Characterizations of Long-term Oxycodone/Acetaminophen Prescriptions in Veteran Patients

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Background: Long-term management of chronic pain with opioids may be stable over time or may be complicated by problematic dose increases, drug dependencies, and toxic effects. To determine clinical contexts in which stability or problems may occur, we examined the pharmacologic and clinical correlates of long-term prescriptions of oxycodone/acetaminophen, a commonly prescribed short-acting opioid formulation.

Methods: We analyzed linked, archival outpatient pharmacy and clinical databases from the New England Veterans Integrated Service Network between January 1, 1998, and June 30, 2001. Durations, doses, and dose changes of oxycodone/acetaminophen prescriptions and concurrent use of long-acting opioids, benzodiazepines, tricyclic antidepressants, and anticonvulsants were determined.

Results: In aggregate, 2195 patients (31% with cancer diagnoses per the International Classification of Diseases, Ninth Revision, Clinical Modification) received oxycodone/acetaminophen for more than 9 months at a mean prescribed daily dose of 3.9 tablets per day (range, 0.5-13.0 tablets per day) with minimal changes in daily prescribed mean dose over time. Patients with cancer were more likely than other patients to receive concurrent long-acting opioids. For patients without cancer, a higher mean daily dose was associated with duration, older age, human immunodeficiency virus (HIV) and/or AIDS, and with prescribed benzodiazepines and long-acting opioids; concurrent benzodiazepine prescriptions were associated with anticonvulsant prescriptions and with psychogenic pain and alcohol abuse and/or dependence diagnoses.

Conclusions: In veteran patients who received long-term oxycodone/acetaminophen prescriptions, mean daily doses were typically modest and stable, likely reflecting a selection of patients with successful, long-term management. Among patients without cancer, however, associations of higher oxycodone/acetaminophen doses with benzodiazepine prescriptions, psychogenic pain, alcohol abuse, and HIV/AIDS may portend opioid prescription management problems.

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The long-term use of opioids for the treatment of chronic pain of nonmalignant origin has been generally supported by specialists in pain management as a less than ideal but often necessary and humane course of treatment.1-4 The main theses presented are quite consistent, specifically that patients without cancer deserve maximum treatment for chronic pain, that fears of consequential clinical dependencies are generally not warranted, and that management problems and liability risks can be reduced by following established published guidelines (eg, from the American Academy of Pain Medicine and American Pain Society [1996]3 and the Federation of State Medical Boards of the United States Inc [1998]5). Furthermore, high-risk patients for opioid prescriptions may already have overt substance abuse, psychopathologic conditions, multiple and ill-defined complaints, and drug-seeking behaviors that alert physicians either to not prescribe these drugs or to do so within very strict guidelines. However, other authors, typically from an addiction medicine perspective, have cited the medical, psychological, and social difficulties inherent in long-term opioid prescribing.7-10 Furthermore, the risk of drug diversion for “street” use may concern practitioners because nonmedicinal use of opioids has increased substantially among street-drug abusers.11 Hence, long-term prescribing of opioid drugs for the management of chronic, nonmalignant pain may seem necessary but typically remains worrisome for physicians who...
either start or are obliged to continue this course of treatment.

The goal of our study was to analyze the long-term use of opioid prescriptions within a large veteran patient population. We have used the archival pharmacy database of the Veterans Integrated Service Network for the New England region (VISN 1) to analyze patterns of dispensed opioid prescriptions to determine doses and duration of use and key clinical and pharmacologic correlates of these prescription patterns. Our analysis focused on long-term prescriptions for the most commonly used opioid formulation, oxycodone (5 mg)/acetaminophen (325 mg), an agent used for both acute and chronic pain. A key focus of our analyses was to compare prescription patterns and correlates for patients with and without cancer diagnoses. We sought to determine whether and to what extent patients without cancer receiving long-term oxycodone/acetaminophen treatment showed characteristics in prescription patterns and clinical correlates indicative of potentially high-risk opioid prescribing.

PHARMACY AND ADMINISTRATIVE DATABASES

At the time of the analysis, there were 8 distinct Veterans Affairs (VA) health care sites and affiliated clinics in VISN 1, which included the 6 New England states: Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont. The VISN 1 pharmacy files were obtained from Information Resource Management, Boston, Mass, and cleaned via an established, standard process. The data elements of the outpatient pharmacy prescription files include patient identification, date of birth, drug name and dose, administration route, quantity, cost, VA drug class, internal drug identification No., date of original prescription, days' supply, refill date(s), number of refills remaining, discontinuation date, provider identification, and VA site number. The files are checked quarterly for validity and consistency. Comorbidities reported for these patients between January 1, 1997, and June 30, 2001, were captured by accessing the VA administrative databases (Patient Treatment File and Outpatient Care File) located at the Austin Automation Center, Austin, Tex.

The databases used in this study were stored on a secure server housed in the Massachusetts Veterans Epidemiology and Research Information Center at the VA Boston Healthcare System. Periodic magnetic tape backups of these databases are locked in a secured fireproof safe. Access to the server is doubly password protected. Use of these databases is confined to a limited number of investigators and programmers who sign a confidentiality and usage agreement, which details the responsibilities for safety and security of the files. All patient information has been kept confidential; no patient-level information is contained in the present report; and all information for this publication is presented as aggregate data. No provider information was recorded or analyzed for this report. The institutional review board of the VA Boston Healthcare System approved use of the VISN 1 pharmacy database and the VA administrative databases for this study.

PRESCRIPTION VARIABLES

Pharmacy data were analyzed for the 42-month period from January 1, 1998, through June 30, 2001. For all opioids, prescriptions were expressed only by the number of fills (initial prescription and refills). For oxycodone/acetaminophen, there was only 1 formulation available (oxycodone [5 mg] acetaminophen [325 mg]), so the number of tablets prescribed accurately reflects the total dose. Mean daily dose was determined by the number of pills prescribed over the number of days of the prescription. Total number of months of dispensed oxycodone/acetaminophen was determined by adding up the number of 30-day prescriptions and prescriptions of shorter duration and was expressed as total months dispensed within the 42-month window of observation. The mean interval between prescriptions for each patient was the mean number of days between the end date of the previous prescription (determined by the actual days' supply noted in the prescription record) and the dispense date of the next prescription. Long-term oxycodone/acetaminophen users were defined as patients within the 90th to 100th percentiles of months used, in this cohort ranging from just over 9 months to 42 months. Because of the limits imposed by the 42-month window in which prescriptions were analyzed, the durations of oxycodone/acetaminophen prescriptions reported for the sample is an understimation.

Changes in prescribed daily dose over time for the long-term oxycodone/acetaminophen users were determined by linear regressions of dose by month for each individual over the course of treatment. Concurrent prescriptions of long-acting opioids, benzodiazepines, tricyclic antidepressants, or anticonvulsants were defined for the long-term oxycodone/acetaminophen users as, at a minimum, 3 prescriptions of oxycodone/acetaminophen and 3 prescriptions for 1 of the other 3 types of drugs within the same 120-day period.

CLINICAL VARIABLES

The age recorded for each patient was that achieved by March 1, 1998, using the date of birth listed in the pharmacy database. Approximately 95% of the subjects were men. For each subject, the presence or absence of each of the following clinical diagnoses was determined from the Patient Treatment File and Outpatient Care File: nonskin malignancies (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 140-165, 170-176, 179-208, and 235-239); psychogenic pain, site unspecified (ICD-9-CM code 307.8); specified pain syndromes within neuropathic pain (ICD-9-CM codes 053.12 and 053.13, 337.0-337.29, and 356-357); rheumatologic/orthopedic disorders (ICD-9-CM codes 712-739); chronic headache diagnoses (ICD-9-CM codes 207.81 and 346); alcohol dependence and abuse syndromes (ICD-9-CM code 305); drug dependence and abuse syndromes (ICD-9-CM codes 304 and 305.2-305.9); and human immunodeficiency virus (HIV) syndromes (ICD-9-CM code 042).

DATA ANALYSIS

Means and standard deviations as well as frequencies and proportions were used to describe the sample. Linear regressions were used to calculate the slope for the dose variation over time for each subject. Multivariate linear regression was used for testing for an association between clinical variables and mean daily oxycodone/acetaminophen dose. Multivariate logistic regression was used for testing for an association between clinical variables and concomitant benzodiazepine use. All trend tests were performed using a Mantel-Haenszel test for trend on SAS software, version 8 (SAS Institute Inc, Cary, NC). For significance, P≤.05 was used.

RESULTS

During the 42-month study period at the 8 VISN 1 medical centers and their affiliated clinics, 47,302 patients re-
ceived 177,840 prescriptions (initial and renewals) for short-acting opioid formulations, and 69,366 patients received 53,083 prescriptions for long-acting opioids (Table 1). Individual patients were counted more than once if they received prescriptions for different short- or long-acting opioid formulations during this period; thus, these data represent “treatment episodes” with a particular opioid. Prescriptions for oxycodone/acetaminophen account for 58% of the short-acting agents and 46% of the “treatment episodes” analyzed. Excluding prescriptions for mild opioids (codeine, acetaminophen/codeine, acetaminophen/hydrocodone, and naloxone/pentazocine), oxycodone/acetaminophen accounted for over 80% of the number of prescriptions and treatment episodes. Considering the additional use of oxycodone and oxycodone controlled release, it is clear that oxycodone in its various formulations was the dominant oral opioid analgesic prescribed for these veteran patients.

The percentiles for total months of dispensed oxycodone/acetaminophen and the means and ranges of daily doses within each percentile are listed in Table 2. Patients prescribed oxycodone/acetaminophen for only half a month or less received the highest mean daily doses (5.2-7.1 tablets per day), consistent with treatment of acute pain. With longer treatment episodes, mean daily doses increased modestly from 3.4 to 4.1 tablets per day, but the ranges in daily prescribed doses were wide. Most of the 2195 long-term users in the sample, those in the highest 10% of months dispensed, tended to receive these prescriptions continuously rather than intermittently: 25% had a mean interval between prescription refills of 0.2 days; 50% had a mean interval of only 4 days; and 75% had a mean interval of 15.6 days.

Of the 2192 patients designated as long-term users, 1324 (60.3%) filled prescriptions during either the first month (January 1998), last month (June 2001), or both the first and last months of the observation window. These patients most likely had contiguous previous or subsequent oxycodone/acetaminophen prescriptions. The median number of months of use within the 42-month window was 27.3 months for these 1324 patients compared with 15.8 months in the remaining 871 patients, a further indication of genuine long-term oxycodone/acetaminophen use within the cohort of long-term users.

Among the 2195 long-term oxycodone/acetaminophen users, 686 (31.3%) had ICD-9-CM diagnoses of non-skin malignancies, and 1506 (68.7%) of these patients did not. Mean ± SD ages were 60.0 ± 11.9 years for the patients with cancer and 52.8 ± 12.3 years for the patients without. Those with ICD-9-CM diagnoses for non-skin malignancies were equally distributed within short-term (<1.2 months), intermediate-term (>1.2-9 months), and long-term (>9 months) oxycodone/acetaminophen users (Table 3). Conversely, for all other chronic pain syndromes, alcohol and drug abuse/dependence diagnoses, and HIV/AIDS cases, there was a statistically significant trend for long-term oxycodone/acetaminophen use.

### Table 1. Dispensed Opioid Prescriptions, January 1998 Through June 2001*

<table>
<thead>
<tr>
<th>Opioids</th>
<th>Fills</th>
<th>Patients</th>
<th>Mean No. of Fills per Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen/codeine</td>
<td>37,757</td>
<td>14,842</td>
<td>2.54</td>
</tr>
<tr>
<td>Acetaminophen/hydrocodone</td>
<td>13,632</td>
<td>4,789</td>
<td>2.85</td>
</tr>
<tr>
<td>Oxycodone/acetaminophen</td>
<td>103,288</td>
<td>22,125</td>
<td>4.67</td>
</tr>
<tr>
<td>Codeine</td>
<td>3,190</td>
<td>1,315</td>
<td>2.43</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>841</td>
<td>269</td>
<td>3.13</td>
</tr>
<tr>
<td>Meperidine</td>
<td>1,352</td>
<td>304</td>
<td>4.45</td>
</tr>
<tr>
<td>Morphine</td>
<td>6,082</td>
<td>1,287</td>
<td>4.73</td>
</tr>
<tr>
<td>Naloxone/pentazocine</td>
<td>445</td>
<td>44</td>
<td>10.11</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>11,253</td>
<td>2,327</td>
<td>4.84</td>
</tr>
<tr>
<td>Total</td>
<td>177,840</td>
<td>47,302</td>
<td>3.76</td>
</tr>
<tr>
<td>Long-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine, slow release</td>
<td>18,488</td>
<td>2178</td>
<td>8.49</td>
</tr>
<tr>
<td>Oxycodone, controlled release</td>
<td>20,801</td>
<td>2,918</td>
<td>7.13</td>
</tr>
<tr>
<td>Transdermal fentanyl</td>
<td>9,388</td>
<td>1,383</td>
<td>6.79</td>
</tr>
<tr>
<td>Methadone tablets</td>
<td>4,406</td>
<td>457</td>
<td>9.64</td>
</tr>
<tr>
<td>Total</td>
<td>53,083</td>
<td>69,366</td>
<td>7.65</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are numbers (percentages).

### Table 2. Mean Prescribed Daily Doses of Oxycodone/Acetaminophen by Total Months of Prescriptions

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Treatment Episode Duration, mo*</th>
<th>No. ofPatient Treatment Episodes</th>
<th>Mean (Range) Prescribed Daily Dose, Tablets†</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.033-0.100</td>
<td>2785</td>
<td>7.14 (0.33-30)</td>
</tr>
<tr>
<td>25</td>
<td>0.101-0.167</td>
<td>3342</td>
<td>6.49 (1.00-15)</td>
</tr>
<tr>
<td>50</td>
<td>0.168-0.533</td>
<td>4960</td>
<td>5.20 (0.07-14)</td>
</tr>
<tr>
<td>75</td>
<td>0.334-1.97</td>
<td>5491</td>
<td>3.39 (0.07-13)</td>
</tr>
<tr>
<td>90</td>
<td>1.98-9.00</td>
<td>3352</td>
<td>3.48 (0.07-16)</td>
</tr>
<tr>
<td>92.5</td>
<td>9.01-13.9</td>
<td>537</td>
<td>3.71 (0.69-13)</td>
</tr>
<tr>
<td>95</td>
<td>13.9-21.8</td>
<td>552</td>
<td>3.86 (0.49-12)</td>
</tr>
<tr>
<td>97.5</td>
<td>21.8-31.1</td>
<td>553</td>
<td>4.07 (0.74-10)</td>
</tr>
<tr>
<td>99</td>
<td>31.1-40.7</td>
<td>332</td>
<td>4.08 (0.52-12)</td>
</tr>
</tbody>
</table>

†Tablets of oxycodone (5 mg)/acetaminophen (325 mg).
For long-term oxycodone/acetaminophen users, changes in prescribed daily doses over time were determined for each patient by linear regression of dose by month for patients with and without cancer diagnoses; the median slopes of these curves showed no mean dose increase over time and were essentially the same for those with cancer (0.000; range, −0.502 to 1.170) and those without (0.002; range, −0.739 to 0.601) (Wilcoxon rank-sum test $P = .19$).

Patients with cancer diagnoses were more likely to be concurrently prescribed long-acting opioids with oxycodone/acetaminophen, specifically sustained-release morphine or transdermal fentanyl, but controlled-release oxycodone was the long-acting opioid used most commonly and equally for those with and without cancer diagnoses (Table 4). Benzodiazepines were prescribed concomitantly for about 40% of patients with or without cancer, and tricyclic antidepressants and anticonvulsants (classes of drugs often recommended in chronic pain management) were prescribed in about 20% of both groups.

The proportion of patients with concurrent prescriptions for benzodiazepines increased with the daily prescribed doses of oxycodone/acetaminophen (Figure). This association was particularly strong for the patients without cancer where concurrent prescriptions for benzodiazepines increased from 34.5% for patients prescribed fewer than 3 oxycodone/acetaminophen tablets daily to 54.6% for those prescribed more than 9 tablets per day. (Mantel-Haenszel $\chi^2 = 18.205$, $P < .001$).

Variables that predict the mean daily dose of oxycodone/acetaminophen and concomitant use of benzodiazepines were determined by linear and logistic regressions for the long-term oxycodone/acetaminophen users (Table 5 and Table 6). For patients with cancer, a higher mean daily dose of oxycodone/acetaminophen was associated only with concurrent long-acting opioid prescriptions ($P < .001$); for patients without cancer, higher mean daily oxycodone/acetaminophen doses were associated with duration of oxycodone/acetaminophen use ($P < .001$), older age ($P = .05$), HIV/AIDS diagnosis ($P = .04$), and concomitant use of benzodiazepines ($P < .001$) and long-acting opioids ($P = .003$) (Table 5). For patients with cancer, concurrent benzodiazepine prescriptions were associated with total months of prescribed oxycodone/acetaminophen prescribed ($P = .004$) and the concomitant use of anticonvulsants ($P = .003$); for patients without cancer, concomitant use of benzodiazepines was associated with total months of prescribed oxycodone/acetaminophen ($P = .001$) and mean daily prescribed dose ($P < .001$) as well as with concomitant use of anticonvulsants ($P < .001$) and the diagnoses of psychogenic chronic pain ($P = .03$) and alcohol abuse/dependence ($P < .001$).

Table 3. International Classification of Diseases, Ninth Revision, Clinical Modification Diagnoses Among Oxycodone/Acetaminophen Users by Total Months of Prescriptions*

<table>
<thead>
<tr>
<th>Cancer Diagnosis</th>
<th>Oxycodone Continual Release</th>
<th>Morphine Sustained Release</th>
<th>Transdermal Fentanyl</th>
<th>Any Long-Acting Opioid</th>
<th>Benzodiazepines</th>
<th>Antidepressants</th>
<th>Anticonvulsants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (n = 686)</td>
<td>19.24</td>
<td>13.12</td>
<td>7.43</td>
<td>34.69</td>
<td>42.42</td>
<td>20.12</td>
<td>22.89</td>
</tr>
<tr>
<td>No (n = 1506)</td>
<td>16.73</td>
<td>8.17</td>
<td>5.31</td>
<td>27.49</td>
<td>42.42</td>
<td>20.12</td>
<td>22.89</td>
</tr>
<tr>
<td>$P$ value</td>
<td>.15</td>
<td>&lt;.001</td>
<td>.05</td>
<td>&lt;.001</td>
<td>.52</td>
<td>.25</td>
<td>.86</td>
</tr>
</tbody>
</table>

*At least 3 fills of both oxycodone/acetaminophen and the designated medication within any 129-day period within a treatment episode.
†Unless otherwise indicated, data are percentages of patients.
the commonly used short-acting opioid formulation oxy-
codone/acetaminophen and some key clinical correlates for
patients with and without cancer diagnoses. Among the
2195 long-term users (ie, patients who received oxy-
codone/acetaminophen prescriptions for more than 9
months within the 42-month period of analysis), we found
generally modest doses and stability of dosing over time.
It is likely that these results reflect, in part, a selection of
patients who over a prolonged period had been treated
successfully with long-term opioids. We also found sta-
tistical associations among patients without cancer that
suggest potentially high-risk prescribing situations, spe-
cifically, higher mean oxycodone/acetaminophen daily
doses were associated with concurrent benzodiazepine
prescriptions and H1N1 diagnoses. Additionally, concurrent
benzodiazepine prescriptions were associated with higher
daily oxycodone/acetaminophen doses and with alcoholism
and psychogenic chronic pain diagnoses. Be-
cause we have not further explored the clinical courses
of these potentially higher-risk patients, we can only
speculate on the significance of these associations.

Since the actual duration of opioid prescriptions ex-
ceeded that recorded for about 60% of the long-term oxy-
codone/acetaminophen users, we are confident that as a
group they are readily distinct from 75% of the entire co-
hort who received this agent for 2 months or less,
prematurely for the treatment of acute pain. Our analyses may
have missed substantial increases or decreases in oxy-
codone/acetaminophen doses as well as use of concurrent
psychotropic medications that may have occurred with
these long-term users outside of the 42-month ob-
servation window. As well, this analysis of only long-
term users did not include patients who had opioid treat-
ment discontinued after only short periods because of
management difficulties that might have included pre-
scription drug misuse. Thus, our findings indicating gen-
eral dose stability over time are tempered by the time lim-
its imposed by our database.

In using ICD-9-CM diagnoses from the Veterans Health
Administration Patient Treatment File and Outpatient
Care File, we did not determine the types of nonskin can-
cer diagnoses, nor did our analysis determine if those pa-
tients with cancer received oxycodone/acetaminophen for
cancer pain or for benign conditions. Use of administra-
tive files to ascertain diagnoses is known to have a posi-
tive predictive value ranging from 60% to 90%, depend-
ing on specific diagnoses. Misclassification may occur
for a number of reasons, including that some of the pa-
ients classified as having cancer actually had ICD-
9-CM diagnoses of “history of” or “rule out” cancer. Our
data show that the patients with cancer had an age dis-
tribution and patterns and correlates of oxycodone/
acetaminophen prescribing different from those with-
out cancer, so we are confident that these 2 clinical groups
are reasonably distinct. For patients without cancer di-
gnoses, many had multiple diagnoses associated with
chronic pain, and we did not determine for which diag-
noses they were prescribed opioids.
have demonstrated supports previous observations from may reduce the generalizability of our long-term data. Available in private medical care settings, and this fact monitoring and integrated specialty services may not be readily capable of determining if prescriptions have been filled at concurrent. Acetaminophen doses when these prescriptions were azepine use in our sample and the higher oxycodone/ the high proportion of concurrent opioid and benzodi- logical conditions predicted prescribed opiate abuse.10

Studies of patients without cancer indicate that while pain may be reasonably controlled, long-term social and occupational functioning may not be substantially improved, and operant pain behaviors and drug-seeking behaviors may persist. Concurrent use of benzodiazepines and oxycodone/acetaminophen in 40% of our sample raises concerns of polydrug abuse, dependencies, and/or toxic effects. Whether the issues are polysubstance dependencies or toxic effects among this group of patients, we would view with some concern the high proportion of concurrent opioid and benzodi- azepine use in our sample and the higher oxycodone/ acetaminophen doses when these prescriptions were concurrent.

All VA pharmacies in VISN 1 have the electronic capability to determine if prescriptions have been filled at other VA facilities. Additionally, most sites have policies that require single providers and fixed intervals between opioid prescriptions or that oblige patients to be assessed in a pain management clinic. Such close monitoring and integrated specialty services may not be readily available in private medical care settings, and this fact may reduce the generalizability of our long-term data. However, the apparent long-term dose stability that we have demonstrated supports previous observations from both VA and non-VA settings. Future studies on the ongoing health status, psychosocial functioning, and prescription use of these seemingly stable patients and of those with potentially high-risk prescription characteristics may be useful in providing guidance to physicians in prescribing opioid analgesics to patients with chronic pain.

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REFERENCES