

Trends in prescriptions for oxycodone and other commonly used opioids, 2000–2010, United States

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Contributor Statement

Kristen Kenan compiled data, performed data analysis, participated in developing study methodology, and was the principal writer of the manuscript. Karin Mack oversaw data collection, participated in developing the study methodology and in all phases of writing and editing the manuscript. Leonard Paulozzi conceived the project, oversaw the data collection and analysis, participated in finalizing the study methodology, participated in all phases of writing and editing the manuscript, and is the guarantor.

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Abstract (now 300; needs to be under 300 words)

Background: Little information has been published on the status of opioid analgesic prescribing in the United States for any year since 2005, despite increased use and increased overdoses. The objective of this study is to describe trends from the past decade in prescribing rates and prescription sizes for commonly used opioids.

Methods: We used two data systems. Vector One®: National (VONA, 2000–2009) is a service that can estimate the number of prescriptions dispensed by retail pharmacies. The Automation of Reports and Consolidated Orders System (ARCOS, 2000–2010) is a mandatory reporting system that allows the Drug Enforcement Administration to monitor certain controlled substances from point-of-manufacture to point-of-sale. ARCOS data represent the amount of controlled substances legitimately distributed at the retail level. We calculated crude rates of prescriptions from VONA data, milligrams per 100 persons from ARCOS data, and milligrams per prescription by combining both data sources.

Results: Roughly one-third more opioid prescriptions were dispensed in 2009 than in 2000. The distribution of opioids to US pharmacies in milligrams per 100 persons increased by at least 100% for all major opioids between 2000 and 2010. The average prescription size increased for some opioids and declined for others.

Interpretation: Results show a steady increase in the population-based rate of prescribing opioid analgesics that might have stabilized in 2009. However, the volume of opioid analgesics in grams per 100 persons more than doubled through 2010. Effective measures addressing drug overdoses have yet to be identified and employed in the United States. A good first step would be establishing timely national surveillance specific to prescription drug abuse and examining the prescription histories of persons dying of prescription drug overdoses. This review could determine the specific factors, such as high daily dosage or nonmedical use that might contribute to these deaths.

Background:

The use of opioid analgesics for pain treatment has increased, attributed in part to the liberalization of laws governing opioid prescribing for treating chronic non-cancer pain and the introduction of new pain management standards [1]. Prior to 1990, US physicians took a minimalist approach to treating chronic noncancer pain with opioid analgesics—however, currently opioids such as oxycodone and hydrocodone are prescribed to one in 25 adults for chronic pain **[2-4]**. The use of opioid analgesics is now both unprecedented in the history of the United States and unparalleled compared with other parts of the world. In 1990, the world's population consumed four tons of hydrocodone; by 2009, worldwide consumption had risen to 39 tons, most of which was consumed by Americans. Similarly, three tons of oxycodone were consumed in 1990 worldwide. By 2009, Americans alone consumed 62 tons (81%) of the world's consumption [5].

While beneficial for the treatment of pain, the increased use of opioid analgesics in the United States was also accompanied by a concerning trend in the increased non-medical use of these drugs. By 2000, investigative news reports revealed patients' inappropriate use of these pain-relieving drugs and their diversion to non-patients [6]. Fatal and nonfatal overdoses, or poisonings, due to opioid analgesics increased markedly and the death rate involving opioid analgesics closely tracks with sales of opioids analgesics [7]. Opioids analgesics are currently the source of more overdose

deaths nationwide than heroin and cocaine combined [7]. By 2009, the National Survey of Drug Use and Health showed that approximately 4.9% (12.4 million) of persons over the age of 12 years reported using prescription opioid analgesics non-medically in the past year [8]. In addition, opioid analgesics are also some of the most commonly used drugs at initiation into illicit drug abuse [9-11].

In the United States, studies using medical claims data for selected populations have shown increases in the annual prescribing rates of opioid analgesics [12, 13]. They also show a shift toward use of long-acting or extended-release opioids [4] and increasing dosages [14, 15] through 2005. A similar trend toward increasing use and dosage has been noted in Canada through 2008 [16, 17]. However, little information has been published on the status of opioid prescribing in the United States as a whole for any year since 2005. The objective of this study is to describe the trends in prescribing rates, proportion of long-acting/extended release (LA/ER) opioids prescribed, and in prescription size for oxycodone and other commonly used opioids from 2000 through 2010 in the United States. These trends will provide a background for understanding related trends in fatal and nonfatal drug overdoses.

Methods

Data Sources:

Vector One®: National (VONA)

Vector One®: National (VONA) is a national commercial prescription and patient measurement service [18]. VONA can estimate the number of prescriptions for all prescription drugs dispensed by retail pharmacies. It collects information on nearly half of the retail prescriptions in the United States from 59,000 retail pharmacies and develops national estimates from this data using a proprietary methodology. The term “retail pharmacy” includes national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups. VONA does not include drugs dispensed by hospitals, via mail order, or long term care pharmacies. Prescription counts generated by VONA have been previously published [19].

Automation of Reports and Consolidated Order Systems (ARCOS)

The Automation of Reports and Consolidated Orders System (ARCOS) is an automated, comprehensive, mandatory reporting system that allows the Drug Enforcement Administration (DEA) to monitor certain controlled substances from the point of manufacture, through commercial distribution channels, to the point of sale at the dispensing/retail level [20]. ARCOS data tallies the cumulative sale of licit drugs in grams and reflects the amount of controlled substances legitimately distributed at the retail level.

Manufacturers and distributors of bulk and/or dosage form controlled substances must report inventories, acquisitions, and dispositions in

Schedules I and II, and narcotic and Gamma-Hydroxybutyric Acid (GHB) substances in Schedule III. These analyses were restricted to drugs distributed to pharmacies to correspond to the scope of the VONA data. ARCOS data, however, also captures drug acquisitions by hospitals and practitioners. We obtained study data by special request to the DEA. Data were used from 2000–2010, although in 2000, data were only available for two opioids: oxycodone and hydrocodone.

Study Drugs: We chose to focus on the opioid analgesics that were reported by both data sources from 2001 forward: fentanyl, hydrocodone, hydromorphone, methadone, morphine, and oxycodone. When analyzing the number of prescriptions dispensed, we subdivided fentanyl, morphine, and oxycodone into extended release (ER) and immediate release (IR) formulations. The ER or long-acting (LA) category included the ER formulations of these three drugs plus methadone and oxymorphone. “Other opioids” in the VONA analysis included oxymorphone, propoxyphene, codeine, tramadol, pentazocine, dihydrocodeine, meperidine, butorphanol, levorphanol, and buprenorphine.

Statistical Analysis: We calculated crude rates of prescriptions per 100 persons from VONA data, milligrams per 100 persons from ARCOS data, and milligrams per prescription by combining both data sources. Population denominators were post-censal estimates [21]. We used two assumptions to

calculate oral morphine milligram equivalents (MME) to compare prescription size: (1) all drugs other than fentanyl are taken orally; fentanyl is applied transdermally or transmucosally, and (2) these doses are approximately equianalgesic: morphine: 30mg; oxycodone and hydrocodone: 30mg; hydromorphone: 7.5 mg; methadone: 4 mg; fentanyl: 0.4 mg [22].

Results

The number of prescriptions per 100 persons increased to a rate of almost one prescription per person per year between 2000 and 2009 for the specified opioids (61.9 to 83.7 per 100 persons, Table 1). Roughly one-third more opioid prescriptions were dispensed in 2009 than in 2000. Rates increased each year for every drug until 2009, when small declines occurred for fentanyl ER, hydrocodone, methadone, and morphine IR. The proportion of all prescriptions dispensed for extended release (ER) or long-acting (LA) opioids grew every year until 2009, when the proportion stabilized at 8.9%.

The distribution of opioids to US pharmacies in milligrams per 100 persons increased by at least 100% for all major opioids between 2000, 2001, and 2010 (Figure 1). The greatest increases were seen in oxycodone (287.3%), methadone (232.4%), and hydromorphone (227.7%). Oxycodone consistently had the largest volume of drugs purchased by pharmacies during the study period—and purchases accelerated after 2005. After such time, it accounted for most of the increased rate for these opioids.

Methadone was the only opioid whose distribution declined in milligrams/100 persons in any year from 2007 to 2010.

The average prescription size decreased for morphine, methadone, and hydromorphone and increased for other opioids (Fig 2). Morphine consistently had the highest MME per prescription dispensed, remaining at approximately 3,000 MME per prescription throughout the time period, with a net decline of 3% by 2009. Methadone prescriptions were 1,400–1,500 MME/prescription until 2007 and declined to 1,330 MME in 2008. However, the average size of an oxycodone prescription increased 69.7% (from 615 MME to 1,044 MME) during this time period, while the average hydrocodone prescription increased 69.1% (from 170 MME to 288 MME). Fentanyl showed a smaller relative increase (20.9%).

Interpretation

Our analyses of VONA and ARCOS data systems expand the description of trends previously reported based on more limited cohort studies that made use of medical claims data as well as previous releases of ARCOS data. The VONA results show a steady increase in the population-based rate of prescribing opioid analgesics that have stabilized by 2009. However, ARCOS results show that the volume of opioid analgesics in grams per 100 people more than doubled through 2010. Taken together, the data systems illustrate an overall increase in the size of each prescription, especially for hydrocodone and oxycodone.

Our data, however, do not allow determining whether the increase in prescription size was a result of an increase in the number of days per prescription or the daily dosage. A shift to a higher proportion of ER formulations for a given type of opioid could increase the average number of days per prescription since ER/LA opioids tend to be prescribed more for chronic pain. (The mean number of days of therapy per prescription during this decade was 8–21 for IR opioids and 23–28 for ER/LA opioids) [19]. A shift toward ER formulation use did occur for fentanyl in this data and might explain the increase in the size of fentanyl prescriptions. However, the proportion of oxycodone prescriptions that were ER actually declined, so the increase in the average oxycodone prescription size was not likely due to an increase in the number of days per prescription.

The values obtained here for prescription size are consistent with other data sources where comparisons are possible. For example, the average hydrocodone prescription size in 2009 was 288 MME, which would result in a daily dosage of 14 MME–36 MME over the range of 8 to 21 days per prescription. Eighty-four percent of the average oxycodone prescription of 1,044 MME was IR formulations in 2009; this results in a daily dosage of 50 MME–130 MME if we assume a duration typical of IR drugs and 37 MME if we assume a 28-day duration common for ER opioids. In one large US study during 1997–2005, the mean prescribed opioid daily dosage was 30 MME–60 MME [23]. The increase in prescription size is also consistent with the literature. In the workers’ compensation population in Washington State, the

average daily dose increased from 88 to 132 MME/day during 1996–2002 [14]. The mean daily dosage in the Arkansas Medicaid population went from 54 MME to 50 MME from 2000 through 2005, but the median number of a day's supply of opioids per year increased from 25 to 38 [15].

The most concerning finding is the trend toward greater use of opioid analgesics in general, and LA/ER opioids in particular, in the United States since 1990—its use has shown little sign of abating through 2010. The prescribing rate leveled off in 2009, but the volume of opioids in grams continued to increase through 2010. Continued assessment of these trends in the context of recent changes in laws and in the implementation of prescription drug monitoring programs, will be critical to forecasting trends in drug overdoses. The only encouraging sign is that the volume of methadone prescribed after 2007 declined, which may have been a result of the publicity regarding overdose deaths, the revised dosage instructions and warning placed on the drug in 2006, or the voluntary restriction of the largest (40 milligram) formulation to discourage its use for pain as of January 1, 2008 [24, 25]. Otherwise, there have been no measurable effects of the educational strategies to induce physicians to prescribe more judiciously or of the regulatory efforts to reduce the nonmedical consumption of opioids during the 10 years since the problem first came to public attention in the United States.

As discussed above, treatment of pain in non-cancer patients has moved toward more active treatment including the increased use of opioids,

as untreated pain can also have serious health outcomes. Chou et al [26], concluded that chronic opioid therapy can be an effective therapy for patients that are carefully selected and monitored. However, they also caution that opioids can be associated with potentially serious harms, including adverse effects and abuse. Non-medical use has also increased. The number of individuals using pain relievers non-medically for the first time within the past year increased 41% from 1998 to 2008[1]. So accompanying the increasing trend in treating non-cancer pain patients with opioids, there are also rising trends in non-medical use and illicit use. The rising trends portend worsening health outcomes because measures of opioid supply strongly correlate with the numbers of opioid related overdoses in the United States [7, 27] and because higher daily dosages have been recently associated with greater risk of overdose death [16, 28, 29]. The Drug Abuse Warning Network has reported steady increases in emergency department visits involving the nonmedical use of opioid analgesics, especially oxycodone, through 2009 [30]. Although the latest available data on opioid-related deaths in the United States are from 2007, the results of this study show that such deaths will likely continue to increase through 2010.

The VONA system is limited by its inability to capture prescriptions written and dispensed by authorized dispensing prescribers. Its estimation methods are proprietary and therefore cannot be validated. One limitation of using ARCOS data includes overrepresentation of drug consumption

because unknown quantities are used for veterinary purposes [2]. Another limitation is that the system includes amounts re-ordered to replace drugs stolen from pharmacies or other retail-level dispensers, and amounts distributed to the retail level that were not actually dispensed or consumed by patients in the same year. No evaluation of the completeness of ARCOS data has been published. This study examined different parts of the distribution chain of the licit opioid supply (sales to pharmacies and prescriptions) and did not directly assess individual use of opioid analgesics. Previous work, however, provides support for the connection between sales of opioid analgesics and associated death rates [7].

The ongoing problem in the United States should serve as a warning to other countries with a growing consumption of opioid analgesics such as Canada, Australia, and Great Britain [5], which are already beginning to see increases in prescription drug overdoses and deaths [17, 31, 32]. Effective measures to address the problem have not been fully identified in the United States. Good first steps, however, would be establishing timely national surveillance for prescription drug use and non-medical use and examining the prescription histories of persons dying of prescription drug overdoses to determine the specific factors, such as high daily dosage or nonmedical use, that might contribute to overdose deaths.

Table 1. Rate of opioid analgesic prescriptions dispensed by retail pharmacies per 100 persons, United States, Vector One®: National, 2000–2009

	Fenta nyl ER	Fenta nyl IR	Hydro- codon e	Hydro- morpho ne	Methado ne	Morphi ne ER	Morphi ne IR	Oxycodo ne ER	Oxycodo ne IR
2000	0.61	0.01	27.79	0.18	0.30	0.45	0.26	1.94	6.06
2001	0.82	0.02	29.41	0.20	0.42	0.53	0.27	2.30	6.63
2002	1.03	0.05	30.45	0.25	0.56	0.65	0.32	2.16	7.10
2003	1.28	0.09	31.76	0.29	0.75	0.77	0.36	2.27	7.79
2004	1.40	0.11	33.70	0.34	0.95	0.95	0.40	2.15	8.52
2005	1.45	0.12	36.00	0.41	1.16	1.09	0.40	2.17	9.49
2006	1.59	0.12	38.23	0.47	1.31	1.25	0.40	2.33	10.34
2007	1.72	0.11	40.11	0.54	1.39	1.39	0.43	2.50	11.52
2008	1.77	0.10	40.92	0.62	1.46	1.59	0.47	2.57	12.79
2009	1.64	0.08	40.10	0.71	1.44	1.68	0.42	2.52	13.62
% Change 2000- 2009	167.2	890.9	44.3	293.4	373.2	274.6	62.2	29.8	124.8

ER=extended release

IR=immediate release

Figure 1. Distributions of selected opioids to pharmacies in mg per 100 persons, United States, Automation of Reports and Consolidated Orders System, 2000–2010

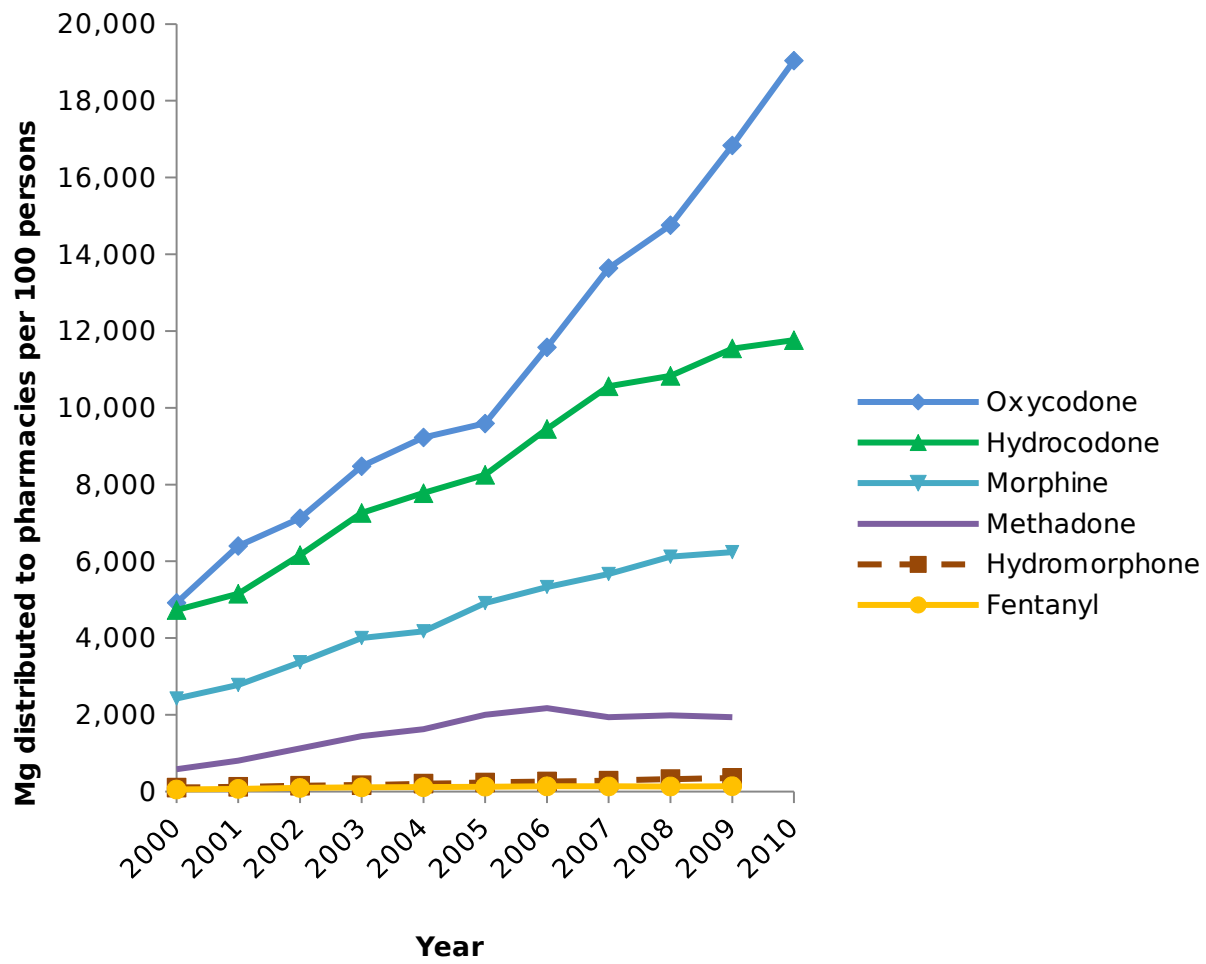
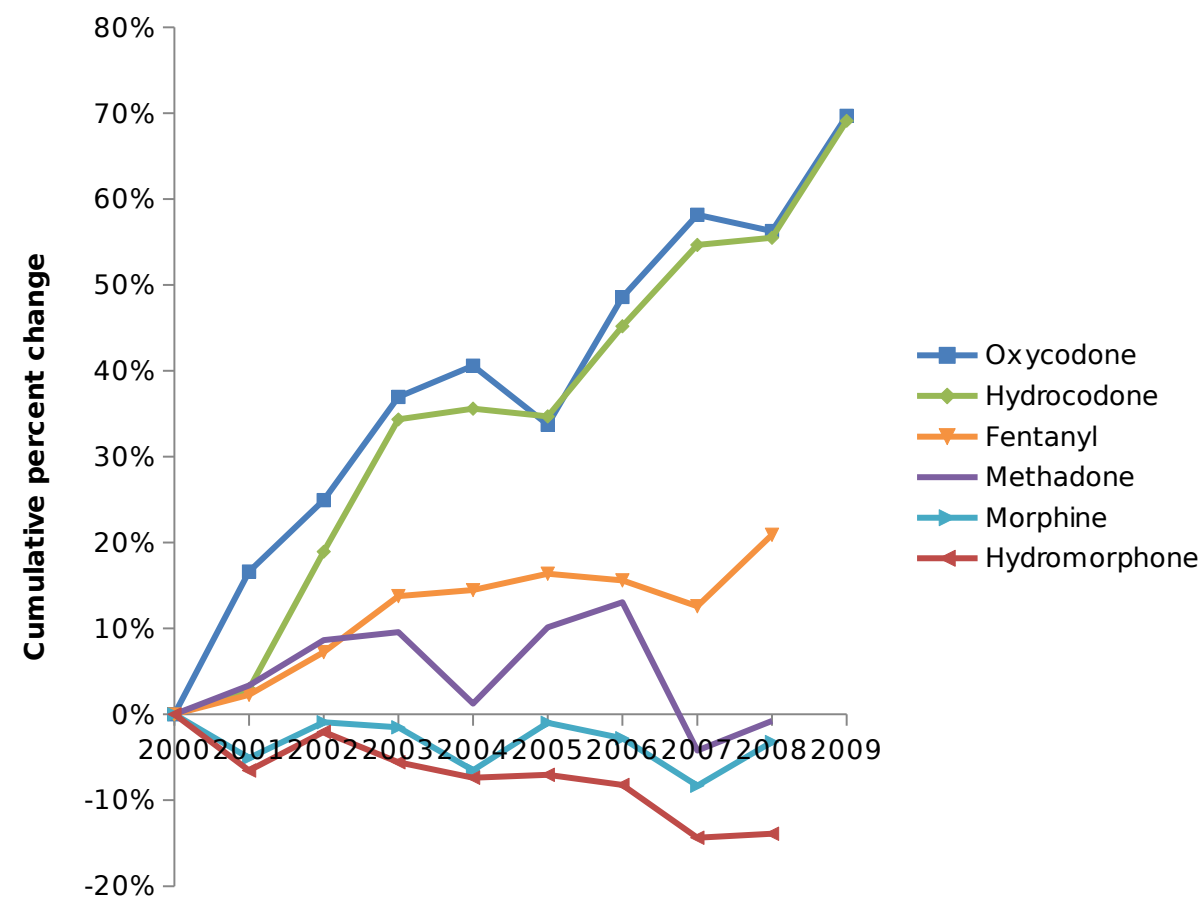


Figure 2. Percent change in milligrams per prescription for selected opioid analgesics, United States, Vector One: National and Automation of Reports and Consolidated Orders System, 2000–2009



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