation of the MCS12 in participants with noncancer pain showed a “dose related” decrease with increasing number of chronic conditions, which signifies increasing debility (Hayes et al. 2017).

Overall, these results suggest that opioid use for CNCP is not associated with better HRQoL as measured by the PCS12 and MCS12 of the SF-12v2. Considering the risk of development of opioid dependence and addiction and unclear benefit on HRQoL, clinicians should carefully evaluate a treatment goal and whether participants with CNCP should continue receiving opioid therapy.

Several limitations exist with this study. First, it was unclear whether residual confounding by indication, or selection bias, exists in the relationship between PCS12 and MCS12 and opioid use. It is possible that we did not see an improvement in PCS12 and MCS12 scores because patients with worse health status and pain are more likely to be placed on opioid therapy. However, we have calculated a comorbidity index, limited to new opioid users (by at least 8 weeks), and adjusted for baseline MCS12 and PCS12 scores which take pain limitations into account. Second, prescription fill dates are not available in MEPS PM files other than the first date in which the participant started taking the medication; therefore, exact dates of opioid exposure within the survey round are unknown. Third, the results of this analysis are only generalizable to those participants who lie in the common support region, those that matched. For example, with the match between chronic and nonchronic opioid users, almost 44 percent of chronic opioid users did not have a suitable match. Demographic characteristics of the participants for whom a suitable match was not found are presented in Tables S4–S6. Comparing the demographics of the whole sample as compared to those that did not match (Table S6), chronic opioid users who did not match to nonchronic users were more concentrated in the greater than 50 age ranges, male, publically insured, lower income, and have more other medication use. Lastly, the final sample size of our study was limited with only around 300 chronic opioid users, which limits some subanalyses by pain severity and drug categories.

This study showed that mental and physical HRQoL were not significantly different among those who had CNCP and use opioids chronically as compared to those with CNCP who used opioids nonchronically or did not use opioids.

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REFERENCES

- Abdel Shaheed, C., C. G. Maher, K. A. Williams, R. Day, and A. J. McLachlan. 2016. "Efficacy, Tolerability, and Dose-Dependent Effects of Opioid Analgesics for Low Back Pain: A Systematic Review and Meta-Analysis." *Journal of the American Medical Association Internal Medicine* 176 (7): 958–68.
- Aetna. 2014. "Q&A on New DEA Pain Medicine Prescriptions" [accessed on August 11, 2016]. Available at <https://news.aetna.com/2014/10/qa-on-new-dea-pain-med-rules/>
- Agency for Healthcare Research and Quality. n.d.b. "Medical Expenditure Panel Survey Home" [accessed on May 3, 2016]. Available at <http://meps.ahrq.gov/mepsweb/>
- Allan, L., U. Richarz, K. Simpson, and R. Slappendel. 2005. "Transdermal Fentanyl Versus Sustained Release Oral Morphine in Strong-Opioid Naïve Patients with Chronic Low Back Pain." *Spine* 30 (22): 2484–90.
- Anastassopoulos, K. P., W. Chow, S. J. Ackerman, C. Tapia, C. Benson, and M. S. Kim. 2011. "Oxycodone-Related Side Effects: Impact on Degree of Bother, Adherence, Pain Relief, Satisfaction, and Quality of Life." *Journal of Opioid Management* 7 (3): 203–15.
- Ashworth, J., D. J. Green, K. M. Dunn, and K. P. Jordan. 2013. "Opioid Use among Low Back Pain Patients in Primary Care: Is Opioid Prescription Associated with Disability at 6-Month Follow-Up?" *Pain* 154 (7): 1038–44.
- Austin, P. C. 2008. "Goodness-of-Fit Diagnostics for the Propensity Score Model When Estimating Treatment Effects Using Covariate Adjustment with the Propensity Score." *Pharmacoepidemiology and Drug Safety* 17 (12): 1202–17.
- . 2011. "An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies." *Multivariate Behavioral Research* 46 (3): 399–424.
- Bartoli, A., E. Michna, E. He, and W. Wen. 2015. "Pain Intensity and Interference with Functioning and Well-Being in Subgroups of Patients with Chronic Pain Treated with Once-Daily Hydrocodone Tablets." *Journal of Opioid Management* 11 (6): 519–33.

- Bostick, G. P., C. Toth, E. C. J. Carr, L. W. Stitt, P. Morley-Forster, A. J. Clark, M. Lynch, A. Gordon, H. Nathan, C. Smyth, M. A. Ware, and D. E. Moulin. 2015. "Physical Functioning and Opioid Use in Patients with Neuropathic Pain." *Pain Medicine (Malden, Mass.)* 16 (7): 1361–8.
- Braden, J. B., A. Young, M. D. Sullivan, B. Walitt, A. Z. Lacroix, and L. Martin. 2012. "Predictors of Change in Pain and Physical Functioning among Post-Menopausal Women with Recurrent Pain Conditions in the Women's Health Initiative Observational Cohort." *The Journal of Pain* 13 (1): 64–72.
- Cheak-Zamora, N. C., K. W. Wyrwich, and T. D. McBride. 2009. "Reliability and Validity of the SF-12v2 in the Medical Expenditure Panel Survey." *Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation* 18 (6): 727–35.
- Chou, R., G. J. Fanciullo, P. G. Fine, J. A. Adler, J. C. Ballantyne, P. Davies, M. I. Donovan, D. A. Fishbain, K. M. Foley, J. Fudin, A. M. Gilson, A. Kelter, A. Mauskop, P. G. O'Connor, S. D. Passik, G. W. Pasternak, R. K. Portenoy, B. A. Rich, R. G. Roberts, K. H. Todd, C. Miaskowski, and American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel. 2009. "Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain." *The Journal of Pain* 10 (2): 113–30.
- Devulder, J., U. Richarz, and S. H. Nataraja. 2005. "Impact of Long-Term Use of Opioids on Quality of Life in Patients with Chronic, Non-Malignant Pain." *Current Medical Research and Opinion* 21 (10): 1555–68.
- Deyo, R. A., D. C. Cherkin, and M. A. Ciol. 1992. "Adapting a Clinical Comorbidity Index for Use with ICD-9-CM Administrative Databases." *Journal of Clinical Epidemiology* 45 (6): 613–9.
- Dobscha, S. K., T. I. Lovejoy, B. J. Morasco, A. E. Kovas, D. M. Peters, K. Hart, J. L. Williams, and B. H. McFarland. 2016. "Predictors of Improvements in Pain Intensity in a National Cohort of Older Veterans with Chronic Pain." *The Journal of Pain* 17 (7): 824–35.
- Edlund, M. J., B. C. Martin, A. Devries, M.-Y. Fan, J. B. Braden, and M. D. Sullivan. 2010a. "Trends in Use of Opioids for Chronic Noncancer Pain among Individuals with Mental Health and Substance Use Disorders: The TROUP Study." *The Clinical Journal of Pain* 26 (1): 1–8.
- Edlund, M. J., B. C. Martin, M.-Y. Fan, A. Devries, J. B. Braden, and M. D. Sullivan. 2010b. "Risks for Opioid Abuse and Dependence among Recipients of Chronic Opioid Therapy: Results from the TROUP Study." *Drug and Alcohol Dependence* 112 (1–2): 90–8.
- Eriksen, J., P. Sjøgren, E. Bruera, O. Ekholm, and N. K. Rasmussen. 2006. "Critical Issues on Opioids in Chronic Non-Cancer Pain: An Epidemiological Study." *Pain* 125 (1–2): 172–9.
- Freburger, J. K., G. M. Holmes, R. P. Agans, A. M. Jackman, J. D. Darter, A. S. Wallace, L. D. Castel, W. D. Kalsbeek, and T. S. Carey. 2009. "The Rising Prevalence of Chronic Low Back Pain." *Archives of Internal Medicine* 169 (3): 251–8.

- Garrido, M. M., A. S. Kelley, J. Paris, K. Roza, D. E. Meier, R. S. Morrison, and M. D. Aldridge. 2014. "Methods for Constructing and Assessing Propensity Scores." *Health Services Research* 49 (5): 1701–20.
- Gran, J. T. 2003. "The Epidemiology of Chronic Generalized Musculoskeletal Pain." *Best Practice & Research. Clinical Rheumatology* 17 (4): 547–61.
- Gureje, O., M. Von Korff, G. E. Simon, and R. Gater. 1998. "Persistent Pain and Well-Being." *Journal of the American Medical Association* 280 (2): 147.
- Guy, G. P., K. Zhang, M. K. Bohm, J. Losby, B. Lewis, R. Young, L. B. Murphy, and D. Dowell. 2017. "Vital Signs: Changes in Opioid Prescribing in the United States, 2006–2015." *MMWR. Morbidity and Mortality Weekly Report* 66 (26): 697–704.
- Hayes, C. J., T. J. Hudson, M. M. Phillips, Z. Bursac, J. S. Williams, M. A. Austin, M. J. Edlund, and B. C. Martin. 2015. "The Influence of Propoxyphene Withdrawal on Opioid Use in Veterans." *Pharmacoepidemiology and Drug Safety* 24 (11): 1180–8.
- Hayes, C., N. Bhandari, N. Kathe, and N. Payakachat. 2017. "Reliability and Validity of the Medical Outcomes Study Short Form-12 Version 2 (SF-12v2) in Adults with Non-Cancer Pain." *Healthcare* 5 (2): 22.
- IMS Health. 2012. "IMS LifeLink Health Plan Claims Database: Overview and Study Design Issues" [accessed on November 21, 2015]. Available at http://www.imstestarea.com/heor_emailer/IMS_Lifelink_PHX_1012.pdf
- Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education. 2011. "Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research." *The National Academies Collection: Reports funded by National Institutes of Health*.
- Kea, B., R. Fu, R. A. Lowe, and B. C. Sun. 2016. "Interpreting the National Hospital Ambulatory Medical Care Survey: United States Emergency Department Opioid Prescribing, 2006–2010." *Academic Emergency Medicine: Official Journal of the Society for Academic Emergency Medicine* 23 (2): 159–65.
- Kowal, J., K. G. Wilson, L. A. McWilliams, K. Pélouquin, and D. Duong. 2012. "Self-Perceived Burden in Chronic Pain: Relevance, Prevalence, and Predictors." *Pain* 153 (8): 1735–41.
- LaValley, M. P. 2008. "Logistic Regression." *Circulation* 117 (18): 2395–9.
- Lemke, M. 2015. "Prescription Opioid Use in the U.S. in 2012: Characterizing Sustained vs. Infrequent Use Using the Medical Expenditure Panel Survey" [accessed on May 11, 2016]. Available at http://www.lexjansen.com/sesug/2015/182_Final_PDF.pdf
- Meldrum, M. L. 2003. "A Capsule History of Pain Management." *Journal of the American Medical Association* 290 (18): 2470–5.
- Nelson, L. S., and J. Perrone. 2012. "Curbing the Opioid Epidemic in the United States: The Risk Evaluation and Mitigation Strategy (REMS)." *Journal of the American Medical Association* 308 (5): 457–8.
- Niemann, T., L. G. Madsen, S. Larsen, and N. Thorsgaard. 2000. "Opioid Treatment of Painful Chronic Pancreatitis." *International Journal of Pancreatology: Official Journal of the International Association of Pancreatology* 27 (3): 235–40.

- Noble, M., S. J. Tregear, J. R. Treadwell, and K. Schoelles. 2008. "Long-Term Opioid Therapy for Chronic Noncancer Pain: A Systematic Review and Meta-Analysis of Efficacy and Safety." *Journal of Pain and Symptom Management* 35 (2): 214–28.
- Parker, S. L., O. Adogwa, S. K. Mendenhall, D. N. Shau, W. N. Anderson, J. S. Cheng, C. J. Devin, and M. J. McGirt. 2012a. "Determination of Minimum Clinically Important Difference (MCID) in Pain, Disability, and Quality of Life after Revision Fusion for Symptomatic Pseudoarthrosis." *The Spine Journal: Official Journal of the North American Spine Society* 12 (12): 1122–8.
- Parker, S. L., S. K. Mendenhall, D. Shau, O. Adogwa, J. S. Cheng, W. N. Anderson, C. J. Devin, and M. J. McGirt. 2012b. "Determination of Minimum Clinically Important Difference in Pain, Disability, and Quality of Life after Extension of Fusion for Adjacent-Segment Disease." *Journal of Neurosurgery. Spine* 16 (1): 61–7.
- Portenoy, R. K., and K. M. Foley. 1986. "Chronic Use of Opioid Analgesics in Non-Malignant Pain: Report of 38 Cases." *Pain* 25 (2): 171–86.
- Ronan, M. V., and S. J. Herzig. 2016. "Hospitalizations Related to Opioid Abuse/Dependence and Associated Serious Infections Increased Sharply, 2002–2012." *Health Affairs (Project Hope)* 35 (5): 832–7.
- Sites, B. D., M. L. Beach, and M. A. Davis. 2014. "Increases in the Use of Prescription Opioid Analgesics and the Lack of Improvement in Disability Metrics among Users." *Regional Anesthesia and Pain Medicine* 39 (1): 6–12.
- Skinner, M. A., E. T. Lewis, and J. A. Trafton. 2012. "Opioid Use Patterns and Association with Pain Severity and Mental Health Functioning in Chronic Pain Patients." *Pain Medicine* 13 (4): 507–17.
- Smith, M., M. A. Davis, M. Stano, and J. M. Whedon. 2013. "Aging Baby Boomers and the Rising Cost of Chronic Back Pain: Secular Trend Analysis of Longitudinal Medical Expenditures Panel Survey Data for Years 2000 to 2007." *Journal of Manipulative and Physiological Therapeutics* 36 (1): 2–11.
- Stockbridge, E. L., S. Suzuki, and J. A. Pagán. 2015. "Chronic Pain and Health Care Spending: An Analysis of Longitudinal Data from the Medical Expenditure Panel Survey." *Health Services Research* 50 (3): 847–70.
- Sullivan, M. D., M. J. Edlund, M.-Y. Fan, A. Devries, J. Brennan Braden, and B. C. Martin. 2010. "Risks for Possible and Probable Opioid Misuse among Recipients of Chronic Opioid Therapy in Commercial and Medicaid Insurance Plans: The TROUP Study." *Pain* 150 (2): 332–9.
- Teunis, T., N. Stoop, C. J. Park, and D. Ring. 2015. "What Factors Are Associated with a Second Opioid Prescription After Treatment of Distal Radius Fractures with a Volar Locking Plate?" *Hand (New York, N.Y.)* 10 (4): 639–48.
- U.S. Department of Justice Drug Enforcement Administration Office of Diversion Control. 2014. "Rules – 2014 – Final Rule: Rescheduling of Hydrocodone Combination Products from Schedule III to Schedule II" [accessed on August 11, 2016]. Available at http://www.deadiversion.usdoj.gov/fed_regs/rules/2014/fr0822.htm
- Verhaak, P. F., J. J. Kerssens, J. Dekker, M. J. Sorbi, and J. M. Bensing. 1998. "Prevalence of Chronic Benign Pain Disorder among Adults: A Review of the Literature." *Pain* 77 (3): 231–9.

- Ware, J. 2005. *How to Score Version 2 of the SF-12 Health Survey (With a Supplement Documenting Version 1)*. Lincoln, RI; Boston, MA: QualityMetric Inc.; Health Assessment Lab.
- Warkentin, L. M., S. R. Majumdar, J. A. Johnson, C. B. Agborsangaya, C. F. Rueda-Clausen, A. M. Sharma, S. W. Klarenbach, S. Karmali, D. W. Birch, and R. S. Padwal. 2014. "Weight Loss Required by the Severely Obese to Achieve Clinically Important Differences in Health-Related Quality of Life: Two-Year Prospective Cohort Study." *BMC Medicine* 12: 175.
- Zondervan, K. T., P. L. Yudkin, M. P. Vessey, M. G. Dawes, D. H. Barlow, and S. H. Kennedy. 1999. "Prevalence and Incidence of Chronic Pelvic Pain in Primary Care: Evidence from a National General Practice Database." *British Journal of Obstetrics and Gynaecology* 106 (11): 1149–55.

SUPPORTING INFORMATION

Additional supporting information may be found online in the supporting information tab for this article:

Appendix SA1: Author Matrix.

Figure S1: Distribution of Propensity Scores Pre and Post-Match for Non-Opioid Users Matched to Non-Chronic Opioid Users.

Figure S2: Distribution of Propensity Scores Pre and Post-Match for Non-Chronic Users Matched to Chronic Opioid Users.

Figure S3: Distribution of Propensity Scores Pre and Post-Match for Non-Opioid Users Matched to Chronic Opioid Users.

Table S1: Validation of Propensity Score Matching with Pre-Post Standard Differences and *p* Values for Non-Chronic vs. Non-Opioid users.

Table S2: Validation of Propensity Score Matching with Pre-Post Standard Differences and *p* Values for Chronic Opioid Users vs. Non-Chronic Opioid Users.

Table S3: Validation of Propensity Score Matching with Pre-Post Standard Differences and *p* Values for Chronic Opioid Users vs. Non-Opioid Users.

Table S4: Demographic Characteristics of Non-Opioid Users and Chronic Opioid Users with CNCP Who Did Not Match.

Table S5: Demographic Characteristics of Non-Opioid Users and Non-Chronic Opioid Users with CNCP Who Did Not Match.

Table S6: Demographic Characteristics of Chronic Users and Non-Chronic Opioid Users with CNCP Who Did Not Match.