Lack of Correlation Between Opioid Dose Adjustment and Pain Score Change in a Group of Chronic Pain Patients

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Abstract: Despite the increasing use of opioid analgesics for chronic pain management, it is unclear whether opioid dose escalation leads to better pain relief during chronic opioid therapy. In this study, we retrospectively analyzed clinical data collected from the Massachusetts General Hospital Center for Pain Medicine over a 7-year period. We examined 1) the impact of opioid dose adjustment (increase or decrease) on clinical pain score; 2) gender and age differences in response to opioid therapy; and 3) the influence of clinical pain conditions on the opioid analgesic efficacy. A total of 109 subjects met the criteria for data collection. We found that neither opioid dose increase, nor decrease, correlated with point changes in clinical pain score in a subset of chronic pain patients over a prolonged course of opioid therapy (an average of 704 days). This lack of correlation was consistent regardless of the type of chronic pain including neuropathic, nociceptive, or mixed pain conditions. Neither gender nor age differences showed a significant influence on the clinical response to opioid therapy in these subjects. These results suggest that dose adjustment during opioid therapy may not necessarily alter long-term clinical pain score in a group of chronic pain patients and that individualized opioid therapy based on the clinical effectiveness should be considered to optimize the treatment outcome.

Perspective: The study reports a relationship, or lack thereof, between opioid dose change and clinical pain score in a group of chronic pain patients. The study also calls for further investigation into the effectiveness of opioid therapy in the management of chronic nonmalignant pain conditions.

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Key words: Opioid therapy, chronic pain, opioid dose adjustment, numeric pain score.

Although opioid analgesics are frequently used for the treatment of acute, chronic, and cancer-related pain conditions, it remains unclear whether opioid therapy is effective in chronic pain management. The effectiveness of opioid analgesia may be influenced by the occurrence of opioid tolerance, opioid-induced hyperalgesia, and a history of substance abuse, as well as other factors such as genetics and comorbid mental illness. At the center of this debate are the issues as to whether 1) opioid therapy is effective for pain relief; and 2) opioid dose escalation during a prolonged course of opioid therapy would improve pain relief. These issues appear to have a significant impact on physicians’ decisions to initiate and maintain opioid therapy for chronic nonmalignant pain.

The aim of this study was to examine the relationship between opioid dose and the effectiveness of pain relief reflected by changes in pain score. To achieve this goal, we retrospectively analyzed clinical data collected from the Massachusetts General Hospital (MGH) Center for Pain Medicine over a 7-year period. Specifically, we examined 1) the relationship between opioid dose increase or decrease and changes in clinical pain score; 2) gender and age differences in response to opioid therapy; and 3) the influence of clinical pain conditions on the opioid analgesic efficacy. The findings of this study are discussed in the context of the methodological limitations of this study and the available clinical literature on this topic.
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Methods

Data Sources

With the approval from the Partners Healthcare Institutional Review Board, we accessed patient charts at the MGH Center for Pain Medicine dated from January 2001 to December 2007. Using the Research Patient Database Registry (RPDR), we searched for patients who were on opioid medications identified at more than 2 visits to the MGH Center for Pain Medicine during this period. RPDR is a database maintained by the Partners Healthcare System including the Massachusetts General Hospital, Brigham and Women’s Hospital, and other affiliated hospitals. Patients who are interested in participating in clinical research are registered in this database. Investigators can request a list of potential study subjects based on the study protocol approved by the institutional review board. The RPDR search yielded 871 charts that met this initial cutoff criterion. To avoid exclusion of the most recent patients who may not have been entered into the RPDR, we also reviewed current physician schedules at the MGH Center for Pain Medicine. Fifty-six additional patient charts were identified using this method. In total, 927 (871 + 56) charts were identified using these 2 methods, and review of these charts was completed in an alphabetical order by last name.

Selection Criteria

The final set of charts used for the data collection were determined using the following criteria: 1) patients who have nonmalignant chronic pain conditions; 2) patients who are on opioid medication(s) during 3 or more office visits; and 3) clinical charts containing information on opioid medication, opioid dose, clinical pain condition, medical history, other medications, and clinical pain score (numeric pain score). Since this is a retrospective study, there was no single protocol that was followed by treating physicians. All pain scores are numeric pain scores (0–10; 0 being no pain and 10 being the worst pain) recorded at the time of office visit and are not recollections or average pain score among various office visits. A total of 109 charts were identified for the final analysis based on these criteria. It should be pointed out that the goal of this study was not to focus on month-to-month changes in opioid dose; instead, our focus was to examine the outcome of long-term opioid therapy by comparing the difference in opioid dose and pain score between the recorded initial and last visits at the MGH Center for Pain Medicine during a 7-year period. This approach minimized the fluctuation of month-to-month dose adjustment and allowed us to examine whether long-term opioid therapy would improve clinical pain score regardless of the fluctuation of opioid dose change. Specifically, the data are presented by providing 1) a summary table for the overall dose change in each subgroup of subjects (opioid dose increase, decrease, or no change between these 2 time points) with the corresponding change in pain score (ie, group analysis); and 2) a plot of each individual subject in each subgroup with regard to his/her opioid dose adjustment and pain score change.

Data Collection and Statistics

The following data were collected from the charts: patient demographics, diagnosis and any change of pain condition, medical condition, opioid medication(s), opioid dose, other medications, pain score, and side effects documented at each office visit. Raw data was entered into a Microsoft ACCESS database (Microsoft Corp, Redmond, WA). To compare the opioid analgesic effect across all patients, all opioid regimens were converted into oral morphine equivalent dose (MED; in milligrams) according to our published report.

We then divided all subjects into 3 subgroups based on the difference in opioid dose between the initial and last visits, ie, opioid dose increase, decrease, or no change, corresponding to at least 20% increase, 20% decrease, or less than 20% change from the initial visit, respectively. Chi-square test or Student t-test was used, when appropriate, to determine the statistical significance at α = .05. In addition, Spearman correlation coefficient analysis was used to determine correlations, or lack thereof, between 2 sets of clinical data (eg, opioid dose and numeric pain score).

The primary endpoint of our analyses was to determine the relationship between changes in opioid dose and clinical pain score by comparing these 2 values between each subject’s initial visit and last visit at the MGH Center for Pain Medicine (up to the point of data collection). Secondary endpoints of our analyses included the relationship between age, gender, opioid dose, and clinical pain condition and changes in clinical pain score. Although functional status was documented in most charts, the statement was often vague and not well defined. This information did not allow us to make a quantitative analysis and, therefore, is not included in this report.

Results

Overview

Data from 109 subjects were used in our analyses. These subjects had a minimum of 3 office visits and a maximum of 58 office visits, with a mean of 10 office visits, to the MGH Center for Pain Medicine. The average interval between 2 office visits was 66 days (1 to 1,070 days) among these subjects. The total follow-up time was, on average, 704 days (29 to 1,866 days) (Table 1). Subjects’ ages ranged from 14 to 83 years at the time of their first visit, with the mean age of 49.5 years (Table 1).

A total of 52 male and 57 female subjects were included. There was no documented progression of chronic pain conditions for which opioid therapy was intended, nor were there significant changes in medical conditions (eg, new onset of comorbid medical condition such as depression) and pain treatment regimen (eg, new adjunctive medications, interventional procedures) between the recorded initial and last office visit during the study period.
their opioid therapy. Therefore, the subjects included in our analyses represent a group of chronic pain patients who are placed on pain treatment regimens consisting of primarily opioid analgesics. At the initial office visit to the MGH Center for Pain Medicine, 100 out of 109 subjects were already taking opioid medications prescribed by a primary care physician or a specialty care physician. Nine subjects were started on opioid medication by physicians at the MGH Center for Pain Medicine. A total of 12 single opioid regimens (Table 2) and 21 opioid combination regimens (Table 3) were prescribed to these subjects during the course of their treatment. For comparisons, opioid doses in various opioid regimens were converted to daily MED as described in our previous report.7

**Table 1. Demographic Data for All Subjects (n = 109)**

<table>
<thead>
<tr>
<th>MEAN</th>
<th>STANDARD DEVIATION</th>
<th>RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>49.5</td>
<td>13.1</td>
</tr>
<tr>
<td>Male</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>MED (mg)</td>
<td>169.8</td>
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</tr>
<tr>
<td>Initial pain score</td>
<td>6.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Number of visits</td>
<td>10.3</td>
<td>9.9</td>
</tr>
<tr>
<td>Interval between visits (days)</td>
<td>66.3</td>
<td>120.7</td>
</tr>
<tr>
<td>Follow-up time (days)</td>
<td>704.1</td>
<td>513.3</td>
</tr>
</tbody>
</table>

**Table 2. List of Single Opioid Analgesics Used by All Subjects**

- Darvocet
- Darvon
- Dilaudid
- Fentanyl patch
- Fentanyl transmucosal
- Methadone
- Morphine (sustained release; MS Contin)
- Morphine (immediate release)
- Oxycodone (immediate release)
- Oxycodone (sustained release: Oxycontin)
- Tylenol #3
- Vicodin

**Table 3. List of Opioid Combinations Used by All Subjects**

- Dilaudid/Oxycodone
- Fentanyl/Dilaudid
- Fentanyl/Morphine (immediate release)
- Fentanyl/Oxycodone
- Fentanyl/Vicodin
- Methadone/Oxycodone
- Methadone/Dilaudid
- Methadone/Fentanyl
- MS Contin/Dilaudid
- MS Contin/Fentanyl
- MS Contin/Oxycodone
- MS Contin/Vicodin
- MS Contin/Morphine (immediate release)
- Oxycodone/Percocet
- Oxycodone/Vicodin
- Oxycodone with Vicodin
- Oxycontin/Dilaudid
- Oxycontin/Oxycodone
- Oxycontin/Roxicet
- Oxycontin/Vicodin
- Tylenol #3/Oxycodone
- Methadone/Oxycontin/Oxycodone

At the initial visit, 100 of 109 subjects were already taking opioid medications prescribed by a primary care physician or a specialty care physician. Nine subjects were started on opioid medication by physicians at the MGH Center for Pain Medicine. A total of 12 single opioid regimens (Table 2) and 21 opioid combination regimens (Table 3) were prescribed to these subjects during the course of their treatment.

**Relationship Between Opioid Dose Change and Clinical Pain Score for All Subjects**

At the initial visit, the average daily MED of all 109 subjects was 170.0 ± 178.7 mg, ranging from 0 to 1,920 mg. The average pain score was 6.5 ± 2.1, ranging from 0 to 10 on a 0 to 10 numeric pain scale. At the last visit, 36 subjects had an overall opioid dose decrease (33%), 49 had opioid dose increase (45%), and 24 had no change in opioid dose (22%), as compared to their opioid dose at the initial visit. There was no correlation between overall opioid dose and clinical pain score point change across all 109 subjects \( (R^2 = .0027; P > .05; 95\% \text{ CI}, 6.11 \text{ to } 6.89) \). The data suggest that opioid dose change did not significantly alter clinical pain score among all subjects as compared between their first and last office visits. However, this global analysis does not reflect individual changes in opioid dose and pain score. To provide a detailed analysis on clinical pain score change between the last visit and the initial visit, 109 subjects were divided into 3 groups based on subjects’ opioid dose increase, decrease, or no change at the last recorded visit as compared to the initial recorded visit, as shown in the following sections.

**Relationship Between Opioid Dose Increase and Clinical Pain Score**

Forty-nine subjects (49/109; 45%) experienced an overall opioid dose increase when compared between their last visit and initial visit. In this subgroup, the average MED was 80.7 ± 76.1 mg and 183.9 ± 110.9 mg at the initial and last visits, respectively. The percent opioid dose increase ranged from 11 to 1,400% over that of the initial visit, and the point change in pain score for all 49 subjects was \( /C0 \) 2.2 ± 21.8% (Table 4; Fig 1). Of them, 24/49 (49%) subjects reported an average of 19.4 ± 13.7% decrease in their pain score (initial visit, 7.7 ± 1.8; last visit, 5.8 ± 2.4; \( P > .05 \)); 15/49 (30.6%) subjects reported an average of 23.7 ± 9.9% increase in their pain score (initial visit, 5.8 ± 2.0; last visit, 8.1 ± 1.8; \( P > .05 \)); and 10/49 (20.4%) reported no change in their pain score (initial visit, 8.0 ± 1.3; last visit, 8.0 ± 1.3; \( P > .05 \)). As such, there was no overall correlation between opioid dose increase and clinical pain score point change in this subgroup \( (R^2 = .0248; P > .05; 95\% \text{ CI}, -8.30 \text{ to } 3.90) \). These results suggest that opioid dose increase did not significantly improve clinical pain score over the course of opioid therapy in these subjects.
**Relationship Between Opioid Dose Decrease and Clinical Pain Score**

Thirty-six subjects (36/109; 33%) experienced an overall dose decrease at their last visit as compared to that at the initial visit. In this subgroup, the average MED was 281.5 ± 378.9 mg and 111.8 ± 131.8 mg at the initial and last visits, respectively. The percent opioid dose decrease ranged from −6.3 to −100% (tapered off) over that of the initial visit, and the overall point change of pain score was −5.1 ± 21.5% (Table 5; Fig 2). Of them, 18/36 (50%) subjects reported an average of 21.9 ± 13.3% decrease in their pain score (initial visit, 7.1 ± 1.4; last visit, 4.9 ± 3.0; P > .05); 10/36 (27.8%) subjects reported an average of 21.0 ± 11.0% increase in their pain score (initial visit, 5.5 ± 2.1; last visit, 7.6 ± 1.7; P > .05); and 8/36 (22%) reported no point change in their pain score (initial visit, 7.5 ± 1.9; last visit, 7.5 ± 1.9; P > .05). Overall, there was no correlation between opioid dose decrease and clinical pain score point change in this subgroup (R² = .0052; P > .05; 95% CI, −12.12 to 1.92). These results suggest that opioid dose decrease also did not significantly alter clinical pain score over the course of opioid therapy in these subjects.

**Relationship Between No Overall Opioid Dose Change and Clinical Pain Score**

Twenty-four subjects (24/109; 22%) experienced no overall opioid dose change at their last visit as compared to that at the initial visit. In this subgroup, the average MED was 155.9 ± 179.9 mg and 183.9 ± 110.9 mg at the initial and last visits, respectively. The overall point change of pain score was −5.2 ± 20.0% at the last visit as compared to that of the initial visit (Table 6). Of these subjects, 11/24 (45.8%) reported an average of −21.4 ± 12.3% decrease in their pain score (initial visit, 7.7 ± 12.3; last visit, 5.6 ± 2.3; P > .05); 6/24 (25.0%) reported an average of 18.3 ± 16.0% increase in their pain score (initial visit, 6.0 ± 2.0; last visit, 7.8 ± 2.4; P > .05); and 7/24 (29.2%) reported no point change in their pain score (initial visit, 7.5 ± 1.1; last visit, 7.5 ± 1.1; P > .05). These results again suggest that clinical pain score varied over the course of opioid therapy even in the absence of opioid dose change.

**Table 4. Effect of Opioid Dose Increase on Clinical Pain Score**

<table>
<thead>
<tr>
<th>Sample Size = 49</th>
<th>Number of Subjects</th>
<th>Percent of Subjects With Increased MED</th>
<th>Mean % Point Change in VAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects in this category</td>
<td>49</td>
<td>45.0%*</td>
<td>−2.2 ± 18.8%</td>
</tr>
<tr>
<td>Decreased pain score</td>
<td>24</td>
<td>49.0%</td>
<td>−19.4 ± 13.7%</td>
</tr>
<tr>
<td>No change in pain score</td>
<td>10</td>
<td>20.4%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Increased pain score</td>
<td>15</td>
<td>30.6%</td>
<td>+23.7 ± 9.9%</td>
</tr>
</tbody>
</table>

*Percent of subjects with increased MED out of a total sample size of 109 study subjects.

**Figure 1.** Illustration of each individual subject with opioid dose increase and the corresponding clinical pain score point change. MED, daily morphine equivalent dose.

**Figure 2.** The relationship between opioid dose increase and clinical pain score change. The MED, daily morphine equivalent dose.
Collectively, these results show a lack of correlation between changes in opioid dose and clinical pain score in this group of chronic pain patients regardless of clinical pain conditions for which opioid therapy was intended.

**Relationship Between Age, Gender, and the Effectiveness of Opioid Analgesia**

For all male subjects (52/109), the mean daily MED at the initial visit was 146.7 ± 169.6 mg, ranging from 0 to 870 mg, and the average pain score was 6.8 ± 1.8, ranging from 3 to 10 on a 0 to 10 numeric pain scale. At the last visit, the mean daily MED of all male subjects was 159.2 ± 128.5 mg, ranging from 0 to 480 mg, with the average pain score of 6.4 ± 2.5, ranging from 1 to 10.

For all female subjects (57/109), the mean daily MED at the initial visit was 178.9 ± 310.2 mg, ranging from 8 to 1,920 mg, and the average pain score was 7.3 ± 2.0, ranging from 1 to 10. At the last visit, the mean daily MED of all female subjects was 149.1 ± 146.7 mg, ranging from 0 to 720 mg, with the average pain score of 6.9 ± 2.1, ranging from 2 to 10.

To examine the relationship between age and the effectiveness of opioid therapy, 109 subjects were divided into 3 age groups: < 40 years old (n = 8), 40 to 60 years old (n = 60), and > 60 years old (n = 41). The response to opioid dose change (increase or decrease) was examined in these age groups by comparing the percent point change in clinical pain score between the initial and last visits. There were no statistical differences in the percent point change of clinical pain score, nor were there differences between male and female subjects, among all 3 age groups in response to opioid dose change (Fig 6; P > .05). These results suggest that opioid dose change does not significantly alter clinical pain score in both genders and across different age groups in this group of chronic pain patients.

**Relationship Between Opioid Dose and the Effectiveness of Opioid Analgesia**

We also examined whether the opioid dose at initial visit would influence the effectiveness of chronic opioid therapy. We divided 109 subjects into low dose (< 75 mg) versus high dose (> =75 mg) groups based on their daily MED at the initial visit. This division was referenced from our previous report for the purpose of data analysis.

For the low dose group (49/109), the mean daily MED at the initial visit was 4.5 ± 18.4 mg, ranging from 0 to 60.0 mg, and the average pain score was 6.8 ± 2.0, ranging from 3 to 10. At the last visit, the mean daily MED of this low dose group was up to 97.6 ± 76.82 mg but the average pain score remained at 6.3 ± 2.4, ranging from 1 to 10.

Moreover, 26/49 (53.1%) subjects in the low dose group experienced an average reduction of pain score (22.1 ± 15.7%) in response to an average increase of 278.5 ± 410.3% MED. But 13/49 (26.5%) subjects experienced an average increase of pain score (25.0 ± 14.4%) in response to an average increase of 134.7 ± 196.3% MED. The remaining subjects (10/49; 20.4%) in this group showed no point change in pain score.

For the high dose group (60/109), the mean daily MED at the initial visit was 264.0 ± 305.9 mg, ranging from 75.0 to 1,920.0 mg, and the average pain score was 7.2 ± 1.87, ranging from 1 to 10. At the last visit, the mean daily MED of this high dose group was 199.92 ± 158.62 mg with the average pain score of 6.9 ± 2.2, ranging from 2 to 10.

Similarly, 27/60 (45.0%) subjects in the high dose group experienced an average reduction of pain score (19.3 ± 10.2%) in response to an average increase of 3.8 ± 80.6% MED. Another 18/60 (30.0%) subjects experienced an average increase of pain score (19.4 ± 8.2%) in response to an average increase of 27.7 ± 132.5% MED. The remaining subjects (15/60; 25.0%) showed no point change in pain score.

Collectively, these results suggest that opioid dose at initial visits had little influence on clinical pain score at the last visit during a course of chronic opioid therapy.
Discussion

We have shown that an overall correlative relationship was not present between opioid dose change (increase or decrease) and clinical pain score in a group of chronic pain patients on a prolonged course of opioid therapy (an average of 704 days). This lack of correlation was across various chronic pain conditions including neuropathic, nociceptive, or mixed pain for which opioid therapy was intended. Neither gender nor age differences significantly influenced the clinical response to opioid therapy in these patients. Collectively, these results suggest that chronic opioid therapy does not necessarily alter clinical pain score despite opioid dose adjustment. While this study is not intended to discourage physicians from providing opioid therapy for chronic noncancer pain, the data suggests that individualized opioid therapy based on the clinical effectiveness should be considered to optimize the treatment outcome.

Methodological Considerations

A retrospective chart review study has both advantages and disadvantages as compared to randomized and controlled clinical trials. A major advantage of a chart review study is that the data collected from this study represent an authentic clinical practice setting without sanitizing the study population, whereas a prospective study is highly valuable in testing a standardized clinical treatment protocol. A major disadvantage is that clinical conditions are not controlled, including disease progression, comorbidities, adjunctive medications, and interventional pain procedures. As mentioned in the Results section, we believe that these factors are unlikely to have influenced the effectiveness, or lack thereof, of chronic opioid therapy in these subjects because no apparent changes in these clinical factors were documented in their clinical charts. Nonetheless, the outcome of this study should be viewed with the limitations pertinent to a chart review study. In addition, several important caveats should be clearly noted: 1) this study may be underpowered considering the negative results; 2) the patient population in this study represents only a small group of chronic pain patients treated at a teaching hospital and the results should not be interpreted as being representative of the general population of chronic pain patients receiving opioids; and 3) our intention was not to examine how a decision of opioid adjustment was made by clinicians during a course of opioid therapy. This issue by itself can be rather complex and influenced by multiple factors. Instead, our focus was to examine the outcome of opioid dose change in relation to clinical pain score changes. Therefore, the data presented in this study do not establish a cause-effect relationship between opioid dose change and clinical pain relief but rather a correlative relationship or lack thereof.

In this study, we compared opioid dose adjustment and clinical pain score change between the initial and last visits, although these subjects had multiple office visits (from 3 to 58 visits) and multiple opioid dose changes (up to 10 dose adjustments in some subjects) during this period. We opted not to examine each dose change at each interim office visit because the between-visit interval varied from 1 day to 1,070 days among these subjects, making it difficult to make valid comparisons at

<table>
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<th>Percent of Subjects w/No Change in MED</th>
<th>Mean % Point Change in VAS</th>
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<tbody>
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<td>All subjects in this category</td>
<td>24</td>
<td>22.2%*</td>
<td>−5.2 ± 20.0%</td>
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<td>11</td>
<td>45.8%</td>
<td>−21.4 ± 12.3%</td>
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<tr>
<td>No change in pain score</td>
<td>7</td>
<td>29.2%</td>
<td>.0%</td>
</tr>
<tr>
<td>Increased pain score</td>
<td>6</td>
<td>25.0%</td>
<td>+18.3 ± 16.0%</td>
</tr>
</tbody>
</table>

*Percent of subjects with no change in MED out of a total sample size of 109 study subjects.

Figure 3. Illustration of all subjects with neuropathic pain, showing the relationship between changes in opioid dose and point change in clinical pain score.

Figure 4. Illustration of all subjects with nociceptive pain, showing the relationship between changes in opioid dose and point change in clinical pain score.
these interim office visits. However, we did analyze the effect of significant opioid dose changes, defined as at least 15% dose increase or decrease at an interim office visit, on clinical pain score. This analysis also did not detect any correlation between opioid dose adjustment and clinical pain score point change (data not shown). Therefore, comparisons between the initial and last visits should reveal the final outcome of a chronic opioid therapy in these subjects.

Another possible explanation for the lack of correlation between opioid dose adjustment and point change in clinical pain score is a relatively small sample of subjects (109) included in the analyses, which is likely to introduce a type II error. Since power analysis was not performed due to the lack of a reference dataset in the literature, it is difficult to determine a proper sample size. Nonetheless, our analyses failed to reveal meaningful correlations in this subset of chronic pain patients. We would like to emphasize that the present study analyzed only a limited part of clinical practice of opioid therapy that are documented in these charts. Other clinical factors (eg, substance abuse history, aberrant behavior) may have an influence on the outcome as well. Future studies with a larger patient population and a more comprehensive dataset may provide more insights on these issues.

Effectiveness of Long-Term Opioid Therapy for Nonmalignant Chronic Pain

A pressing issue in evaluating the effectiveness of opioid therapy for chronic nonmalignant pain treatment is the lack of long-term, double-blinded, placebo controlled clinical studies. In a meta-analysis of available randomized, placebo controlled studies involving 15 trials using World Health Organization step 3 opioids, it showed that opioid therapy decreases pain intensity in at least 30% chronic pain patients. However, about 80% of patients experienced at least 1 adverse event and only 44% of patients continued opioid therapy after 7 to 24 months. In another meta-analysis of 41 randomized trials involving 6,019 patients, the authors found that only strong opioids were superior to naproxen or nortriptyline for pain relief, whereas nonopioid medications such as nonsteroidal anti-inflammatory drugs and antidepressants showed better functional outcomes than opioids. In addition, opioid therapy is limited by significant side effects such as constipation and nausea. In a study of 121 patients who had been on opioids for at least 3 years, the average treatment time was 66 months (37–105 months; 87% more than 5 years) and the pattern of opioid dose changes was similar to what we observed in the current study (no change, 33%; decrease, 16%; slight increase, 27%; and major increase, 19%). In a retrospective study, 48,986 subjects were included in the analysis. Of them, 99% of subjects had intermittent opioid exposure and only 1% had continuous exposure. The mean duration of opioid exposure was 477 days and only 7% percent of the subjects were exposed to a dose at or above 180 mg morphine at some points. Unfortunately, this study did not specifically examine the relationship between changes in opioid dose and clinical pain score. A Denmark study pointed out that opioid dose escalation occurred in only a small percentage of patients, and opioid dose increase and decrease were almost equally frequent in that study. Thus, our findings are in general agreement with these previous studies. Our data further demonstrate that the effectiveness of opioid therapy, or lack thereof, does not have a direct relationship with opioid dose adjustment in a group of chronic pain patients on a prolonged course of opioid therapy.

Clinical Factors and the Effectiveness of Chronic Opioid Therapy

A number of clinical factors may influence the outcome of chronic opioid therapy, including age, gender, opioid dose, opioid tolerance, and opioid-induced hyperalgesia. With regard to age differences, opioids have been shown to be effective in elderly patients with nonmalignant pain, but it is still unclear which opioid regimen would be superior in maintaining the analgesic efficacy. In many cases, drugs are often chosen based on the safety and tolerability by elderly patients.
For example, in a retrospective chart review of 206 patients, younger patients reached a maximum dose of opioid that was twice higher than that in older patients. However, only older patients demonstrated a reduction in pain score. Our data also indicate that gender differences did not significantly influence the opioid responsiveness in chronic pain patients, which appears to be consistent with a previous study showing that male and female patients treated with intrathecal and oral opioids had similar dose escalation over a 12-month period.14

Rapid opioid dose escalation in chronic pain patients could lead to the development of tolerance, although clinical assessment of opioid tolerance remains a challenge.21 Some investigators have suggested that patients at higher risk may experience more subjective pain, making it even more difficult to adequately assess the clinical effectiveness of opioid therapy.15 While our study was not designed to differentiate these clinical factors, the data do seem to suggest that both opioid-induced hyperalgesia and opioid tolerance may have contributed to the clinical outcome. For example, a significant percentage of subjects had increased clinical pain score in response to opioid dose increase, whereas opioid dose decrease concurrently reduced clinical pain score, suggesting opioid-induced hyperalgesia. On the other hand, some of these subjects showed pain score decrease with opioid dose increase, whereas opioid dose decrease yielded an opposite outcome, suggesting clinical opioid tolerance.

Relationship Between Pain Conditions and the Effectiveness of Long-Term Opioid Therapy

Our data showed that the type of chronic pain condition including neuropathic, nociceptive, or both did not change the opioid analgesic efficacy. Previous studies have shown that opioid therapy up to 2 years was effective in the treatment of chronic low back pain but opioid dose escalation was not related to the severity of chronic pain conditions.9 A chart review study showed that opioid use is rather common in patients with fibromyalgia, and among this subgroup more than 60% using strong opioids. In addition, opioid use was more commonly associated with lower education, unemployment, disability payments, current unstable psychiatric disorder, history of substance abuse, and previous suicide attempts.12

Neuropathic pain is another chronic pain condition for which opioid has been commonly used, although initial higher opioid doses appear to be needed as compared to the treatment of non-neuropathic pain conditions.27 Several opioid analgesics with unique pharmacological profiles such as methadone and buprenorphine might have a better efficacy in treating intractable neuropathic pain conditions,23,26 but the long-term efficacy of using these opioids is still unclear. Our data again showed a lack of correlation between changes in opioid dose and pain score change in patients with chronic neuropathic pain.

Rational and Individualized Use of Opioid Therapy for Chronic Nonmalignant Pain Management

Prescribing opioids for chronic nonmalignant pain has raised several concerns, including 1) lack of evidence supporting long-term effectiveness; 2) misuse of prescription opioids including abuse and diversion; and 3) a dearth of clinical data on adverse drug events including endocrine dysfunction, immunosuppression, opioid-induced hyperalgesia, overdose, falls and fractures, and psychosocial complications.5 To date, several recommendations have been documented in the literature, including 1) proper patient selection and risk stratification; 2) informed consent; 3) plan for long-term management including dose adjustment and necessary weaning; 4) close monitoring of patients on chronic opioid therapy and proper documentation; 5) rational dose adjustment; and 6) plan for prevention and management of opioid-related adverse effects including instructions on driving, work safety, and pregnancy.8,28 Moreover, education for both physicians and patients will be necessary as shown in our recent survey study.6 Primary care providers are also very receptive to tools and education materials on opioid therapy.22 In addition, several alternative approaches may be considered including opioid rotation, drug holidays, and use of adjuvants such as ketamine and dextromethorphan.10,18,19,24,29

In summary, our data suggest that dose escalation during chronic opioid therapy may not reliably correlate with changes in clinical pain score. More studies will be needed to determine the effectiveness, or lack thereof, of opioid therapy for nonmalignant chronic pain and provide meaningful and individualized guidelines for opioid dose adjustment.

References

Correlation Between Opioid Dose and Pain Score


