Trends in Medical Use and Abuse of Sustained-Release Opioid Analgesics: A Revisit

Suzanne Novak, MD,* William C. Nemeth, MD,† and Kenneth A. Lawson, PhD*

*Pharmacy Administration Division, College of Pharmacy, The University of Texas at Austin, Austin, Texas; †Texas Worker’s Compensation Commission, Austin, Texas

ABSTRACT

Objective. Previous literature suggests that increases in the medical use of opioids over the early 1990s did not contribute to increased morbidity secondary to opioid abuse. Our objective was to evaluate the period 1997–2001 to analyze trends in medical use and medical abuse of three classes of opioid analgesics that are commonly used in sustained-release formulations: fentanyl, morphine, and oxycodone.

Design and Setting. A retrospective analysis of the Drug Abuse Warning Network (DAWN) database and the Automation of Reports and Consolidated Orders System (ARCOS) database for the years 1997–2001 was used for this study.

Results. The analysis of the DAWN database showed that there was an 83.5% increase in all opioid analgesic mentions from 1997 to 2001. Mentions involving any fentanyl compound increased 249.8%, any morphine compound increased 161.8%, and any oxycodone-containing compound increased 267.3%. Mentions of each of these three classes of opioids remained less than 2% of all total drug mentions per year for each year studied. Medical use of the selected opioid classes, as reported in the ARCOS database and measured by grams distributed, all increased substantially (fentanyl 151.2%, morphine 48.8%, oxycodone 347.9%).

Conclusion. Using this method of analysis, the rates of drug abuse, and resultant morbidity secondary to the use of opioid analgesics, remain low in spite of the increase in medical use of these substances.

Key Words. Opioid Analgesics; Therapeutic Use; Substance Abuse; Oxycodone; Fentanyl; Morphine

Introduction

The adequate treatment of chronic pain remains a major public health concern. It has been suggested that 40–80% of patients with cancer pain experience inadequate pain management [1]. This statistic is bothersome when one considers that current pain medicine specialists suggest that as many as 90% of patients with cancer pain may be effectively treated with present pharmacological therapies [2]. Chronic nonmalignant pain also continues as a significant problem throughout the industrialized world, with a reported prevalence of 10–55%, depending on the definition used to characterize this disorder [3].

The treatment of chronic pain is complicated by evidence that nonmedical use and abuse of prescription opioids are rising in the United States. The National Survey on Drug Use and Health, which was formally called the National Household Survey on Drug Abuse (NHSDA), reported that 2 million people in the United States aged 12 and older used a prescription opioid for nonmedical use for the first time in the year 2000 [4,5]. This number was approximately four times the value.

Reprint requests to: Suzanne Novak, M.D., College of Pharmacy, The University of Texas at Austin, PHAR-Pharmacy Admin, 1 University Station A1930, Austin, TX 78712-0127. Tel: (512) 471-6892; Fax: (512) 471-8762; E-mail: snovak@mail.utexas.edu.
reported per year in the mid 1980s. The NHSDA also reported that survey questions pertaining to prescription opioid dependence yielded data that indicated a significant increase \((P < 0.05)\) from 443,000 persons meeting the criteria for this disorder in 2000 to 656,000 in 2001 [4,5].

In April 2000, Joranson et al. analyzed the trends of use and potential drug abuse of five major classes of opioid analgesics—morphine, fentanyl, oxycodone, hydromorphone, and meperidine [6]. The methodology they employed was a comparison of mentions of each class of opioid, using the Drug Abuse Warning Network (DAWN) database, to the trends of cumulative distribution of grams of these opioid classes, using the U.S. Drug Enforcement Administration’s Automation of Reports and Consolidated Orders System (ARCOS) database, over a period from 1990–1996. Those authors’ results included the finding that, as measured by the DAWN system, opioid analgesics were responsible for a small proportion of emergency department (ED) visits due to drug abuse during the period studied. The proportion of mentions of opioid abuse relative to the total number of reports of drug abuse actually decreased from 5.1% to 3.8% over the 7-year period, and all of the classes of opioids studied had a decline in mentions in the DAWN database except for morphine, which increased by 3.2%. The mentions of all five classes of drugs compared with the total mentions were less than 1% for each year studied. These findings all occurred as the trends in medical use of four of the five classes of opioids in both total distribution and grams, adjusted per population, increased (meperidine showed a decrease). The authors concluded that “the trend of increasing medical use of opioids to treat pain does not appear to contribute to increases in the health consequences of opioid analgesic abuse” [6].

Can today’s health care provider continue to draw this same conclusion, or has newer data revealed other trends of special importance in opioid prescriptive patterns? This is of special concern to generalists, who see the vast majority of the aging population that is experiencing chronic pain. The aim of this study is to conduct an analysis similar to that done by Joranson et al. to provide a more recent comparison of trends of medical use and possible abuse of opioid analgesics.

Methods

Given that there has been an increased availability of sustained-release opioids to treat severe pain during the period since the previous study (1990–1996), the decision was made to evaluate the three major classes of these compounds—oxycodone, morphine, and fentanyl—currently used by generalists to treat chronic pain.

The DAWN database was used as the source for trends in drug abuse. This data source, which is sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA) of the U.S. Department of Health and Human Services, is described in detail in the original Joranson et al. article [6]. All statistical information involving the incidence of drug abuse used for this analysis was obtained using the SAMHSA website [7].

DAWN traces drug-related ED episodes through retrospective examination of medical records. It is not a measure of prevalence of drug use in a population [8]. It may be more accurate to describe it as a measure of drug-related morbidity and mortality [9]. The 2001 DAWN report describes itself as a probability sample of hospitals designed to produce representative estimates of ED drug episodes and drug mentions for the coterminous United States and 21 metropolitan areas [8].

Drug episodes include ED visits that are induced by or related to the use of illegal drugs or the nonmedical use of legal drugs in patients aged 6–97 years. Drug mentions refer to drugs mentioned per episode. There may be up to four drugs mentioned per episode, with an average of 1.8 drugs mentioned per episode in 2001. Multidrug episodes were reported 56.2% of the time during that year. Drugs reported are divided into two major categories. “Major substances of abuse” includes the most common illicit drugs reported to DAWN (cocaine, marijuana, and heroin) and alcohol reported in combination with other substances. (Alcohol is not recorded unless it is used in combination with another substance.) “Other substances of abuse” includes generic classifications of drugs that are prescription or over-the-counter preparations. The three categories of drugs studied fall into this category. Substances referred to as narcotic analgesics in DAWN publications have been renamed opioid analgesics for this analysis. It is extremely important to note that DAWN publications acknowledge that estimates from the database may not be used to make direct estimates of drugs marketed under trade names, so all conclusions made from estimates are at best, trends of classes of substances mentioned.

Examples of the types of drug episodes reported include drug-induced suicide attempts, nonlethal drug overdoses, withdrawal episodes requiring
ED attention, or undesired drug reactions [10]. DAWN data are attractive to researchers because the nonmedical use of legal drugs is included in the database. Unfortunately, information as to whether the drug was obtained by a legal prescription method, or by drug diversion, is not included. Information regarding how the drug was ingested is also not included.

Data from the U.S. Drug Enforcement Administration’s ARCOS database were again used to analyze trends in the medical use of opioids. Manufacturers and distributors of Schedule I, II, and III narcotic materials, and selected Schedule III and IV psychotropic drugs, are required to report commercial distribution to hospitals, retail pharmacies, practitioners, midlevel practitioners, and teaching institutions under this system [11]. The data are intended for use in identifying the diversion of controlled substances. All information used for this analysis involving the medical use of opioids was obtained from the U.S. Department of Justice, Drug Enforcement Administration’s ARCOS retail drug summary website [12]. Information used for this analysis includes reports of the three drug compounds in grams distributed and grams per 100,000 population. It is important to note that information was not provided on this website for compounds containing fentanyl or morphine for the year 2000.

To aid in the interpretation of the ARCOS data, grams per 100,000 population values were also adjusted for equivalency, with morphine as the reference standard. For example, with respect to potency, 30 mg of sustained-release morphine is equivalent to 20 mg of controlled-release oxycodone, or a 25-μg transdermal fentanyl patch [13,14]. For our analysis requiring equivalency conversion, grams of opioid substance distributed per 100,000 population was adjusted by a conversion factor. Oxycodone grams per 100,000 population were multiplied by a factor of 1.5 and fentanyl grams per 100,000 population were multiplied by a factor of 100. The fentanyl conversion factor was calculated by first using the fact that a 25-μg/hour fentanyl patch delivers 1,800 μg of drug over a 72-hour period. This is an equivalent dose of approximately 30 mg sustained-release morphine every 12 hours, or 180 mg in 72 hours (the standard dosing period of a fentanyl patch).

Results

DAWN ED mentions and percentages of DAWN ED mentions to total drug abuse mentions for major classes of drug substances for the years 1997 and 2001 are listed in Table 1. There were 1,165,367 drug mentions in the DAWN database in 2001. Opioid analgesics were mentioned 99,317 times (8.5% of total mentions). To allow for further comparison, Table 1 includes the percentage increase of these substances over the time range of study (1997–2001). Total drug mentions increased by 23.7%. Total opioid mentions increased by 83.5%, which is a larger percentage increase than for the three major substances of abuse (cocaine 19.8%, marijuana 70.8%, and heroin 31.6%).

<table>
<thead>
<tr>
<th>Substances mentioned</th>
<th>1997</th>
<th>Percentage of total mentions</th>
<th>2001</th>
<th>Percentage of total mentions</th>
<th>Percentage change from 1997 to 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major substances of abuse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>161,083</td>
<td>17.09%</td>
<td>193,034</td>
<td>16.56%</td>
<td>19.84%</td>
</tr>
<tr>
<td>Marijuana</td>
<td>64,720</td>
<td>6.87%</td>
<td>110,512</td>
<td>9.48%</td>
<td>70.75%</td>
</tr>
<tr>
<td>Heroin</td>
<td>70,712</td>
<td>7.50%</td>
<td>93,064</td>
<td>7.99%</td>
<td>31.61%</td>
</tr>
<tr>
<td>Alcohol-in-combination</td>
<td>171,963</td>
<td>18.25%</td>
<td>218,005</td>
<td>18.71%</td>
<td>26.77%</td>
</tr>
<tr>
<td>All other mentions of major substances of abuse*</td>
<td>42,560</td>
<td>4.52%</td>
<td>54,944</td>
<td>4.71%</td>
<td>29.10%</td>
</tr>
<tr>
<td>Other substances of abuse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid analgesics†</td>
<td>54,116</td>
<td>5.74%</td>
<td>99,317</td>
<td>8.52%</td>
<td>83.53%</td>
</tr>
<tr>
<td>All other analgesics‡</td>
<td>86,269</td>
<td>9.15%</td>
<td>75,183</td>
<td>6.45%</td>
<td>–12.85%</td>
</tr>
<tr>
<td>Other drugs§</td>
<td>290,959</td>
<td>30.87%</td>
<td>321,308</td>
<td>27.57%</td>
<td>10.43%</td>
</tr>
<tr>
<td>Total drug abuse mentions</td>
<td>942,382</td>
<td>100.00%</td>
<td>1,165,367</td>
<td>100.00%</td>
<td>23.66%</td>
</tr>
</tbody>
</table>

* Includes amphetamines, methamphetamine, hallucinogens, inhalants, and other illicit substances.
† Includes oxycodone, fentanyl, morphine, codeine, hydrocodone, methadone, and all other opioid analgesics.
‡ Includes nonsteroidal anti-inflammatory agents, salicylates, and miscellaneous analgesics.
§ Includes antidepressants, antipsychotics, sedatives/hypnotics, central nervous stimulants, and all other substances.
Table 2 gives DAWN ED mentions for the specific opioids analyzed in our study (fentanyl, morphine, and oxycodone) as raw numbers and as percentages of total mentions per year. Dawn ED data delineates mentions of the drugs analyzed in this study according to mentions of the substance alone and in combination with another drug, and this information is reflected in the table. Fentanyl and morphine single-compound mentions were essentially the same as those in combination, so those compounds were not separated. Once again, it is important to note that any estimate made by this method cannot be attributed to drugs marketed under particular brand names. For further analysis, the percent change of mentions over the 5-year time period is also included.

There were large percentage increases for the opioid classes analyzed (oxycodone 267.3%, morphine 161.8%, and fentanyl 249.8%), but all three classes of drugs continued to account for less than 2% of total mentions in 2001.

The largest percentage increase in mentions for a drug compound studied were those mentions associated with oxycodone-only compounds (2,883.9%). This is in contrast to all oxycodone mentions (single compound and in combination 267.3%), oxycodone with acetaminophen mentions (66.2%), and oxycodone with aspirin mentions (−58.5%). It is important to note that, while there was a percentage increase in the number of mentions over the time period studied, the percentage of mentions to total mentions remains low for all compounds, including those that contain oxycodone only.

Trends in the medical use of the opioids studied are listed in Table 3. The largest percentage increase is noted for oxycodone-containing compounds. It is important to remember when analyzing these data that fentanyl is approximately 100 times more potent than morphine and that fentanyl usage is currently similar on a unit-dosage basis to the other long-acting opioid compounds.

Figure 1 allows for a comparison of trends in abuse of the compounds studied. Grams per 100,000 population, as listed in Table 3, were first adjusted for equivalency, as described in Methods. Total mentions for compounds (both as single drugs and in combination with other substances), as listed in Table 2, were divided by these adjusted values. The figure shows that oxycodone-containing compounds had the greatest number of mentions per grams per 100,000 population as adjusted for equivalency for all years. There was a decrease in mentions per grams until 1999, when there was an upturn.

Table 2  DAWN mentions of study opioids, with percentage change from 1997 to 2001*

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl†</td>
<td>203 (0.02)</td>
<td>286 (0.03)</td>
<td>337 (0.03)</td>
<td>576 (0.05)</td>
<td>710 (0.06)</td>
<td>249.75</td>
</tr>
<tr>
<td>Morphine†</td>
<td>1,300 (0.14)</td>
<td>1,955 (0.20)</td>
<td>2,217 (0.22)</td>
<td>2,483 (0.23)</td>
<td>3,403 (0.29)</td>
<td>161.77</td>
</tr>
<tr>
<td>Oxycodone†</td>
<td>5,012 (0.53)</td>
<td>5,211 (0.53)</td>
<td>6,429 (0.63)</td>
<td>10,825 (0.98)</td>
<td>18,409 (1.58)</td>
<td>267.30</td>
</tr>
<tr>
<td>Oxycodone only</td>
<td>372 (0.04)</td>
<td>1,034 (0.11)</td>
<td>1,804 (0.18)</td>
<td>3,792 (0.34)</td>
<td>11,100 (0.95)</td>
<td>2,883.87</td>
</tr>
<tr>
<td>Oxycodone/acetaminophen</td>
<td>4,353 (0.46)</td>
<td>3,841 (0.39)</td>
<td>4,503 (0.44)</td>
<td>6,637 (0.60)</td>
<td>7,190 (0.62)</td>
<td>65.17</td>
</tr>
<tr>
<td>Oxycodone/aspirin</td>
<td>287 (0.03)</td>
<td>335 (0.03)</td>
<td>121 (0.01)</td>
<td>396 (0.04)</td>
<td>119 (0.01)</td>
<td>−58.54</td>
</tr>
<tr>
<td>Total drug abuse mentions</td>
<td>942,382</td>
<td>981,764</td>
<td>1,014,243</td>
<td>1,099,306</td>
<td>1,165,367</td>
<td>23.66</td>
</tr>
</tbody>
</table>

* Values are expressed as raw mentions (percentage of total mentions).
† Includes all mentions of substance alone as well as substance in combination with another drug.

Table 3  Medical use of selected opioid classes*

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>74,085</td>
<td>90,618</td>
<td>107,141</td>
<td>—†</td>
<td>186,083</td>
<td>151.18% (141.32%)</td>
</tr>
<tr>
<td></td>
<td>(27.76)</td>
<td>(33.96)</td>
<td>(38.57)</td>
<td></td>
<td>(66.99)</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>5,922,872</td>
<td>6,408,322</td>
<td>6,804,935</td>
<td>—†</td>
<td>8,810,700</td>
<td>48.76% (42.91%)</td>
</tr>
<tr>
<td></td>
<td>(2,219.66)</td>
<td>(2,401.59)</td>
<td>(2,450.02)</td>
<td></td>
<td>(3,172.17)</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>4,449,562</td>
<td>6,579,719</td>
<td>9,717,600</td>
<td>15,305,914</td>
<td>19,927,287</td>
<td>347.85% (328.51%)</td>
</tr>
<tr>
<td></td>
<td>(1,667.52)</td>
<td>(2,465.82)</td>
<td>(3,498.69)</td>
<td>(5,510.69)</td>
<td>(7,145.55)</td>
<td></td>
</tr>
</tbody>
</table>

* Values are expressed as grams (grams/100,000 population).
† Dash (—) indicates that data are unavailable for this time period.
Discussion

ARCOS data indicate that there has been a substantial increase in retail distribution of oxycodone, morphine, and fentanyl over the period 1997–2001. This, hopefully, is an indication that progress is continuing in the improvement of pain management. Since the original Joranson et al. study [6], there have been multiple national consensus statements published about the use of opioids for chronic pain, as well as task force meetings and study groups to study this issue [15].

The data analyzed in this study suggest that opioid analgesics continue to be a small part of drug abuse as measured by the DAWN system. As Joranson et al. originally noted, abuse levels, as reflected by this database, have remained low in spite of the greater availability of these substances. These data are consistent with those reported for the Treatment Episode Data Sets (TEDS) in the year 2000 [16]. Only 1.6% of admissions to treatment centers reported in that database were attributed to “opiates other than heroin.” This classification included nonprescription use of methadone, codeine, morphine, oxycodone, hydromorphone, meperidine, opium, and other drugs with morphine-like effects. In fact, the National Drug Intelligence Center has stated that, “The illegal abuse of pharmaceuticals, medicinal drugs legally available by prescription or over the counter, is the lowest threat among major drug categories” [17].

On the other hand, total opioid analgesic abuse has continued to rise as evidenced by total number of mentions (83.5%) and percentage of total mentions (from 5.7% to 8.5%, an increase of 48.4%). The large percentage increase in mentions of compounds containing oxycodone alone (2,883.9%) also cannot be ignored.

There are many limitations to a study using this methodology. Joranson et al. mentioned problems with the DAWN database itself, including the fact that the system obviously underreports the true extent of drug abuse as it only reports admissions to an ED. Caulkins et al. have also extensively critiqued the DAWN database [18]. One particular area of concern is that there are numerous factors that influence ED usage that can vary over location and time. The SAMHSA is aware of the concerns about the limitations of the DAWN system and has developed a new design that will be implemented in the field in 2003 [19].

Another concern of the DAWN system of collection is that suicide attempts are included in the total numbers of mentions [20]. As there have been a substantial number of reports of psychiatric comorbidity, and especially depression, in patients with drug abuse problems, there remains a question as to whether the use of the controlled substance is actually related to abuse or to a psychiatric disorder.

A final limitation is that we are unable to identify any specific drug by brand name using this methodology. The analyses simply allow for an overview of trends in abuse and use of classes of drugs that are available in sustained-release formulations.

There are multiple areas of further research suggested by this analysis. The effect of the extensive media focus in the lay literature on opioid use and abuse on provider prescribing patterns of these substances is an area that should be examined. This analysis should also examine the effect of the media on a patient's willingness to accept opioids for the treatment of chronic pain. The effect of Drug Enforcement Agency reactions to the potential of “escalating abuse and diversion” of prescription opioids is also an area that may provide insight into government regulatory influence on health care provider treatment regimens [21]. The reasons that opioid use has increased, and for what classes of patients, are important potential areas of research, at least in part, to measure our successes and shortcomings in pain management. Finally, there continues to be a need to design better methods of determining the actual medical use and abuse of sustained-release opioids.
prevalence of prescription drug abuse, and especially that of opioids in their use for chronic pain treatment.

**Conclusion**

How then does one address the question of whether the trend of increasing use of opioids to treat pain contributes to increases in opioid analgesic abuse and related morbidity? Prescription opioid abuse continues, as measured by the DAWN system, and this abuse is growing. This increase in prescription opioid abuse is substantiated by other epidemiologic data sources such as the NHSDA. This trend in increased opioid abuse has been accompanied by a large number of media reports that have often been sensational [22,23]. These reports have fueled physician fears about increased addiction potential as well as potential governmental investigation of prescribing practices involving controlled substances [15,24]. There is tremendous concern that these reports could potentially undo advances that have been made in improvement in chronic pain control. To avoid the possibility of this occurrence, the health care system must continue to provide education about pain control and addiction. At the same time, diversion control programs must continue to strive to improve detection of opioid abuse without interfering with their appropriate medical use.

**References**

16. Substance Abuse and Mental Health Services Administration. Treatment Episode Data Set


