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Research Article

Does the Long-Term Use of Oral Opioids for Chronic Noncancer Pain (CNCP) Increase Depressive Symptoms in Department of Defense Retiree Population?

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Abstract

The optimal medical therapy for patients with chronic noncancer pain (CNCP) continues to be a challenging prospect. The use of oral opioids for the treatment of CNCP continues to be controversial because the true extent of their long-term efficacy, safety and effect on mental and physical functional status remains unclear. Recent studies have shown a correlation between long term opioid use and depression.

Retrospective chart reviews of retired Department of Defense patients, without a diagnosis of depression, were randomly selected from files maintained in the Chronic Pain Clinic located at Wilford Hall Medical Center. Changes in patients' depressive symptoms were assessed based on changes in patients' reported Beck Depression Inventory (BDI) score from each of their clinic visit throughout the course of their therapy.

A statistically significant increase in BDI scores was discovered in patients on high dose opioids (>50mg oral morphine equivalents per day) when compared to low dose opioid group (<50mg oral morphine equivalents per day). No significant changes were found in pain scores over the course of therapy.

This finding suggests that long term opioid therapy could increase a patient's depressive symptoms and those patients on such therapy should continue to be monitored closely for depression.

ABBREVIATIONS

CNCP: Chronic NonCancer Pain; WHMC: Wilford Hall Medical Center; BDI: Beck Depression Inventory; IRB: Institutional Review Board; NRS: Numeric Rating Scale; OME: Oral Morphine Equivalents; NMDA: N-Methyl-D-Aspartate (NMDA) ANOVA: A One-Way Analysis of Variance

INTRODUCTION

The optimal medical therapy for patients with chronic noncancer pain (CNCP), pain lasting beyond three months, continues to be a challenging prospect. Ideally, medical therapy for this patient population would provide objective improvements in the patients' pain levels and their functional status while displaying minimal side effects over the duration of their therapy. Attempts to achieve these goals have led to many approaches, including the use oral opioids over the years. An early study showed that the use of oral opioids, in selected patient populations, was safe and produced few significant side effects [1]. However, as the use of oral opioids in the treatment of CNCP increased, the evidence to support the long term efficacy and safety became less clear. While some systematic reviews demonstrated evidence for the efficacy of long term use of opioids [2-4], others questioned the significance of the amount of pain relief and improvement in function achieved [5] while others emphasized the need for caution and recommended further study [6-10].

The decision to initiate long term oral opioid therapy for CNCP must involve considerations for balancing the benefits (pain relief, improvement in functional status) with the many common side effects (constipation, nausea, sedation, etc.) and

the potential significant adverse reactions (abuse, addiction, overdose, opioid induced hyperalgesia, immunosuppression, etc). While studies have demonstrated both that the use of oral opioids in the short term result in pain relief [11-18], and improvements in mental and physical functional status [19-29], there is enough evidence of decreased in functional status, including depressive symptoms, despite adequate pain relief [12-16] to cause concern and warrant further study in patients using oral opioids for the long term.

Recently, it has been demonstrated that patients with CNCP are more likely to receive a diagnosis of depression based on the duration of their opioid use [30-32]. Given this evidence, a retrospective chart review of retired Department of Defense members receiving oral opioids therapy in the Wilford Hall Medical Center (WHMC) (now called the Wilford Hall Ambulatory Surgical Center) Chronic Pain Clinic was investigated to look for early signs of depression in patients that didn't carry an active diagnosis of depression over the course of their long term therapy. The tool used to monitor for depressive symptoms was the Beck Depression Inventory (BDI), which was filled out at the beginning of each clinic visit. Use of the BDI as a measure of depression is well-studied in various fields, including opioids and chronic noncancer pain [33-34].

Identifying depressive symptoms early in patients receiving varying doses of long-term oral opioid therapy would be valuable in the care of our patients and would warrant further study.

MATERIALS AND METHODS

A retrospective chart review was conducted at the former WHMC Chronic Pain clinic between the dates of August 2009 and December 2010 after approval by the WHMC Institutional Review Board (IRB) in October of 2008 (Protocol # FWH20090018H). Patient charts were randomly selected from the files maintained in the clinic. Data was maintained in encrypted double password protected files located on protected servers at WHMC.

Primary outcomes were changes in patients' depressive symptoms and pain scores over the course of therapy.

Change in patients' depressive symptoms was assessed based on changes in patients' reported Beck Depression Inventory (BDI) score. BDI scores between 0-9 reflected minimal depression, scores between 10-18 reflected mild depression, 19-29 reflected moderate depression and scores greater than 30 reflected severe levels of depression. BDI were completed at every clinic visit.

Pain scores were also collected to determine whether or not a change in the BDI was caused by an increased in pain. Pain scores were reported by the patient using a Numeric Rating Scale (NRS) from 0 (no pain) to 10 (maximum level of pain). Pain scores reported by patients at each clinic visit included: current, worst and best pain levels since their last visit. All pain scores were collected; however, current pain score was primarily data point for each clinic visit.

Inclusionary criteria included patients that were referred to the clinic with CNCP greater than 18 years of age, were no longer in active duty status, had greater than five clinical visits and at least twelve months of monitored therapy while being prescribed tramadol, oxycodone, hydromorphone, morphine, hydrocodone or methadone as their primary analgesic. Exclusionary criteria included any patient not meeting inclusionary criteria, patients with an existing diagnosis of depression or a new diagnosis of depression during the study period, patients with a fibromyalgia diagnosis, patients on duralgesic therapy, and any patient receiving advanced pain management interventions such as peripheral nerve stimulators or intrathecal catheters. Additionally, any patient charts that met criteria but contained incomplete data in critical areas (pain scores, BDI scores, medication regimens, etc) were also excluded.

Of note, patients were not excluded if they received any procedural interventions (epidural steroid injections, medial branch blocks, trigger point injections, etc) or if they received common chronic pain adjuncts (gabapentin, pregabalin, antidepressants, non-steroidal anti-inflammatory drugs, etc) as it is common for patients with greater than twelve months of therapy in this particular clinic to receive a procedural intervention or be given a trial of adjuncts during some portion of their comprehensive clinic care. Of note, patients on antidepressant therapy were only included if their antidepressant regimen was prescribed by the chronic pain clinic. Nearly all patients (n=128, 96.2%) were on at least one adjunct for some portion of their therapy and many (n=121, 90.9%) were on at least two adjuncts for some portion of their therapy. Table (1) lists a summary of key demographic and clinic visit related information.

Patients were then placed into one of three groups based on their oral opioid dosing: low dose, high dose and methadone. Oral Morphine Equivalents (OME) was calculated in order to group the patients. Patients with OME < 50mg per day were placed in the low dose group, patients with OME >50mg per day were placed in the high dose group and those patients prescribed methadone as their primary oral opioid were placed in the methadone group. Given the N-Methyl-D-Aspartate (NMDA) receptor activity that methadone has and its potential for antidepressant effects, it was determined that those patients should be separated out.

Table 1: Study Demographics.

	N (range or %)
Age	Mean= 45 (23-87)
Gender	
-Male	51 (53%)
-Female	45 (47%)
Number of Clinic Encounters	18 (5-77)
Duration of Therapy (months)	63 (12-128)
Regions of Pain	
Single	68 (70.8%)
Two	24 (25.0%)
>Two	4 (4.2%)
Region of Pain	
-Back	71
-Neck	15
-Lower extremities (included hip)	27
-Upper extremities (included shoulder)	11
Pain Type	
-Nociceptive (somatic, visceral)	66 (68.7%)
-Neuropathic (including sympathetic)	9 (21.9%)
-Mixed	21 (21.9%)

Final grouping classifications for each patient were based on the regimen for which they were prescribed for the longest period of time during the period evaluated during the chart review. Table (2) displays the opioid conversions used to calculate the OME. Figure (1) summarizes the study flow chart.

Mean baseline, twelve-month and current (last clinic visit reviewed during the study) pain and BDI scores were then determined for each of the three dosing groups. A one-way analysis of variance (ANOVA) was selected as the initial statistical tool to determine if at least one of the three groups (low dose opioid, high dose opioid and methadone group) had either mean BDI or pain scores that were statistically significant from each other. Fischer's Least Significant Difference (LSD) was then used to determine which of the three groups had statistically significant differences between each other in their mean BDI and pain scores. The LSD was considered a reasonable post hoc method for this study given that it allows α level (0.05) to remain constant through the multiple comparisons between the three groups scores that were measured at three different intervals during the patient's therapy.

Table 2: Oral Opioid Conversion Table.

Tramadol	0.2
Hydrocodone	1
Morphine	1
Oxycodone	1.5
Methadone	3
Hydromorphone	5

*adapted from Foley KM. The treatment of cancer pain, N Eng J Med. 1985; 84-95; Vieweg WVR, et al. Opioids and Methadone Equivalents, J Clin Psychiatry. 2005; 7(3):86-88, Twycross R, et al. Primary Care Formulary (PCF2) 2nd edn, 2002 Radcliffe Medical Press.

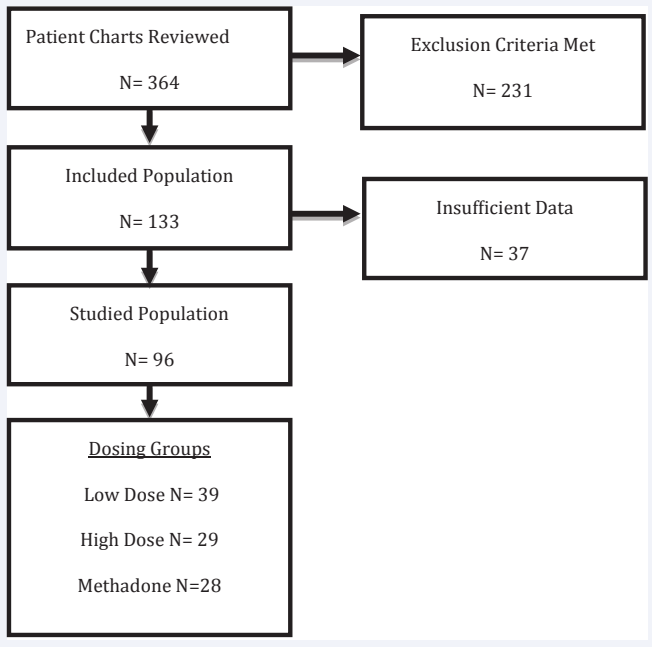

Figure 1 Study Flow Chart.

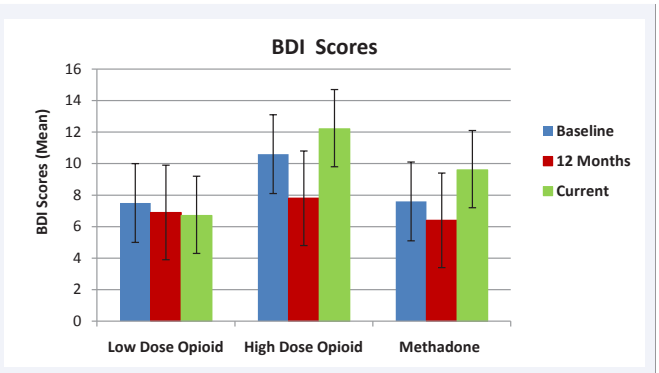

Figure 2 BDI Scores.

RESULTS AND DISCUSSION

A statistically significant difference between the three dosing groups' BDI scores was determined by the one-way ANOVA (F=4.986, p=0.009). Post Hoc analysis using the Fisher LSD analysis (LSD = 5.15) revealed that the high dose opioid group (mean BDI of 12.2) was found to have a statistically significant higher overall BDI than the low dose opioid group (mean BDI of 6.7) (Figure 2, Table 3).

One-way ANOVA determined that there were no significant differences in the mean pain scores between the three groups (F=0.954, p=0.389) (Figure 3, Table 4).

The statistically significant higher mean BDI scores for the high dose opioid group compared to the low dose opioid group after undergoing long term therapy suggests that high dose opioids could be increasing depressive symptoms in these patients. Of additional concern is that the overall BDI score of 12.2, up from a mean of 7.8 at the twelve-month point, represents a change from the mild depression category to the moderate depression category on the BDI scale. The exact mechanism of this relationship is unclear.

Given that the pain scores that were statistically unchanged from baseline, it makes it unlikely that the increase in BDI scores is from worsening pain and, therefore, more likely due to either the dose or the duration of the opioid therapy. This finding is consistent with other larger studies [30-31].

Overall, it is difficult to draw any solid conclusions from the pain score data. The patient's pain scores in this studied population didn't change significantly over the course of their therapy despite their many clinics visits, medications regimens and possible procedural interventions. Without a control group to compare with, it is uncertain where the patient's pain scores would have trended had they not be cared for in the chronic pain clinic. However, it can be said with certainty that their pain scores did not worsen during their care. The methadone group failed to display any statistically significant changes in either BDI or pain scores, so no conclusions can be drawn from this particular cohort of data.

LIMITATIONS

There were several limitations to this study that have to be considered when reviewing the data. This was a small study

Table 3: BDI Scores.

	Baseline Mean (std dev)	12 months Mean (std dev)	Current Mean (std dev)
Low Dose	7.5 (4.7)	6.9 (6.0)	6.7* (5.4)
High Dose	10.6 (6.3)	7.8 (7.6)	12.2* (8.6)
Methadone	7.6 (3.2)	6.4 (4.5)	9.6 (4.9)

*Statistically significant difference ($p<0.05$)

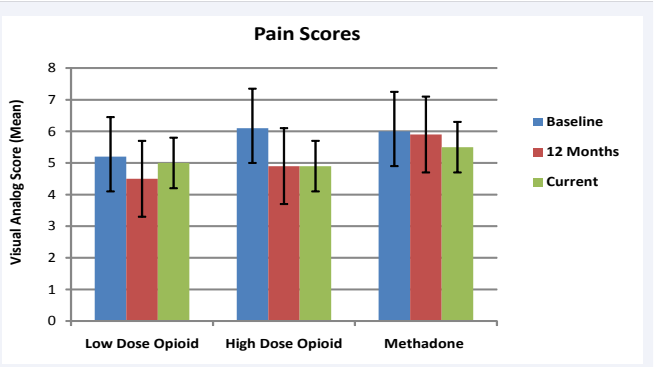

Figure 3 Pain Scores.

Table 4: Pain Scores.

	Initial Mean (std dev)	12 months Mean (std dev)	Current Mean (std dev)
Low Dose	5.2 (2.3)	4.5 (2.5)	5.0 (1.4)
High Dose	6.1 (2.4)	4.9 (2.3)	4.9 (1.7)
Methadone	6.0 (2.2)	5.9 (2.2)	5.5 (1.8)

(n=133) in a specialized population (Department of Defense retiree population). A larger studied group would have helped add more power to this study and perhaps identified either more statistically significant results or trends. The addition of a control group of patients with CNCP not on medical therapy or not on oral opioid therapy would have helped with data interpretation as well, but it is unlikely that such a control group exists.

Selection of patients on only medical therapy would have eliminated the possibility of procedural interventions confounding the pain and BDI scores of those selected for the study. However, most patients in the chronic pain clinic (when followed long term) will likely receive some interventional therapy. Selection of patients with only one type of pain may have removed the confounding factor of certain type of pain (such a neuropathic) that are considered less responsive to opioid therapy (neuropathic pain) than other types of pain (nociceptive). Additionally, selection of patients not on antidepressants at any time in their therapy would have removed this particular treatment modality as a contributor to lower BDI scores, however, antidepressants are a common adjunct in this particular pain clinic and finding such a cohort would have been very difficult.

A different post hoc analysis (i.e. Tukey's honest significant difference test, Fisher-Hayter, Newman-Keuls, etc) may have revealed no significant differences in the data since these tests are less likely than the Fisher's LSD to significantly inflate the likelihood of finding a Type I error (finding a difference when it does not actually exist). However, in the case of depression, it was determined that it would be reasonable to incorporate an analysis that was less likely to miss such a diagnosis. It should also be considered whether or not NRS for pain scores or the BDI scores are the best measures of efficacy and depressive symptoms. While these measures were used in this study because of the data available in the clinic, any prospective studies could assess whether other measures may provide a more accurate assessment of efficacy and functional status.

Lastly, it is recognized that this data was retrospective in nature and reflects only those patients who remained on opioid therapy and doesn't account for any of the attrition that is known to occur in a given population.

CONCLUSION

This small, retrospective study suggests that long term use of high dose opioids contributes to increased BDI scores in patient with CNCP without a previous diagnosis of depression. If opioids are selected as part of a multimodal approach to CNCP, then continue clinical surveillance through tools such as the BDI should be considered to allow for monitoring of increasing depression symptoms in this patient population. Further studies would be warranted to continue monitoring safety and efficacy of opioid therapy for CNCP.

*The view(s) expressed herein are those of the author and do not reflect the official policy or position of the San Antonio Military Medical Center, the United States Air Force Medical Service, the United States Air Force Office of the Surgeon General, the Department of the Air Force, Department of Defense or the United States.

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