Age, gender, and earlier opioid requirement associations with the rate of dose escalation in long-term opioid therapy

Huijun Han, MD, PhD; Philip H. Kass, DVM, PhD; Barth L. Wilsey, MD; Chin-Shang Li, PhD

INTRODUCTION

With the increasing acceptance of opioid therapy in chronic pain management,\textsuperscript{1,2} long-term opioid use has increased dramatically during the last decade.\textsuperscript{3-6} According to a report of Centers for Disease Control and Prevention, ~10-12 million Americans currently are on long-term opioid therapy for their chronic pain.\textsuperscript{7} Some chronic pain conditions can be severe and last for years or decades.\textsuperscript{8-12} In such situations, patients may need prolonged opioid therapy to obtain and maintain effective pain relief and improved physical function and quality of life. In a few publications, the duration of opioid therapy was reported as 10-35 years.\textsuperscript{10-12}

Patients who use opioids for a prolonged period can develop drug tolerance that periodically requires a dose increase to compensate for the loss of efficacy over time.\textsuperscript{13-17} However, little is known about factors associated with dose escalation in long-term opioid therapy, especially in those lasting for many years. Previous studies on opioid therapy for chronic noncancer pain have shown that age, gender, and early dose requirement might be associated with the rate of dose escalation. Specifically, younger age,\textsuperscript{16-18} male gender,\textsuperscript{18} and a higher early dose requirement\textsuperscript{16,17} were associated with a higher rate of dose escalation. However, one study did not find significant age association\textsuperscript{19} and three studies did not find significant gender association.\textsuperscript{16,17,19} Moreover, only two studies examined the effect of early dose requirement on the rate of subsequent dose change. One evaluated the early dose requirement based on the doses needed during an intrathecal trial and did

ABSTRACT

Objectives: To examine the association of risk factors, age, gender, and earlier opioid requirement with the rate of dose escalation in long-term opioid therapy.

Methods: This is a retrospective cohort study of 1,922 individuals identified from California’s prescription drug monitoring program database who continuously used opioids from 1999 to 2007. A linear mixed-effects model was used to examine the association of age, gender, and baseline dose requirement with the rate of subsequent opioid dose change. Because of different reporting requirements before and after January 1, 2005, the analyses were conducted separately for patients’ opioid use in two periods (6 years between 1999 and 2004 and 3 years between 2005 and 2007).

Results: Both the 6-year and the 3-year data showed a significant age association, with younger patients having a higher rate of dose escalation than older patients ($p < 0.0001$). Females had a lower rate of dose escalation than males, although the result did not achieve statistical significance in the 6-year data ($p = 0.165$). The higher the dose requirement a patient had at baseline, the lower the rate of dose escalation ($p < 0.0001$ in both periods).

Conclusions: Age, gender, and earlier dose requirement were associated with the rate of dose change in 9-year long-term opioid therapy. Patients aged 75-100 years, being female or having large dose requirement at an earlier stage of therapy may experience a slower dose escalation or even dose decline.
not examine the association between pretrial oral or parenteral dose requirements and later dose escalation; another evaluated the early dose requirement based on the total dose amount in the first opioid prescription, without accounting for the number of days covered by the prescription which may not accurately reflect a patient’s dose requirement at an early time. In addition, the mean duration of opioid therapies in these studies varied from 12 to 27 months, a relatively short observation period compared to the duration of chronic pain, which may last for years or decades. To better understand opioid tolerance development in long-term opioid therapy, an initial approach may be to document characteristics that were associated with dose escalation among prolonged opioid-therapy receivers.

Using data in California’s prescription monitoring program (PDMP), this study aims to examine the association between risk factors (age, gender, and early dose requirement) and the rate of dose change among patients who continuously used opioids from 1999 to 2007. The result will contribute to an understanding of the epidemiology of prolonged opioid therapy that lasts for nearly one decade.

METHODS

Data source

This retrospective cohort study used data from California’s PDMP, the Controlled Substance Utilization Review and Evaluation System (CURES). This is a statewide database designed for the surveillance of controlled substances by the California Department of Justice. Monitoring of schedule II opioid prescriptions began in 1939 when California established the first PDMP in the nation; monitoring of schedule III opioid prescriptions started in 2005 after legislative mandate. California’s PDMP was converted from a paper based to an electronic controlled substance surveillance system in 1998. Pharmacists would input the drug name, quantity, dosage, and date of the transaction at the point of disbursement into the CURES database. In addition, the patients’ name, date of birth, gender, and address were transmitted, as were the prescriber and pharmacy identities via Drug Enforcement Administration (DEA) registration numbers. To ensure confidentiality and anonymity of the information obtained for this study, the CURES database underwent deidentification as described previously.

Study population

Individuals aged 18-100 years in 1999 who continuously used prescription opioids from January 1, 1999 to December 31, 2007 were included in the study. Because of the unavailability of patients’ daily opioid-taking history and the days covered information for each prescription, we identified eligible patients based on two criteria. First, the interval between an individual’s first and last opioid prescriptions plus an estimate of the number of days covered by his or her last prescription was 9 years, whereby the duration of last prescription was estimated with the “last observation carry forward” method. Further details of this method were discussed in a previous publication. Second, the interval between any two consecutive prescriptions was not more than 6 months. This second criteria were adopted from CONsortium to Study Opioid Risks and Trends research by Korff et al.

Information of prescriptions for 10 types of schedule II opioids and two types of schedule III opioids was queried (Table 1). Prescriptions were excluded if they were incomplete, implausible, for commercial transactions or for medications using special delivery systems. Rationales for these exclusion

<table>
<thead>
<tr>
<th>Schedule II</th>
<th>Drug type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-acting fentanyl</td>
<td></td>
</tr>
<tr>
<td>Long-acting levorphanol</td>
<td></td>
</tr>
<tr>
<td>Long-acting methadone</td>
<td></td>
</tr>
<tr>
<td>Long-acting morphine</td>
<td></td>
</tr>
<tr>
<td>Long-acting oxycodone</td>
<td></td>
</tr>
<tr>
<td>Short-acting fentanyl</td>
<td></td>
</tr>
<tr>
<td>Short-acting hydromorphone</td>
<td></td>
</tr>
<tr>
<td>Short-acting meperidine</td>
<td></td>
</tr>
<tr>
<td>Short-acting morphine</td>
<td></td>
</tr>
<tr>
<td>Short-acting oxycodone</td>
<td></td>
</tr>
<tr>
<td>Schedule III</td>
<td>Drug type</td>
</tr>
<tr>
<td>Short-acting codeine</td>
<td></td>
</tr>
<tr>
<td>Short-acting hydrocodone</td>
<td></td>
</tr>
</tbody>
</table>
criteria were discussed in a previous publication by our group.20

Because of the unavailability of schedule III opioid prescription information in the CURES database before 2005, separate analyses were conducted for two periods, 1999-2004 and 2005-2007. The first quarters in 1999 and 2005 were treated as the two baseline periods. The Institutional Review Board of the University of California, Davis and the Veterans Administration Northern California Health Care System Research and Development Committee granted approvals to conduct this research.

**Dependent variable**

Based on the prescription information, the cumulative opioid amount (in milligrams of morphine equivalents) per consecutive quarter used by each patient was measured repeatedly over the 9 years. The morphine equivalents were calculated as the product of strength, quantity, and an equianalgesic conversion factor.23 We assumed the amount supplied by each prescription would last until the next prescription was written to the same patient. Thus, the opioid amount from each prescription was allocated to each quarter proportionally to the days covered by the prescription in each quarter.

**Independent variables**

Each individual’s baseline age and gender was tallied. Stratification into five age groups was performed in the manner of previous investigations.24 The categorization was 18-34, 35-44, 45-64, 65-74, and 75-100 years of age.

**Dose requirement at baseline**: Based on the average daily dose (the cumulative morphine equivalents in the baseline quarter divided by 90 days), patients’ opioid requirement at baseline was classified as follows:

1. low dose: average daily dose less than or equal to 40 mg;
2. medium dose: average daily dose greater than 40 mg but less than or equal to 100 mg;
3. high dose: average daily dose greater than 100 mg but less than or equal to 300 mg; and
4. extremely high dose: average daily dose greater than 300 mg.

The cutoff of 40 mg between the low and medium dose requirements was related to the common practice of providing a maximum of eight Vicodin™, a combination of hydrocodone 5 mg plus acetaminophen 500 g to patients with chronic pain. This proprietary weak opioid was selected as a reference opioid because of its recognition as the most commonly prescribed medicine in the United States.25 The limit on so-called weak opioids, which was 4,000 mg of acetaminophen (that also included 40 mg of an opioid), was designed to prevent toxicity from this otherwise over-the-counter analgesic.26,27 More than 40 mg/d of the hydrocodone in Vicodin™ often involved the addition of a sustained-release preparation with commensurate increases in dosing. The cutoff of 100 mg daily was selected to distinguish medium from high doses because a daily dose greater than 100 mg was associated with increased risk of overdose.28 The cutoff of 300 mg daily was used to define extremely high dose based on previous studies.29,30

**Statistical analysis**

Because repeated measures were taken from each patient and the outcome variable was continuous, a linear mixed-effects model was used to examine the association between risk factors (age, gender, and baseline dose requirement) and the rate of dose change. Data were balanced (each patient had 36 repeated measurements) with equally (quarterly) spaced time points. Initial data examination showed that the outcome variable did not have a normal distribution and did not have a linear relationship with time, so a log transformation to the outcome variable was conducted for analysis. The PROC MIXED procedure in Statistical Analysis System (SAS) was used for the regression analyses and CONTRAST statements in the procedure were used when examining the association of each factor with the outcome. All three predictors, age gender, and dose requirement at baseline, were used to model both the intercept and slope. The random effect was allowed for both the intercept and slope to take into account substantial individual variation in dose requirements at baseline and later on. The interactions between the three predictors were examined to be statistically insignificant when modeling either the intercept or the slope. Thus, these interaction terms were not included in the final mean structure model. The covariance structure autoregressive (AR (1)) for the repeated measurements and unstructured (UN) for
the random association were selected based on Akaike information criterion of the model fit. The slope parameter estimates and standard errors are presented separately for the 6-year data and 3-year data. All the analyses were conducted with SAS v9.2 (SAS Institute Inc., Cary, NC).

RESULTS

A total of 1,922 individuals who continuously received opioid therapy from 1999 to 2007 were included in this study. Treating the first quarter in 1999 as baseline, we examined patients’ rate of log-dose change for schedule II opioid use during the first 6 years. Similarly, treating the first quarter in 2005 as baseline, we examined patients’ rate of log-dose change for all opioids (schedules II and III) during the later 3 years.

Patients’ characteristics at first baseline (first quarter in 1999) are given in Table 2. The mean (SD) age of patients was 49.7 (11.1) years with a range of 19-93 years. Of these patients, 5.9 percent, 28.3 percent, 55.5 percent, 7.1 percent, and 3.2 percent were 18-34, 35-44, 45-64, 65-74, and 75-100 years old, respectively. Approximately 60 percent were females. The baseline mean daily dose of these patients (first quarter in 1999) showed large variation with a mean (SD) of 153.7 (215.3) mg. About 31.7 percent had low dose requirement, 24.2 percent had medium dose requirement, 29.8 percent had high dose requirement, and 14.5 percent had extremely high dose requirement. The mean (SD) daily dose of schedule II opioids in the last quarter of the 2004 was 237.9 (317.5) mg.

The slope parameter estimates with the 6-year data are given in Table 3. The multivariable analyses showed that baseline age and dose requirement were statistically significantly associated with the rate of schedule II opioid dose change (p = 0.0207 and < 0.0001, respectively). Compared to the rate of log-dose increase among patients aged 75-100 years, patients in the age of 18-34, 35-44, 45-64, and 65-74 years had 3.1 percent, 3.2 percent, 2.0 percent, and 2.2 percent higher rates, respectively, per successive quarter when adjusting for gender and baseline dose requirement. Moreover, on average, females had a 0.6 percent lower rate of log-dose increase than males per successive quarter after adjusting for baseline age and dose requirement, although this difference did not achieve significance. Compared to the rate of log-dose increase among patients in the low dose requirement group, patients in the medium, high, and extremely high dose requirement groups at baseline had 3.9 percent, 6.0 percent, and 7.7 percent lower rates, respectively, for each successive quarter after adjusting for baseline age and gender.

Patients’ characteristics at second baseline (first quarter in 2005) are given in Table 4. The mean (SD) age of patients was 55.7 (11.1) years. Of these patients, 1.5 percent, 11.9 percent, 67.6 percent, 11.9 percent, and 7.1 percent were 18-34, 35-44, 45-64, 65-74, and 75-100 years old, respectively. The baseline mean daily dose among these patients after being on opioid therapy for 6 years showed large variation as before (mean ± SD: 260.7 ± 345.5 mg). About 19.8 percent had a low dose requirement, 18.3 percent had a medium dose requirement, 33.2 percent had a high dose requirement, and 28.7 percent had an extremely high dose requirement. The mean (SD) quarterly cumulative opioid dose at the end of the study was 259.8 (329.3) mg.

The slope parameter estimates with the 3-year data are given in Table 5. The multivariable analyses
showed that all three factors, baseline age, gender, and baseline dose requirement, were statistically significantly associated with the rate of opioid dose change (p < 0.0001, p = 0.0131, and p < 0.0001, respectively). Compared to the rate of log-dose increase among patients aged 75-100 years, patients in the age of 18-34, 35-44, 45-64, and 65-74 years had 5.8 percent, 5.2 percent, 4.9 percent, and 2.9 percent, respectively, higher rates per successive quarter after adjusting for gender and baseline dose requirement. There were no significant differences between the age groups below 75 years. Gender also had a small association with the rate of dose change. On average, females had a 1.2 percent lower rate of log-dose increase than males per successive quarter after adjusting for age and baseline dose requirement. The baseline dose requirement was also statistically significantly associated with the rate of dose change. Compared to the rate of log-dose increase among patients in the low dose requirement group, patients who were in medium, high, and extremely high dose requirement groups had 6.9 percent, 8.5 percent, and 11.3 percent lower rates, respectively, for each successive quarter after adjusting for baseline age and gender.

**DISCUSSION**

Focusing on a group of patients with chronic pain who continuously used opioids for 9 years, this study examined the association of risk factors (age, gender, and early dose requirement) with the rate of longitudinal dose changes. Because of the unavailability of schedule III opioid prescription information in the
CURES database before 2005, the analyses were conducted separately in two periods, 1999-2004 and 2005-2007. Interestingly, the 6-year data generated very similar conclusions as those obtained from the 3-year data, although overall the examined factors showed smaller associations in the 6-year data due to the absence of schedule III opioid dose information. Specifically, both data sets found a statistically significant association between age and the rate with younger patients having a higher rate of dose escalation than older patients. Moreover, both showed that females had a lower rate of dose escalation than males, although the result did not achieve statistical significance in the 6-year data. Additionally, both found a statistically significant association between earlier dose requirement and subsequent rate of change in opioid dose: the higher the dose requirement a patient had at baseline, the lower the rate of dose escalation the patient had in later years.

The finding of an association between age and the rate of dose change is consistent with several previous studies. In 2002, Dominguez et al. investigated 86 patients with chronic noncancer pain who were offered continuous intrathecal opioid infusion after showing good response to a preimplantation trial. They noticed that patients of age below 65 years had a higher dose requirement and a higher rate of dose escalation than older patients over the entire observation time.18 Hayek et al. followed 135 patients who were on long-term intrathecal opioid therapy for 12 months with oral opioid supplement offered simultaneously. Notably, patients of age below 50 years had their baseline intrathecal dose increased by 402 ± 267 percent by the third month, 679 ± 381 percent by the sixth month, and 750 ± 450 percent by the twelfth month; patients of age more than 50 years had a more tempered dose escalation with baseline dose increased by 86 ± 31 percent by the third month, 148 ± 46 percent by the sixth month, and 195 ± 85 percent by the twelfth month (p < 0.005). The simultaneous oral supplement did not change in the younger age group but decreased significantly in older age group.16 Buntin-Mushock et al. investigated 206 patients with chronic noncancer pain on oral opioid therapy. They found that, over a 15-month period, patients of age below 50 years increased their dose an average of 27 mg of daily morphine equivalent dose per month, whereas patients of age more than 60 years increased their dose at a significantly lower rate of 12 mg of daily morphine equivalent dose per month.17 Cifuentes et al. investigated 2,868 patients with new disabling low back pain who were on opioid therapy for a period of from several days to 2 years and did not find a significant association between age and the rate of dose change.19 However, the mean age of their subjects was 40 years, much younger than that in other studies. In our study, the 3-year data with both schedule II and schedule III opioid prescription information suggested that the largest rate difference appeared between the ≥75-year-old group and younger age groups, and the rate differences among younger age groups were small. Other authors’ insignificant findings may be partially due to a relative homogeneous younger study population.

Two factors are routinely believed to be responsible for dose escalation of opioids: disease progression and tolerance development.16,17 Although dose escalation in cancer pain is mainly due to disease progression,32,33 tolerance may be the main reason of dose escalation in nonmalignant pain.16 Supportive evidence for our finding has been found in animal studies, with morphine tolerance occurring more rapidly
Although it is agreed that aging can alter most pharmacokinetic aspects of drug disposition and pharmacodynamic responses to drugs, the underlying mechanism of how aging influences the development of opioid tolerance remains elusive. Pharmacokinetic changes due to aging, such as a slowed down metabolism and a reduced drug elimination, can explain the phenomenon of lower dose requirement in elders, but they do not seem to have an impact on the rate of tolerance development as one animal study indicated. Research on pharmacodynamic mechanisms of opioids is still underway and may uncover the underlying biology of the age differences in development of opioid tolerance.

All four clinical studies mentioned earlier examined the association between gender and the rate of dose escalation, but only one study reported significant results which agreed with our findings. Dominguez et al. found that females had lower dose requirements and lower rates of dose escalation than males, and the gender difference achieved significance at the eighteenth month and the twenty-fourth month of therapy. Animal studies also indicated that morphine was more potent (showed stronger analgesic and adverse effect per dose) in male rodents than in females, and males developed tolerance at a slightly greater rate than females, although no gender difference in tolerance development was seen in two studies. Further studies on the role of gonadal hormone in pharmacokinetic and pharmacodynamic effects of opioids may explain the observed gender difference in dose escalation.

The possibility of dose escalation as a result of addictive behavior should be mentioned given the
importance of this topic in the current management of patients undergoing opioid therapy. Studies have identified a variety of variables associated with an individual’s risk for misuse, abuse or dependence including male gender,47 simultaneous use of another illicit substance or prescription drug abuse,48,49 individuals reporting severe pain,48,50 and daily opioid dose.51,52 Given this perspective, we cannot exclude the possibility of patients with one or more of these aberrant prescription drug use patterns being present in our study.

Two studies have examined the association between early dose requirements and later dose escalation, and their results contradict our findings. In Dominguez’s study, patients were classified to different opioid-response group based on their dose requirements in the intrathecal trial: ≤0.25 mg/d, 0.5 mg/d, or ≥1.0 mg/d. Those researchers found that patients who had a lower level of dose requirement in the trial had a lower rate of dose escalation in the subsequent continuous intrathecal opioid infusion.58 Cifuentes et al. also found a similar result whereby a small but significant positive correlation exists between the dose amount in patients’ first opioid prescription and the rate of dose escalation later on.59 These results suggested that patients who initially responded to opioids (such as those who had a lower dose requirement at the early stage of therapy), tended to be more sensitive to opioids, and have a slower dose escalation over time than poorer responders. The reason for observing an opposite result in our study is not clear. However, although patients in the low dose group at baseline would not have had limitations in upward dose titration, patients in high or extremely high dose groups at baseline may have more of a ceiling effect. Providers may have been reluctant to provide additional opioid and may have even thought it appropriate to decrease the dose for these patients.

This study has several limitations inasmuch as only limited individual information was available in California’s PDMP database. We did not have diagnostic information and may have included patients with cancer in our study population; it may have been advantageous to examine patients with cancer and noncancer separately or while controlling disease progression status. However, given that cancer-related pain usually appears in advanced stages and such patients may not survive long, the likelihood that we had included many patients with cancer in our study was small. In two reports on prolonged opioid therapy that lasted for 10 or more years, all patients had chronic noncancer pain problems which remained stable over years.10,11 Furthermore, disease progression need not necessarily depend on age, gender, or early dose need, so it should not meaningfully confound our results even if patients with cancer were included. We did not have schedule III prescription information in the 6-year data and did not have information on breakthrough pain therapy with hydrocodone or codeine for patients taking sustained released around-the-clock opioids. It is possible that results may have differed if the information had been collected. However, both the use of schedule III opioids or other coanalgesic therapy and the absence of such information were independent of age, gender, and early dose so should not severely affect study validity. We restricted the study population to be patients who continuously used opioids for 9 years, which may affect generalizability. Patients who accepted such long-term opioid therapy may have different characteristics from those receiving less lengthy therapy. For instance, patients tapered off of opioids may have had prescription opioid abuse or developed tolerance precluding long-term therapy with opioids. Thus, caution should be applied when extrapolating our results to other population, and future research with more detailed individual medical information is needed to corroborate our findings.

In addition to more comprehensive patient data, it would be helpful for future studies to include variables associated with practitioners. The present secondary data analysis had limited information on practitioners; only a DEA number was provided in the California PDMP database. Epidemiologists have combined data from medical examiner, prescription drug monitoring program, and opiate treatment program records.55 It is conceivable that a state medical board database containing information could be similarly used to provide information regarding age, gender, date of graduation from medical school, and medical specialty.

Despite the earlier limitations, this is the first study to examine factors associated with dose escalation in long-term opioid recipients for nearly a decade. Moreover, the CURES database allowed us to easily identify all eligible patients in California, which guaranteed a large enough sample size to detect small associations of variables. In addition, compared to most of the previous studies that cross-sectionally examined dose escalation at different follow-up time
points,\textsuperscript{16-18} the present study used a longitudinal data analysis methodology which has the advantage of taking into account the individual correlation among the repeated measures and allow a more accurate evaluation of the rate of dose escalation.

In summary, we found that age, gender, and earlier dose requirement are associated with the rate of dose change in long-term opioid therapy that lasted for a 9-year period. Patients of age more than 75 years, being female or having large dose requirement at an earlier stage of therapy, may experience a slower dose escalation or even dose decline.

**ACKNOWLEDGMENTS**

Authors gratefully acknowledge funding for this project by the Robert Wood Johnson Foundation. Database architect support was derived through Grant Number UL1 RR024146 from the National Center for Research Resources, a component of the National Institutes of Health (NIH) and NIH Roadmap for Medical Research, and its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR of NIH.

Huijun Han, MD, PhD. Graduated Doctorate Student, Graduate Group in Epidemiology, Department of Public Health Sciences, University of California, Davis, Davis, California; current address: Department of Epidemiology and Bio-statistics, Institute of Basic Medical Sciences, Peking Union Medical College/China Academy of Medical Sciences, Beijing, China.

Philip H. Kass, DVM, PhD. Professor and Chair, Department of Population Health and Reproduction, University of California, Davis, Davis, California.

Barth L. Wilsey, MD, VA Northern California Health Care System & Associate Physician, Department of Physical Medicine and Rehabilitation, UC Davis Medical Center, Sacramento, California.

Chin-Shang Li, PhD. Professor, Division of Biostatistics, Department of Public Health Sciences, University of California, Davis, Davis, California.

**REFERENCES**


