Retrospective Review

The Social and Functional Implications of High- Versus Low-Dose Opioids on Chronic Non-Cancer Pain

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Background: Chronic non-cancer pain (CNCP) is a major health concern. Opioids may be a useful treatment option, but their use still remains controversial given the significant risks and epidemic of opioid addiction and abuse. There is limited data on whether opioid therapy is an effective treatment option for chronic non-cancer pain.

Objective: To assess both physical and emotional dimensions of health for patients on opioid therapy for CNCP by reviewing the 36-Item Short Form Health Survey (SF-36) .

Study Design: This study was a retrospective cohort review.

Setting: Outpatient pain clinic

Methods: We recruited 182 patients at the West Penn Pain Institute outpatient pain clinic: 94 patients were recruited for the low-dose opioid group (5-30 morphine milligram equivalents [MME]) while 88 patients were recruited for the high-dose opioid group (> 90 MME). Each patient filled out the SF-36 survey used to assess both the physical and emotional dimensions of their health. We also analyzed patients' employment status, reasons for unemployment, pain diagnosis, side effects, and compliance issues through the electronic medical record (EMR).

Results: Mean scores on General Health Perceptions for the low-dose and high-dose opioid groups were 50.3 ± 21.6 and 44.4 ± 21.9, respectively (P = .07). Though not reaching statistical significance, high-dose patients had lower item scores, indicating a perception of poorer health. There were no significant differences between the low-dose and high-dose opioid treatment groups on any of the mean scores from the 8 domains of the SF-36.
There was a statistically significant association between opioid treatment group and working status, noncompliance, and the self-reported number of side effects. Patients treated with high-dose opioids had significantly higher rates of unemployment (85%) than did low-dose opioid patients (66%) ($\chi^2[1] = 8.48$, P =.004; odds ratio [OR] = 2.89 [95% confidence interval (CI), 1.39-6.01]). Unemployed patients in the high-dose treatment group were more likely to list disability as unemployment while retirement was the most common response in the low-dose treatment group. Patients treated with high-dose opioids had significantly higher rates of self-reported side effects (46%) than did low-dose opioid patients (21%) ($\chi^2[1] = 12.02$, P =.001; OR = 3.08 [95% CI, 1.61-5.89]). Patients treated with high-dose opioids had significantly higher rates of noncompliance (49%) than did low-dose opioid patients (33%) ($\chi^2[1] = 4.75$, P =.029; OR = 1.94 [95% CI, 1.07-3.54]). Thus, the odds of a high-dose opioid patient being unemployed were 2.89 times greater than the odds for a low-dose opioid patient; the odds of a high-dose opioid patient self-reporting side-effects were 3.08 times greater than the odds for a low-dose opioid patient; and the odds of a high-dose opioid patient being noncompliant with their medications were 1.94 times greater than the odds for a low-dose opioid patient.

Limitations: The observation al design prohibits drawing causal relationships, and entry criteria was restricted.

Conclusions: These data suggest that patients receiving low-dose and high-dose opioid treatment do not have significantly different quality-of-life outcomes. Future studies that incorporate longitudinal data are necessary to examine the temporal relationship between quality of life and opioid therapy.

Key words: Chronic pain, chronic non-cancer pain, opioids, pain, quality of life, side effects, noncompliance, unemployment

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Chronic pain is defined as pain that persists beyond the normal tissue healing time of 3 months. When chronic pain is not associated with cancer or end-of-life care, it is often referred to as "chronic non-cancer pain" (CNCP). CNCP is a prevalent health problem and accounts for a large proportion of health care expenditures. In addition, it is the leading cause of disability and can have a major influence on the patient in terms of quality of life, mental health, relationships, and employment. Opioids are one of the most potent analgesics available. They have a large role in the surgical setting and acute pain, but their use as a treatment option for chronic pain – specifically CNCP – remains controversial given the significant risks and given an epidemic of opioid addiction and abuse. There is limited data about the long-term effectiveness of opioids in regard to a patient's physical and emotional health, specifically their functional health, well-being, psychometrically-based physical health, and mental health. There are also concerns about opioid tolerance, their side-effect profile, and anxiety over disapproval by regulatory bodies. These concerns are heightened for patients prescribed high doses of opioids. Despite this, the use of opioids for chronic non-cancer pain has increased substantially since the 1990s. High-dose opioid therapy occurs in 2% to 3% of patients with CNCP or low-back pain and among 8% of patients prescribed chronic opioid therapy (1). There is limited research evaluating the effectiveness of high-dose opioid therapy and its consequences for patients with CNCP, especially in comparison with low-dose opioid treatment.

High-dose opioid use can also lead to hyperalgesia, a form of central sensitization in which a patient's pain level increases in parallel with elevation of his or her opioid use. A retrospective study looked at 23 patients undergoing detoxification from high-dose opioids for chronic pain. Of those 23 patients, 21 reported a significant decrease in pain score after detoxification, which may provide some evidence for the phenomenon of hyperalgesia (2). A similar phenomenon of pain reduction after discontinuation of opioid medications was also examined by Sjogren et al. They reported 4 cases of cancer patients who developed hyperalgesia while on morphine. The hyperalgesia resolved after morphine withdrawal or opioid substitution (3).

One of the major reasons why chronic dose opioid therapy is controversial is concern about developing tolerance. This often occurs in patients maintained on opioids over a prolonged period. As a result, patients will need an increased dose of opioids in order to achieve a level of pain alleviation comparable to that initially achieved. For instance, a prospective cohort study by Campbell et al found that patients taking higher-dose opioids were more likely to have higher pain scores than patient groups taking lower-dose opioids, which may provide some explanation for the phenomenon of tolerance. A prospective study by Chu et al found that patients may have developed tolerance to morphine only after one month of use (4).

Another major concern about high-dose opioid therapy for CNCP is regarding aberrant drug behavior. Morasco et al performed a retrospective cohort study to compare patients on high-dose opioids and traditional-dose opioid therapy. Patients in the high-dose opioid group were more likely to have more medical visits, attempt an opioid taper, receive a urine drug screen, and develop a pain goal than the traditional opioid dose group (1). This may suggest that patients receiving high-dose opioid therapy may be at less risk of aberrant drug behavior than originally thought. However, a prospective cohort study by Campbell et al found conflicting results; patients taking higher-dose opioids were more likely to have aberrant drug behavior (5).

There is also concern that opioid use may lead to a decline in a patients' mental health and lead to functional impairment. A retrospective study by Huffman et al found that patients weaned from opioid therapy after one year showed improvement in depression and anxiety and were less likely to be functionally impaired (6). A randomized control study by Kidner et al showed that patients taking higher dose of opioids were more likely to not return to work, become unemployed, and to be receiving social security disability insurance (7).

The current literature has suggested variable and conflicting results regarding the social and functional implications of chronic opioid therapy for CNCP. This study aims to provide further research regarding the effectiveness of high-dose opioid therapy and compare it to low-dose opioids for CNCP.

Methods

Study Design and Setting

The Institutional Review Board (IRB) at Allegheny Health Network provided approval for this study. We did a retrospective cohort study of patients being treated at the West Penn Pain Institute for chronic non-cancer pain with opioids between June 2016 and June 2018. The West Penn Institute is an outpatient

pain clinic in Pittsburgh affiliated with the teaching hospital of the Allegheny Health Network. Patients are treated with a medical team consisting of nurses, residents, fellows, and attending physicians.

Eligibility Criteria

The study cohort consisted of patients between the ages of 18 and 80 who had been suffering from a pain condition for at least 3 years. Patients were excluded if they had a concurrent diagnosis of cancer, did not speak or understand English, were deemed to be noncompliant, or were receiving end-of-life care. After they were deemed eligible for the study, each patient's current opioid therapy was examined through the Pennsylvania Drug Monitoring Program (PDMP). The PDMP is a statewide program that collects information about controlled substance prescription drugs that are dispensed to patients within the state and surrounding states. Patients were divided into 2 groups based on daily oral morphine milligram equivalents (MME). Patients were placed into the low-dose opioid group if their opioid usage was between 5-30 MME; they were placed in the high-dose opioid group if their opioid usage was equal to or greater than 90 MME. Daily oral MME doses for the opioids taken by the cohort were estimated following review and synthesis of a range of clinical guidelines (8). Patients with MME between these 2 groups were not included for the purpose of this study. After obtaining written informed consent, patients were recruited into the study.

Quality of Life Measures

Quality of life was measured through the 36-Item Short Form Health Survey Instrument (SF-36) survey. All patients were given the SF-36 at the time of visit to the clinic. The SF-36 measures 8 health concepts (also referred to as domains): physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions (9). These domains measure 3 aspects of health – functional status, well-being, and "overall evaluation of health" (10). The domains can also provide a summary of both physical and emotional quality of life. It has been validated, is used widely across medical disciplines, and can be self-administered by the patient with reliability. The SF-36 has been implemented to define disease conditions, to determine the effect of treatment, and to differentiate the effects of different treatments (11).

A single question is also included in the survey that gauges perceived change in health from the prior year. Interpretation of the SF-36 scores is based on the mean (average) scores of patients (12). All items are scored on a scale of 0 to 100 so that a high score defines a more favorable health state. Items that are left blank (missing data) are not taken into account when calculating the scale scores (8). Figure 1 shows the 8 domains of the SF-36 and the percentage contribution of each domain to the survey.

Demographic Data

The following demographic data were obtained through careful review of the patient's electronic medical record (EMR): age, body mass index (BMI), gender, pain diagnosis, complications, and side effects. In addition, employment status and reason for unemployment were obtained through interview of the patient at the time of their visit of clinic.

Statistical Methods

Data analysis began with assessment of the normality of continuous variables using the Kolmogorov-Smirnov test. Continuous

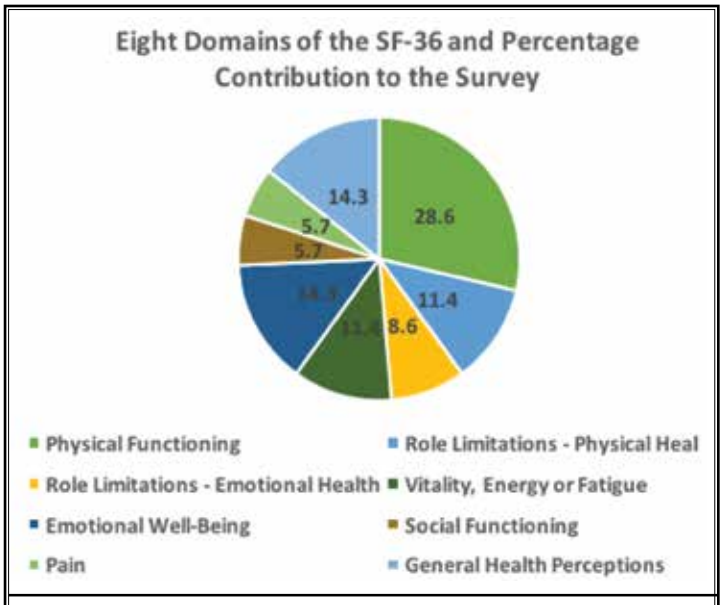

Fig. 1. *Eight domains of the SF-36 and Percentage Contribution to the Survey*

and normally distributed data are reported as means and standard deviations; nonnormally distributed data are reported as median with interquartile range (IQR). Categorical variables are reported as counts and percentages. The independent samples t test or Mann-Whitney test was used to compare continuous variables between the low-dose and high-dose opioid treatment groups. The chi-square test was used to compare categorical variables between groups. Odds ratios (OR) with 95% confidence intervals (CI) are reported when the chi-square test was statistically significant. Cronbach's alpha was used to assess the reliability of the SF-36. A value of $P < .05$ on 2-tailed testing was considered statistically significant. Statistical analyses were performed using SPSS Version 24.0 (IBM Corporation, Armonk, NY).

Results

A total of 182 patients who received treatment with opioids for the relief of non-cancer pain were analyzed. The mean patient age was 59.3 ± 13.0 years (range, 23-94 years) and 65.4% of the patients were women. The median BMI was 30.2 kg/m^2 (IQR = 8.4).

Patients were divided into groups based on their opioid treatment dose. There was a slightly higher proportion of patients receiving low-dose opioids compared with high-dose opioids (52% vs 48%). All patients were given the SF-36 to complete posttreatment.

The 2 opioid treatment groups did not differ significantly in the baseline characteristics of age (P = .99), BMI ($P = .15$) or gender ($P = .08$); however, in both treatment groups, patients were more likely to be women (65.4%) than men (34.6%), and more women were in the low-dose opioid treatment group (71.3%) compared to the high-dose group (59.1%). The baseline characteristics of the patients are reported in Table 1.

When the high-dose and low-dose opioid treatment groups were compared on 6 common diagnoses (e.g., leg pain, leg + hip pain, hip pain (only), back pain, neck + head pain, peripheral pain, and all other pain not falling into the previous categories), the groups did not differ significantly on the number of reported diagnoses ($P = .85$).

Seventy-five percent of the study patients completed the SF-36; completion rates did not differ significantly between the low-dose and high-dose opioid treatment groups (73% vs. 76%, $P = .67$). Although completion of the SF-36 was not significantly related to the baseline characteristics of opioid dosage, gender ($P = .27$), or BMI ($P = .88$), there was a significant difference in completion rates of the SF-36 by patient age. Patients who did not complete the form were significantly older than patients who did complete the form (62.2 ± 13.5 years [n = 46] vs 58.2 ± 12.7 years [n = 136]; t[180] = -1.998, $P = .047$ [95% CI, -8.765 to -0.55]).

There was a statistically significant association between opioid treatment group and working status, noncompliance, and the self-reported number of side effects (Table 2). Patients treated with high-dose opioids had significantly higher rates of unemployment (85%) than did low-dose opioid patients (66%) ($\chi^2[1] = 8.48$, $P = .004$; OR = 2.89 [95% CI, 1.39-6.01]). Patients treated with high-dose opioids had significantly higher rates of self-reported side effects (46%) than did low-dose opioid patients (21%) ($\chi^2[1] = 12.02$, $P = .001$; OR = 3.08 [95% CI, 1.61-5.89]). Patients treated with high-dose opioids had significantly higher rates of noncompliance (49%) than did low-dose opioid patients (33%) ($\chi^2[1] = 4.75$, $P = .029$; OR = 1.94 [95% CI, 1.07-3.54]). Thus, we can say that the odds of a high-dose opioid patient being unemployed were 2.89 times greater than the odds for a low-dose opioid patient; the odds of a high-dose opioid patient self-reporting side-effects were 3.08 times greater than the odds for a low-dose opioid patient; and the odds of a high-dose opioid patient being noncompliant with their

Table 1. *Baseline characteristics of patients treated with low- vs high-dose opioids for non-cancer pain (n = 182)*.*

Variable	Low-Dose Opioid Group (n = 94)	High-Dose Opioid Group (n = 88)	*P* Value
Age in yrs, mean ± SD	59.3 ± 13.1	59.3 ± 13.0	.99
BMI kg/m^2, median (IQR)	30.6 (9.9)	29.9 (8.0)	.15
Gender, n (%)			
Men	27 (28.7)	36 (40.9)	08
Women	67 (71.3)	52 (59.1)	

Abbreviations: BMI, body mass index; IQR, interquartile range; SD, standard deviation; SF-36, 36-Item Short Form Health Survey.
* Data are presented as mean ± SD, median (25%-75% IQR), or count (percentage).

Table 2. *Side effects and noncompliance in patients treated with low- vs high-dose opioids for non-cancer pain (n = 182). Data are presented as count (percentage).*

Variable	Low-Dose Opioid Group (n = 94)	High-Dose Opioid Group (n = 88)	P Value†
Side Effects, n (%)	**n = 94**	**n = 88**	**.67**
None	74 (78.7)	48 (54.5)	
Constipation	15 (16)	26 (29.5)	
Other	3 (3.2)	3 (3.4)	
Constipation + other	2 (2.1)	11 (12.5)	
Diagnoses, n (%)	**n = 94**	**(n = 87)**	**.85**
Leg pain	8 (8.5)	9 (10.3)	
Leg + Hip pain	1 (1.1)	0	
Hip pain (only)	5 (5.3)	4 (4.6)	
Back pain	53 (56.4)	51 (58.6)	
Neck + Head pain	12 (12.8)	9 (10.3)	
Peripheral pain	7 (7.4)	3 (3.4)	
All other pain not falling into the above categories	8 (8.5)	11 (12.6)	

† A *P* value < .05 was considered statistically significant .

Table 3. *Side effects and noncompliance in patients treated with low- vs high-dose opioids for non-cancer pain (n = 182). Data are presented as count (percentage).*

Variable	Low-Dose Opioid Group (n = 94)	High-Dose Opioid Group (n = 88)	P Value†
Side Effects, n (%)	20 (21.3)	40 (45.5)	.001*
Noncompliance, n (%)	31 (33.0)	43 (48.9)	.029*

† A *P* value < .05 was considered statistically significant .

medications were 1.94 times greater than the odds for a low-dose opioid patient.

A total of 135 patients (74.2%) reported that they were unemployed (not working) at the end of the treatment period. Of these 135 patients, 129 provided reasons for their unemployment. Responses were collapsed into one of 3 categories: disability, retirement, and other. These categories included the most responses and made the data more meaningful for analysis. There was a statistically significant relationship between the reported reason for unemployment and opioid treatment group ($\chi^2[2] = 7.18$, $P = .03$). Patients receiving high-dose opioids were more likely to report "disability" as their reason for unemployment than patients receiving low-dose opioids (55.4% vs 34.4%). Patients receiving low-dose opioids were more likely to report "retirement" as their reason for unemployment (37.7% vs 20%). Table 3 summarizes this analysis (Table 4).

A total of 60 patients (33%) reported side effects during the treatment period. Of these 60 patients, 54 patients (90%) reported at least one complication that included constipation. Eighty-five percent of patients receiving low-dose opioid treatment reported at least one complication that included constipation, compared with 92.5% of patients receiving high-dose opioid treatment. There was no statistically significant association between opioid treatment group and the side-effect of constipation ($P = .36$).

The low- and high-dose opioid patients did not differ significantly on their own rating of their perceived general health compared to one year earlier (49.2 ± 23.9 vs 52.8 ± 24.7, $P = .31$).

Table 5 summarizes the results of the SF-36 for each of the 8 domains. There were no significant differences between the low-dose and high-dose opioid treatment groups on any of the mean scores from the 8 domains of the SF-36. High-dose opioid patients scored higher (an indication of less disability or better quality of life)

Table 4. *Reasons for unemployment in patients treated with low-dose vs high-dose opioids for non-cancer pain (n = 135) Data are presented as count (percentage).*

Variable	Low-Dose Opioid Group (n = 94)	High-Dose Opioid Group (n = 88)	*P* Value‡
Reason for Unemployment†, n (%)	(n = 55)	(n = 74)	.03*
Disability	21 (38.2)	41 (55.4)	
Retired	23 (41.8)	15 (20.3)	
Other	11 (20)	18 (24.3)	

Data are presented as count (percentage).
† Of the 61 patients in the low-dose opioid group who indicated that they were unemployed, only 55 patients provided a reason for their unemployment.
‡ A *P* value < .05 was considered statistically significant (*).

Table 5. *Cronbach's alpha and internal consistency for the 8 domains measured by the SF-36 in patients treated with low- vs high-dose opioids for non-cancer pain (n = 182).*

	Low-Dose Opioid Group (n = 94)		High-Dose Opioid Group (n = 88)		# Items
SF-36 Domain	Cronbach's Alpha	Internal Consistency	Cronbach's Alpha	Internal Consistency	
Physical Functioning	(n = 82)		(n = 76)		
	.894	Good	.918	Excellent	10
Role Limitations -Physical Health	(n = 90)		(n = 83)		
	.849	Good	.869	Good	4
Role Limitations -Emotional Health	(n = 91)		(n = 81)		
	.828	Good	.848	Good	3
Vitality, Energy, or Fatigue	(n = 90)		(n = 83)		
	.826	Good	.876	Good	4
Emotional Well-Being	(n = 89)		(n = 84)		
	.852	Good	.850	Good	5
Social Functioning	(n = 92)		(n = 84)		
	.533	Poor	.622	Questionable	2
Pain	(n = 93)		(n = 86)		
	.708	Acceptable	.810	Good	2
General Health Perceptions	(n = 89)		(n = 86)		
	.802	Good	.818	Good	5

Abbreviations: SF-36, 36-Item Short Form Health Survey.

Table 5a. *Interpretation of Cronbach's alpha*

Cronbach's alpha	Internal Consistency Reliability
.9 ≤ α	Excellent
.8 ≤ α < .9	Good
.7 ≤ α < .8	Acceptable
.6 ≤ α < .7	Questionable
.5 ≤ α < .6	Poor
α < .5	Unacceptable

in only 2 domains, though not significantly: Role Limitations – Emotional, and Emotional Well-Being. In the other 6 domains, low-dose opioid patients scored higher, though only General Health Perceptions approached significance. The Physical Functioning domain had the most missing responses (Table 6 and Fig. 2).

Mean scores on General Health Perceptions for the low-dose and high-dose opioid groups were 50.3 ± 21.6 and 44.4 ± 21.9, respectively (*P* = .07). Though

Table 6. *Mean scores for the 8 domains of the SF-36 in patients treated with low- vs high-dose opioids for non-cancer pain (n = 182)**

Variable	Low-Dose Opioid Group (n = 94)	High-Dose Opioid Group (n = 88)	*P* Value
Physical Functioning	**(n = 82)**	**(n = 75)**	
Mean ± SD	41.2 ± 24.4	38.9 26.3	.56
Median (IQR)	35.0 (40.0)	40.0 (45.0)	.49
Role Limitations –Physical Health	**(n = 90)**	**(n = 83)**	
Mean ± SD	30.8 ± 37.7	25.0 36.0	.30
Median (IQR)	25.0 (50.0)	0 (50)	.20
Role Limitations – motional	**(n = 91)**	**(n = 81)**	
Mean ± SD	45.4 ± 42.6	54.7 43.6	.16
Median (IQR)	33.3 (100)	66.7 (100)	.40
Vitality, Energy, or Fatigue	**(n = 90)**	**(n = 83)**	
Mean ± SD	40.7 ± 21.0	39.8 22.7	.79
Median (IQR)	42.5 (30.0)	45.0 (35.0)	.91
Emotional Well-Being	**(n = 89)**	**(n = 84)**	
Mean ± SD	64.7 ± 21.7	67.0 21.7	.49
Median (IQR)	64.0 (38.0)	72.0 (28.0)	.40
Social Functioning	**(n = 92)**	**(n = 85)**	
Mean ± SD	64.7 ± 24.0	63.4 26.4	.73
Median (IQR)	62.5 (37.5)	62.5 (37.5)	.95
Pain	**(n = 93)**	**(n = 87)**	
Mean ± SD	33.2 ± 19.0	29.9 20.5	.26
Median (IQR)	32.5 (22.5)	22.5 (35.0)	.28
General Health Perceptions	**(n = 89)**	**(n = 86)**	
Mean ± SD	50.3 ± 21.6	44.4 21.9	.07
Median (IQR)	50.0 (30.0)	42.5 (30.0)	.11
Health (Compared to Last Year)	**(n = 94)**	**(n = 88)**	
Mean ± SD	49.2 ± 23.9	52.8 24.7	.31
Median (IQR)	50.0 (25.0)	50.0 (50.0)	.34

Abbreviations: IQR, interquartile range; SD, standard deviation; SF-36, 36-Item Short Form Health Survey.
* Higher scores are indicative of better health status. Data are presented as mean ± SD and median (25%-75% IQR). The SF-36 results are usually reported as mean ± SD; however, the distribution of many of the domains are nonnormal. P values are reported for each analysis method (parametric vs nonparametric) showing that no significant values resulted from using either method. Some data are unavailable for each domain analysis.
†A *P* value <0.05 was considered statistically significant

not reaching statistical significance, high-dose patients had lower item scores, indicating a perception of poorer health. Figure 3 shows the mean scores for General Health Perceptions in patients treated with low- versus high-dose opioids for non-cancer pain. A poststudy sample size calculation indicated that 106 patients would have been needed per group for the difference found in this domain to reach statistical significance.

Cronbach's alpha was used as a measure of internal consistency ("reliability") of the SF-36 questionnaire. Internal consistency reliability describes the extent to which all the items in a test measure the same concept or construct; hence, it is connected to the interrelatedness of the items within the test. Cronbach's alpha normally ranges between 0 and 1. The closer Cronbach's alpha coefficient is to 1.0, the greater the internal consistency of the items in the scale (13). According to

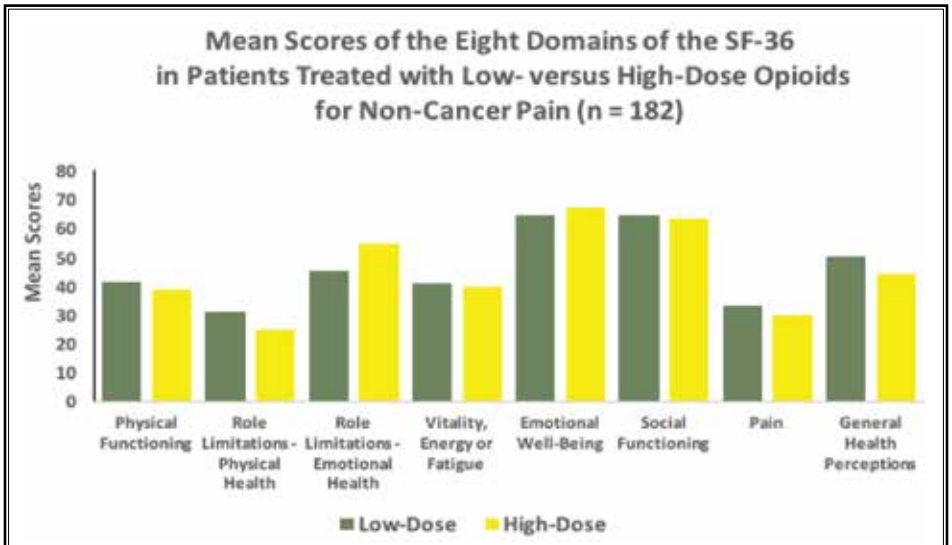

Fig. 2. *Mean scores for the 8 domains of the SF-36 in patients treated with low- vs high-dose opioids for non-cancer pain (n = 182).*

Tavakol and Dennick, if a test has more than one concept, like the SF-36, it may not make sense to report Cronbach's alpha for the test as a whole, as the larger number of questions will decidedly inflate the value of Cronbach's alpha (14). Tavakol and Dennick recommend reporting Cronbach's alpha for each of the domains separately rather than for the entire test.

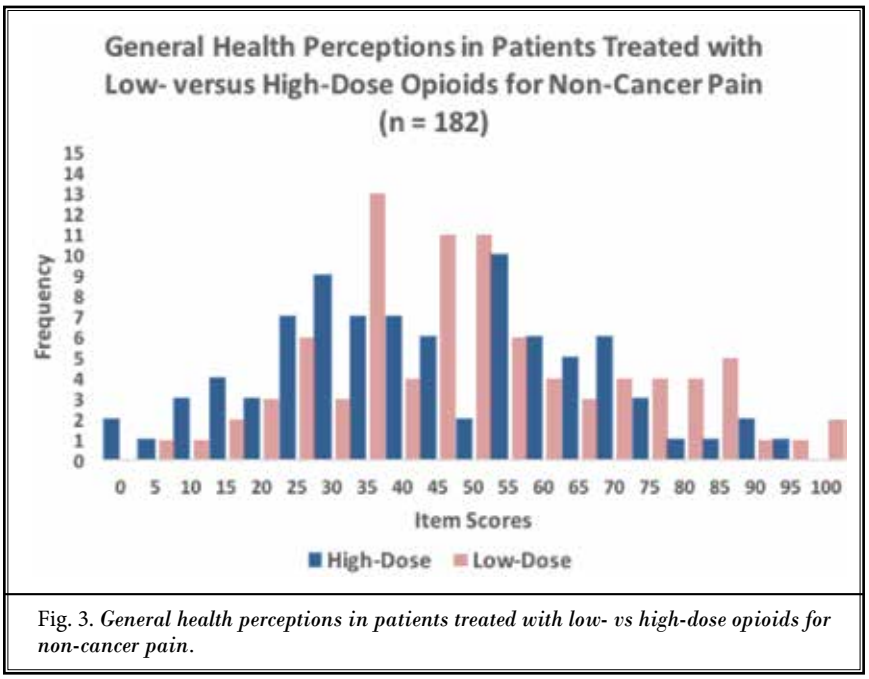

Fig. 3. *General health perceptions in patients treated with low- vs high-dose opioids for non-cancer pain.*

Table 6 reports Cronbach's alpha for the 8 domains measured by the SF-36. Of the 8 domains of the SF-36, only the Social Functioning domain was considered unreliable; all other domains had $\alpha > .70$. The Social Functioning domain, which is based on 2 questions, is a measure of limitations in social activities because of physical or emotional problems. The alpha coefficient for the Social Functioning domain was less reliable in the low-dose opioid treatment group at .533 (n = 92) compared with the alpha coefficient of .622 (n = 84) in the high-dose group.

Discussion

There is increasing concern about the risks of and negative side effects of opioid medications. These concerns are heightened for patients who are prescribed high doses of opioids. We examined the

patients with CNCP who were prescribed daily opioid doses of greater than 90 MME, relative to patients prescribed low-opioid doses, to attempt to better understand the social and functional implications of chronic opioid treatment.

It was interesting to note that the patients receiving high-dose opioids tended to have a poorer perception of health as well as significantly increased reported side effects, increased rates of unemployment, and increased rates of noncompliance. Among the high-dose opioid patients, disability was significantly more likely to be listed as the reason for unemployment, compared to retirement among patients receiving low-dose opioids. It is important to differentiate between retirement and disability as the reason for a patient's unemployment. This is because if a patient retires, that means the patient was able to voluntarily quit working. On the other hand, if the reason is disability, it means that the patient may have had to stop employment prematurely despite their desire to work, which may lead to a lower quality of life. In addition, disability may underlie a more severe pathology or pain, as it restricted them from working. It is not entirely clear whether or not the high-dose opioid patients suffered from worse pain or underlying pathology or functional impairment, but the 2 opioid treatment groups did not differ significantly with respect to baseline characteristics of age, BMI, gender, or 6 common categories of diagnosis. The relationships between lower versus higher doses of opioid treatment and level of pain reduction, amount of functional improvement, as well as any improvement in a patient's physical and emotional health are complex and nonlinear. The results of this study indicate that low-dose opioid patients tend to do significantly better than high-dose opioid patients with respect to fewer reported side effects, lower incidence of noncompliance, and higher rates of employment. Given the significant risks of opioids – especially at higher dosages – including concerns about possible hyperalgesia, and given no statistically significant improvements over low-dose opioid treatment in regard to physical and emotional health parameters, it is reasonable to conclude that high-dose opioid treatment for CNCP should be avoided whenever possible.

There are some limitations to this study. First, its observational design prohibits drawing causal relationships between the use of opioid treatment for non-cancer pain and quality of life. Another limitation is that there were restricted entry criteria into the study: chronic non-cancer pain patients presenting at the West Penn Pain Institute between the ages of 18 to 80 who did not have a concurrent cancer diagnosis and who were not receiving end-of-life care. Also, the study population was one of convenience. The study population included patients who were receiving opioid treatment at a single facility (large urban teaching hospital and Level 1 trauma center), which may limit the generalizability of the findings. Another limitation is that the SF-36 was only given post-opioid treatment. The lack of a baseline SF-36 measure prevented us from quantitatively determining how opioid treatment for non-cancer pain changed the patients' SF-36 scores post treatment.

Another limitation in this retrospective cohort study is that it only provides a single snapshot view of a patient's perception of their current quality of life in relation to their current pain regimen. In order to draw conclusions about a patient's change in quality of life, we would need to collect more information about the patient's baseline level of pain or pathology, previous perception about their quality of life, and previous pain regimen. For instance, it could be that patients on high-dose chronic opioid therapy have failed low-dose therapy and have had to escalate to a higher dose. Alternatively, it could be that patients on high-dose opioid therapy may have had more severe pathology or pain at the start of treatment. It would be interesting to do a longitudinal study incorporating the points above to examine a temporal relationship between opioid dosage and quality of life. Also, patients enrolled in the study had non-cancer pain associated with different conditions as well as different prognoses, thereby raising the possibility of selection bias. Selection bias can often result in patients having less favorable outcomes in one group compared to another group (15). Self-reported data may not always be reliable. Cook and Campbell have pointed out that subjects (a) choose to report what they believe the researcher expects to see; or (b) report what reflects them in a positive light in terms of their abilities, knowledge, beliefs, or opinions (16). Another concern about such data centers on whether subjects are able to accurately recall past behaviors.

A further drawback was the absence of data on prior pain treatments, alcohol use, illegal drug use, patient preference for treatment with low- versus high-dose opioids, patient socioeconomic status, concurrent benzodiazepine usage, psychiatric conditions, and education level. These variables may be factors affecting the SF-36 scores of patients irrespective of their treatment of non-cancer pain with opioids. It would be in-

teresting to look at treatment with benzodiazepines, in particular, for future studies. Concurrent prescriptions of benzodiazepines can be problematic, as sedative-hypnotic medications may interact with opioids to increase the likelihood of adverse events, and non-opioid pain medications are often recommended as one part of a comprehensive pain management program to help enhance pain control. It has been shown that polypharmacy with benzodiazepines may lead to higher risk of aberrant behavior, adverse events including respiratory depression, and overdose (17). Patients' socioeconomic status and concurrent psychiatric conditions would have provided further insight as well. Low socioeconomic status and psychiatric comorbidities may be predictive of aberrant behaviors and are characteristics identified in risk screening tools for prescribing opioids (18).

Conclusion

The SF-36 is a reliable measure of the physical and emotional dimensions of health, specifically a patient's functional health, well-being, psychometrically-based physical health, and mental health. The study also analyzed patients' employment status, reasons for unemployment, pain diagnosis, side effects, and compliance issues through the electronic medical record.

Data analysis suggests that low-dose and high-dose opioid treatment patients do not have significantly different quality-of-life outcomes.

Patients receiving high-dose opioid treatment tended to have a poorer perception of health as well as significantly increased report of side effects, increased rates of unemployment, and increased rates of noncompliance. Among the high-dose opioid patients, disability was significantly more likely to be listed as the reason for unemployment, as opposed to retirement for patients receiving low-dose opioids. Although it is not entirely clear whether or not the high-dose opioid patients suffered from worse pain or underlying pathology or functional impairment, the 2 opioid treatment groups did not differ significantly with respect to baseline characteristics of age, BMI, gender, or 6 common diagnosis categories.

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Author Contributions:

Drs. Denawa, Kurtz, and Conermann had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Denawa and Conermann designed the study protocol. Dr. Denawa managed the literature searches and summaries of previous related work and wrote the first draft of the manuscript. Dr. Denawa and Dr. Kurtz were involved in recruiting patients. Dr. Denawa and Conermann provided revision of intellectual content and final approval of the manuscript.

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