New Opioid Analgesic Approvals and Outpatient Utilization of Opioid Analgesics in the United States, 1997 through 2015

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ABSTRACT

Background: The opioid epidemic, driven in part by increased prescribing, is a public health emergency. This study examines dispensed prescription patterns and approvals of new opioid analgesic products to investigate whether the introduction of these new drugs increases prescribing.

Methods: Prescribing patterns based on dispensed prescription claims from the U.S. retail setting were assessed with new brand and generic opioid analgesic products approved in the United States from 1997 through 2015.

Results: From 1997 through 2015, the U.S. Food and Drug Administration (Silver Spring, Maryland) approved 263 opioid analgesic products, including 33 brand products. Dispensed prescriptions initially increased 80% from 145 million prescriptions in 1997 to a peak of 260 million prescriptions in 2012 before decreasing by 12% to 228 million prescriptions in 2015. Morphine milligram equivalents dispensed per prescription increased from 486 in 1997 to a peak of 950 in 2010, before decreasing to 905 in 2015. In 2015, generic products accounted for 96% (218/228 million prescriptions) of all opioid analgesic prescriptions dispensed. The remaining prescriptions were dispensed for brand products, of which nearly half were dispensed for one brand product (OxyContin, Purdue, USA).

Conclusions: There has been a dramatic increase in prescriptions dispensed for opioid analgesics since 1997 and an increasing number of opioid analgesic approvals; however, the number of prescriptions dispensed has declined since 2012 despite an increasing number of approvals. Examination of dispensed prescriptions shows a shifting and complex market where multiple factors likely influence prescribing; the approval of new products alone may not be sufficient to be a primary driver of increased prescribing.

Visual Abstract: An online visual overview is available for this article at http://links.lww.com/ALN/B705. **(ANESTHESIOLOGY 2018; 128:953-66)**

DURING the past two decades, there has been a marked increase in outpatient utilization of opioid analgesics in the United States, paralleled by increases in abuse, misuse, and adverse outcomes, including addiction, overdose, and death.[1,2] In 2015, a reported 33,091 deaths were attributed to opioid overdose (prescription and illicit), an increase from 8,050 deaths in 1999.[3] Addressing the prescription opioid abuse epidemic is a national priority.[4,5]

While the increased prescribing of opioids is widely considered to have contributed to this public health emergency, the specific factors leading to increased prescribing are the subject of debate.[6] For example, with increasing acknowledgment that pain was often undertreated, Congress declared in 2000 that the upcoming decade would be the "Decade of Pain Control and Research."[7] Pain has also been considered the fifth vital sign since The Joint Commission, an organization that accredits and certifies healthcare organizations such as hospitals, included standards for pain assessment and treatment in 2001.[8]

During the last 20 yr, the U.S. Food and Drug Administration (Silver Spring, Maryland) has approved numerous new opioid analgesic products. However, most of these new products contain active moieties that have been used for decades in older products. In fact, only one new molecular entity opioid analgesic was approved during this period:

What We Already Know about This Topic

- Since 1997 there has been an increasing number of opioid analgesics approved by the U.S. Food and Drug Administration, and an increase in prescriptions dispensed for opioid analgesics
- There are concerns that new opioid products are driving prescribing, but the relationship between prescribing patterns and product approvals is not well understood

What This Article Tells Us That Is New

- Data on new brand and generic opioid analgesic product approvals, and on retail dispensed prescription claims, were used to evaluate the opioid product space
- Opioid prescriptions dispensed and amount per prescription nearly doubled, and total morphine milligram equivalents more than tripled, from 1997 to the peak in 2010, and partially declined thereafter
- Generic products accounted for 68% of total opioid prescriptions in 1997 and 96% in 2015
- Approval of new branded opioid products alone does not appear to be a primary driver of increased opioid prescribing

This article is featured in "This Month in Anesthesiology," page 1A. This is a 2017 Frontiers in Opioid Pharmacotherapy Symposium article.

Submitted for publication June 29, 2017. Accepted for publication February 19, 2018. From the Division of Epidemiology, Office of Pharmacovigilance and Epidemiology, Office of Surveillance and Epidemiology (G.C.), Clinical Safety and Surveillance Staff, Immediate Office, Office of Generic Drugs (J.O.), Division of Anesthesia, Analgesia, and Addiction Products, Office of Drug Evaluation II, Office of New Drugs (M.A.L.), and Office of Surveillance and Epidemiology (G.D.P.), Center for Drug Evaluation and Research; and Office of Public Health Strategy and Analysis (J.X., M.C.), and Economics Staff, Office of Planning, Office of Policy, Planning, Legislation, and Analysis (K.L.M., C.W.), Office of the Commissioner, U.S. Food and Drug Administration, Silver Spring, Maryland. Current position: President, Center for Science in the Public Interest, Washington, D.C. (P.L.). LCDR Chai, CDR Osterhout, and LCDR Liberatore are commissioned officers in the United States Public Health Service (USPHS).

 Anesthesiology 2018; 128:953-66

<zdoi;10.1097/ALN.0000000000002187>

tapentadol (2008). New product development of opioid analgesics has focused on new formulations of existing products, including, in some cases, the development of abuse-deterrent formulations.

In recent years, lawmakers, advocacy groups, and others have voiced concern that approvals of new opioid products are driving prescribing.[9–11] In theory, new products could drive prescribing by expanding the market with new innovator products, thus increasing product choice, or by increasing accessibility to less expensive products (*e.g.*, generic products). Using nationally estimated prescription claims data and U.S. Food and Drug Administration resources, we examine patterns in prescriptions dispensed in the outpatient setting relative to new opioid product approvals to shed light on the relationship between prescribing patterns and product approvals.

Materials and Methods

We obtained data on all new drug applications and abbreviated new drug applications approved for opioid analgesic products between 1997 and 2015.[12] New drug application products include those with new active ingredients, new formulations, and new dosage forms.[13] Abbreviated new drug application products are generic versions of products approved under new drug applications.[14]

National estimates of the number of prescriptions dispensed for opioid analgesics were obtained from a proprietary database available to the U.S. Food and Drug Administration under contract, IQVIA (USA), National Prescription Audit, for January 1997 through December 2015; data before 1997 were not available. The National Prescription Audit captures approximately 3.5 billion prescription claims (88% of U.S. retail prescriptions) annually from a sample of 46,000 out of the approximately 59,400 U.S. outpatient retail pharmacies, which are then projected to provide national-level estimates. Changes to the underlying source data and projection methodologies were conducted by IQVIA over time for greater accuracy. Prescriptions covered by commercial third-party payers, Medicaid, or Medicare, and cash payments are included. Prescription data were analyzed by active moiety (appendix 1), by formulation (*e.g.*, immediate-release, extended-release), and by "brand" (brand or branded generic) or "generic."

Prescriptions in the National Prescription Audit classified as "brand or branded generic" products include all trade name products. "Generic" products in the National Prescription Audit include products with no trade name. Of note, these classifications of "brand" and "generic" prescriptions do not precisely align with the U.S. Food and Drug Administration's definitions of products based on new drug application or abbreviated new drug application approval. Prescriptions for products approved as new drug applications and abbreviated new drug applications were classified as "brand" prescriptions if they had a trade name,[15,16] while prescriptions for products with no trade name, including some approved as new drug applications (appendix 2), were captured as "generic" prescriptions. Under the National Prescription Audit classification system, most abbreviated new drug application products are captured as "generic" prescriptions. Because authorized generics are products marketed under existing new drug applications without separate U.S. Food and Drug Administration approvals, they could not be counted as separate approvals,[17] but were captured as "generic" prescriptions.

All formulations of opioid analgesics were included, except for injectable formulations, which are not commonly dispensed in the outpatient setting. Opioid-containing products used as part of medication-assisted treatment for opioid dependence and opioid-containing cough/cold products were not included in our analysis because of their different indications and patterns of use. Thus, methadone dispensed as medication-assisted treatment from methadone clinics was not captured in the database, but all other methadone prescriptions dispensed from retail pharmacies were included in the analysis.

We also quantified the total amount of morphine milligram equivalents dispensed based on standardization of total dispensed opioid prescriptions across the different active moieties, quantity, and strength of doses. To calculate overall morphine milligram equivalents dispensed per year, we calculated the milligrams of opioids dispensed annually by a morphine milligram equivalents conversion factor for each opioid analgesic using conversion factors outlined in a recent publication by the Centers for Disease Control and Prevention (Atlanta, Georgia).[18]

We first reported new opioid analgesic product approvals in the United States from 1997 through 2015 by year of approval for new drug applications and abbreviated new drug applications. Next, we show the total opioid analgesic market for brand and generic products by both the nationally estimated number of total prescriptions and morphine milligram equivalents dispensed and prescriptions dispensed adjusted for the total U.S. population calculated using U.S. Census data.[19] We also calculated the market share of all new opioid analgesic brand products approved between 1997 and 2015. Our analyses also included all prescriptions dispensed for brand OxyContin (Purdue, USA). OxyContin was originally approved in 1995 before our study period; subsequently another new drug application was approved in 2010 as a reformulation of the original OxyContin, at which time the marketing of the original product ceased. We recorded the approval of the reformulated product as a new brand approval, although we did not distinguish between the original formulation and the new formulation in our calculations of total OxyContin prescriptions dispensed.

Additional supplemental analyses were performed to assess generic opioid analgesic approvals and prescription patterns for the years 1997 through 2015. First, we conducted an analysis of new and additional generic products approved after 1997 for the six most frequently dispensed opioid analgesics in 2015. Next, we analyzed opioid

analgesics for which the first generic was initially dispensed between 2006 and 2015, as these represent the clearest cases for interpretation in the current opioid market. Descriptive statistics and calculation of morphine milligram equivalents were conducted using Excel (Microsoft, USA); no statistical hypothesis testing was performed.

Results

New Product Approvals

From 1997 through 2015, 263 new opioid analgesic applications were approved, including 222 abbreviated new drug applications and 41 new drug applications (fig. 1). Thirty-three (33) of the 41 new drug applications approvals were for brand products. The annual number of approvals, which generally increased over time, was higher in the second half of the study period (2007 through 2015; median, 20 approvals/yr; range, 10 to 27) than in the first half (1997 through 2006; median, 9 approvals/yr; range, 5 to 15).

National Prescription Trends

The nationally estimated number of prescriptions dispensed for opioid analgesics initially increased 80% from 145 million prescriptions in 1997 to a peak of 260 million prescriptions in 2012 before decreasing by 12% to 228 million prescriptions in 2015 (table 1). Adjusted for the total U.S. Census population, the overall trends were similar, but the peak in population-adjusted utilization during the study period was in years 2010 to 2012 (fig. 2). Total morphine milligram equivalents dispensed increased from 70 billion dispensed in 1997 to a peak of 244 billion in 2010 before decreasing by 16% to 206 billion morphine milligram equivalents dispensed in 2015. Morphine milligram equivalents per prescription dispensed nearly doubled from 486 in 1997 to a peak of 950 in 2010 before decreasing to 905 morphine milligram equivalents per prescription in 2015. Generic products accounted for 96% of opioid analgesic prescriptions dispensed in 2015, compared to 68% of total prescriptions in 1997.

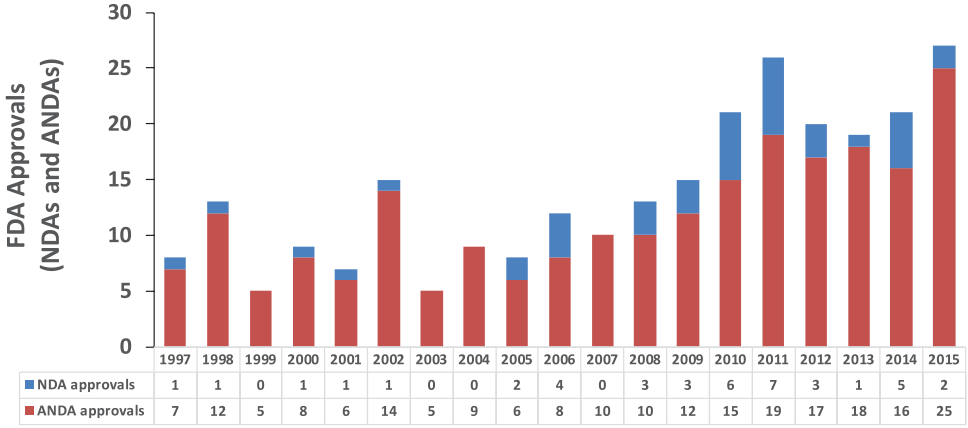
New Brand Product Approvals

Of the 33 brand products approved as new drug application between 1997 and 2015, 23 brand products were dispensed in 2015. The annual combined market share of the 23 brand products accounted for 3% of all opioid analgesic prescriptions dispensed in 2015 (fig. 3 and appendix 3), largely dispensed for a single brand product (OxyContin); the combined market share of the other 22 brand products accounted for only 1% of the total opioid analgesic market in 2015. Tapentadol (Nucynta, 2008, and Nucynta ER, 2011; Ortho-McNeil, USA), the only new molecular entity approved during the study period, accounted for 0.3% of the total opioid analgesic market in 2015.

Figure 4 shows prescriptions dispensed for OxyContin and generic extended-release oxycodone increased from nearly 1 million prescriptions dispensed in 1997 to about 7 to 7.5 million prescriptions dispensed annually between 2001 and 2010 (the year reformulated OxyContin was introduced and original OxyContin marketing ceased), before decreasing by 39% from approximately 7 million prescriptions in 2010 to nearly 4.5 million prescriptions 2015. In terms of morphine milligram equivalents dispensed, approximately 33 billion morphine milligram equivalents were dispensed for extended-release oxycodone at its peak in 2010, accounting for 14% of total morphine milligram equivalents dispensed for the total opioid analgesic market.

Generic Product Approvals

The six most frequently dispensed opioid analgesic products in 2015 were oral immediate-release formulations of hydrocodone/acetaminophen (40% of total opioid analgesic prescriptions), single-ingredient tramadol (17%), oxycodone/acetaminophen (15%), single-ingredient oxycodone (8%), codeine/acetaminophen (7%), and extended-release morphine (3%), together accounting for nearly 90% of all opioid analgesic prescriptions dispensed in 2015. The majority of these prescriptions were dispensed as generics throughout the examined time (fig. 5). For the examined drugs, the number of prescriptions dispensed generally increased as the



	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
NDA approvals	1	1	0	1	1	1	0	0	2	4	0	3	3	6	7	3	1	5	2
ANDA approvals	7	12	5	8	6	14	5	9	6	8	10	10	12	15	19	17	18	16	25

Fig. 1. Number of U.S. Food and Drug Administration (FDA) approvals of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) for opioid analgesic products by year of approval from 1997 through 2015.

Table 1. Nationally Estimated Annual Number of Opioid Analgesics Dispensed in Number of Morphine Milligram Equivalents (MME in B), Total Prescriptions (Rx in M), and Prescriptions Dispensed Adjusted for the U.S. Census Population, by Brand (Brand and Branded Generics) and Generic Products from U.S. Outpatient Retail Pharmacies

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Total Rx	145 M	154 M	166 M	178 M	194 M	199 M	208 M	219 M	230 M	223 M	235 M	244 M	250 M	257 M	258 M	260 M	252 M	244 M	228 M
Brand Rx	46 M	46 M	48 M	51 M	52 M	48 M	41 M	38 M	26 M	16 M	14 M	16 M	18 M	17 M	17 M	14 M	12 M	12 M	9 M
Generic Rx	99 M	108 M	118 M	127 M	142 M	150 M	166 M	181 M	205 M	207 M	221 M	228 M	232 M	240 M	241 M	246 M	239 M	232 M	218 M
Rx per 100 population	53	56	59	63	68	69	72	75	78	75	78	80	81	83	83	83	80	77	71
MME	70 B	79 B	87 B	105 B	121 B	134 B	151 B	167 B	183 B	181 B	199 B	215 B	227 B	244 B	240 B	234 B	224 B	217 B	206 B
MME per Rx	486	511	524	589	621	675	725	763	793	813	848	882	909	950	932	899	890	888	905
MME per capita	256	284	311	373	424	467	520	572	618	608	662	707	740	791	771	745	708	680	641

Estimates were derived from total U.S. Census population projections and estimates and IQVIA, National Prescription Audit. Prescriptions dispensed per 100 persons adjusted to the U.S. Census population. Brand: all trade name products including brand and branded generic products. Excludes injectable formulations, opioid-containing cough/cold products, and opioid-containing medication assistance therapy products. B = billions; M = millions.

cumulative number of generic product approvals increased with the exceptions of hydrocodone/acetaminophen and codeine/acetaminophen. Prescriptions dispensed for hydrocodone/acetaminophen more than doubled from 53 million prescriptions in 1997 to a peak of 129 million prescriptions in 2011 to 2012 before decreasing 29% to 91 million prescriptions in 2015. Prescriptions generally declined for codeine/acetaminophen throughout the examined time before a 27% increase in prescriptions dispensed from 11 million prescriptions in 2013 to 15 million prescriptions in 2015.

Generic versions of six opioid analgesics, which were dispensed for the first time during years 2006 through 2015, are shown in figure 6. Four of the six opioid analgesic products with initial generic approvals between 2006 and 2015 (extended-release hydromorphone, extended-release tramadol, transmucosal immediate-release fentanyl products [excluding sprays], and oxycodone/ibuprofen) showed declines in total dispensing after generic introduction, while two (oxymorphone and extended-release oxymorphone) showed essentially stable total dispensing. In some cases, the decrease in prescriptions began before the introduction of generics.

Discussion

Our examination of brand and generic opioid analgesics product approvals and outpatient dispensing patterns shows that dispensing of opioid analgesics dramatically increased since 1997, both in the number of prescriptions dispensed and in the quantity of opioid per dispensed prescription, as measured by morphine milligram equivalents per dispensed prescription. This increase was accompanied by an increase in the market share of generic drugs, which accounted for 96% of dispensed prescription for opioid analgesics in 2015. The annual number of approvals, which generally increased over time, was higher in the second half of the study period (2007 through 2015) than in the first half (1997 through 2006).

Our data do not suggest a clear relationship between new product approvals and utilization; rather, several observations suggest a shifting and complex market in which multiple factors are at work. First, while the introduction of new products could increase prescribing if additional new molecular entities were brought to market, this had not occurred to any significant extent. Tapentadol, the only new molecular entity approved during the study period, was minimally prescribed, accounting for only 0.3% of the total opioid market in 2015.

Second, our finding that newly approved brand products, which in theory may provide more choice to practitioners and patients, accounted for only 3% of the dispensed prescription opioid analgesic market in 2015, suggesting that the availability of new medicines did not significantly drive prescribing decisions. The finding that OxyContin accounted for approximately 2% of the opioid analgesic market in 2015,

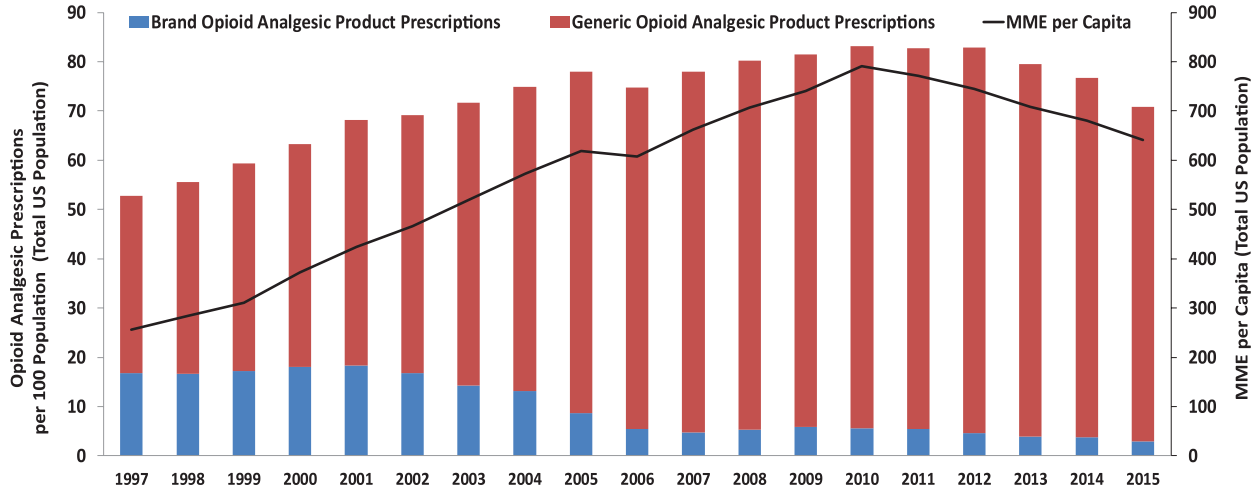


Fig. 2. Nationally estimated annual number of opioid analgesics dispensed in number of morphine milligram equivalents (MME, *right axis, line graph*) and in number of prescriptions (*left axis, bar graph*), by brand (brand and branded generics) and generic product, adjusted for the U.S. population, from U.S. outpatient retail pharmacies. Estimates were derived from the following sources: Total U.S. Census Population projections and estimates and IQVIA, National Prescription Audit. Brand: All trade name products including Brand and Branded Generic products. Excludes injectable formulations, opioid-containing cough/cold products, and opioid-containing medication assistance therapy products.

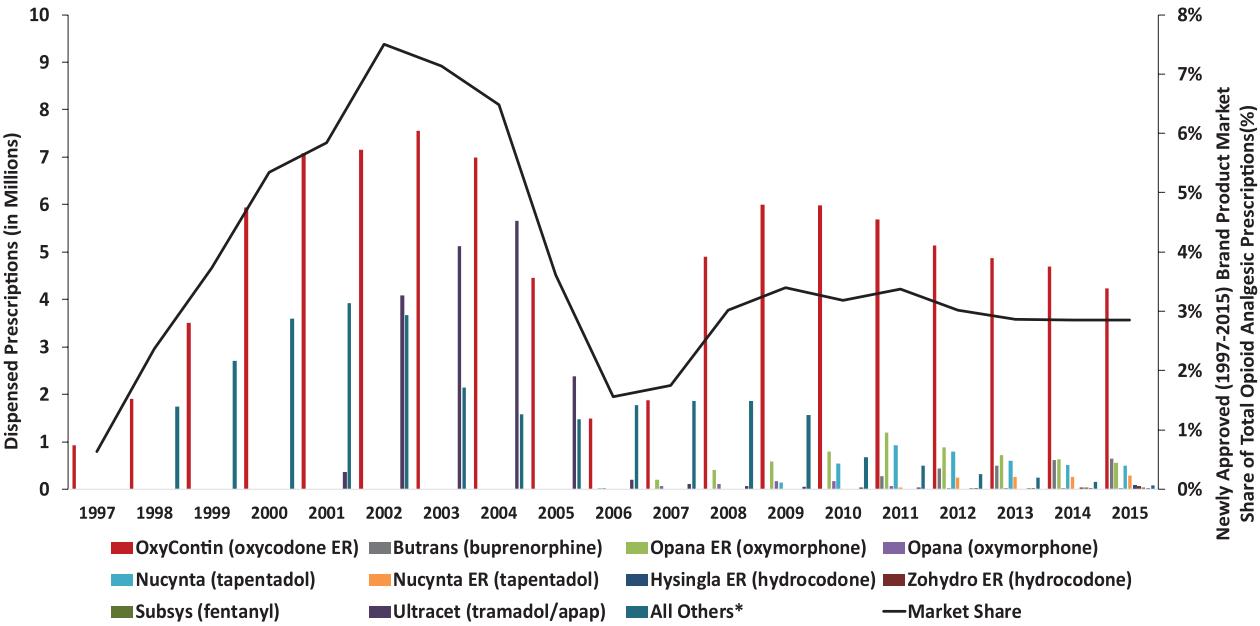


Fig. 3. Nationally estimated annual number of prescriptions dispensed for the top 10 newly approved opioid analgesic brand products (*left axis, bar graph*) and the combined market share of all newly approved opioid analgesic brand products (*right axis, line graph*) in the U.S. outpatient retail pharmacy setting from 1997 through 2015. Source: IQVIA, National Prescription Audit. Individual brand products represent the brand opioid analgesics dispensed in 2015 that were introduced into the market from 1997 to 2015. Only brand utilization is shown—does not include generic utilization. *Solid line* represents the combined market share for all brand products approved between 1997 and 2015, out of the total opioid analgesic market. Opana ER includes original formulation (approved 2006) and reformulation (approved 2011). OxyContin includes original formulation (approved 1995) and reformulation (approved 2010). Utilization excludes injectable formulations, opioid-containing cough/cold products, and opioid-containing medication assistance therapy products. *All Others includes all brand opioid analgesic products approved between 1997 and 2015 that are not individually shown. ER = extended-release formulation.

while the other newly approved brand products collectively accounted for 1% of the opioid analgesic market, suggests that factors specific to OxyContin may have accounted for its relatively widespread usage among this group of products.

Third, among the six most commonly prescribed opioid analgesics, the relationship of cumulative generic drug approvals to the number of dispensed prescriptions was variable. For example, while the increase in

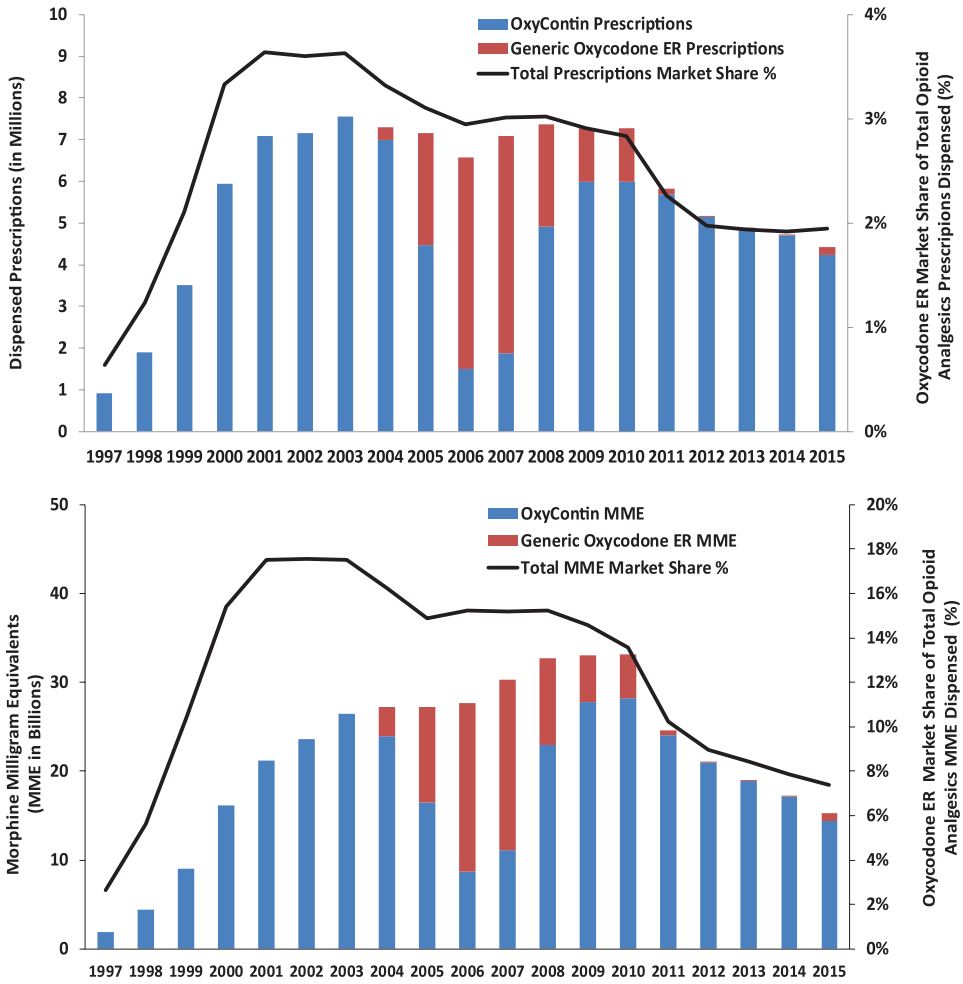


Fig. 4. Nationally estimated annual number of dispensed prescriptions and morphine milligram equivalents (MME) dispensed for extended-release oxycodone (brand and generic products, *left axis, bar graph*) and their market share of total opioid analgesic prescriptions or MME dispensed (*right axis, line graph*) from U.S. outpatient retail pharmacies. Source: IQVIA, National Prescription Audit. ER = extended-release formulation.

the number of generic approvals was similar for three products (immediate-release hydrocodone/acetaminophen, immediate-release oxycodone/acetaminophen, and immediate-release oxycodone), the number of dispensed prescriptions differed markedly across the three products. In addition, the number of dispensed prescriptions for immediate-release codeine/acetaminophen decreased over a time period during which multiple generic versions were approved.

Fourth, the number of dispensed prescriptions for opioid analgesics whose initial generic version was introduced after 2006 was either stable or declined. The introduction of lower-priced generics has the potential to increase patient accessibility and utilization, with lower prices making medicines more accessible to patients,[20] but the data suggest that the introduction of generics in recent years may not increase total dispensing. For example, we observed that the initial introduction of generic extended-release oxycodone did not appear to increase overall prescribing; rather, the increase in use of extended-release oxycodone occurred before the approval of generics. The pattern of stable or declining prescribing observed after introduction of new generic opioid products supports previous research that the approval of generic products may not drive increased utilization.[21]

Fifth, despite an increased number of approvals in the most recent quarter of the study period (2011 through 2015) relative to previous years, the number of prescriptions dispensed and morphine milligram equivalents decreased since 2012. This finding, along with the observed increase, a near doubling, in the quantity of opioids dispensed per prescription during the study period, further suggests that factors other than product approvals drove prescribing decisions.

The declines in total opioid analgesic dispensing observed in the later years of the study period may be driven in part by interventions implemented by federal, state, and local governments, regulatory agencies, medical associations, healthcare systems, and prescribers. Such efforts may include changes in prescribing guidelines,

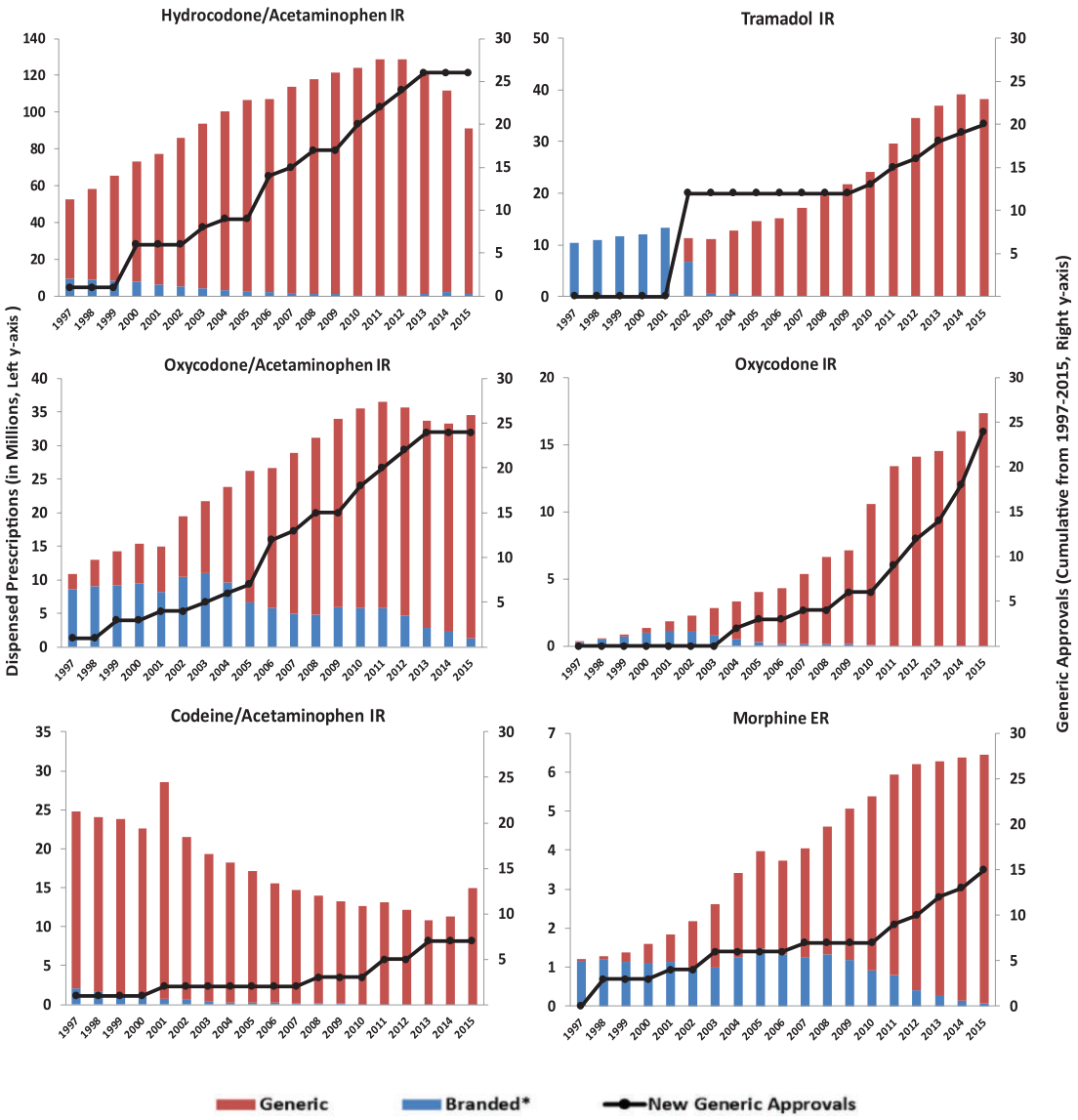


Fig. 5. Cumulative number of new U.S. Food and Drug Administration generic product approvals (*right axis, line graph*) and the nationally estimated annual number of prescriptions dispensed (*left axis, bar graph*) from U.S. outpatient retail pharmacies for the six most frequently dispensed opioid analgesics from 1997 through 2015. Source: IQVIA, National Prescription Audit. *Branded: All trade name products including Brand and Branded Generic products. Excludes injectable formulations, opioid-containing cough/cold products, and opioid-containing medication assistance therapy products. ER = extended-release formulations; IR = immediate-release formulations.

requirements for prescriber education, recommended limitations on opioid dosages, increased law enforcement activities, payer-based dispensing restrictions, prescription drug monitoring programs, and risk evaluation mitigation strategies.[22–27] While the precise contribution of each of these interventions is difficult to ascertain, some patterns observed in this study may be due to actions such as the rescheduling of hydrocodone-combination products in 2014 from Controlled Substance Act Schedule III to Schedule II.[28] Rescheduling to Schedule II precludes phone-in or refill prescriptions, potentially making Schedule III products (*e.g.*, codeine/acetaminophen) and Schedule IV products (*e.g.*, tramadol), which are not subject to the same restrictions, easier to prescribe. One study suggests this may have caused a shift from hydrocodone-combination products to other products, but this effect appears to be smaller than the reduction in hydrocodone-combination product dispensing.[29]

Our study also found that morphine milligram equivalents per prescription dispensed nearly doubled since 1997 to a peak of 950 morphine milligram equivalents per prescription in 2010, before decreasing to 905 morphine milligram equivalents per prescription in 2015. Changes in the annual total of average morphine milligram equivalent dispensed per prescription may be due to changes in drug product prescribed, dosage, strength, or quantity; further investigation is

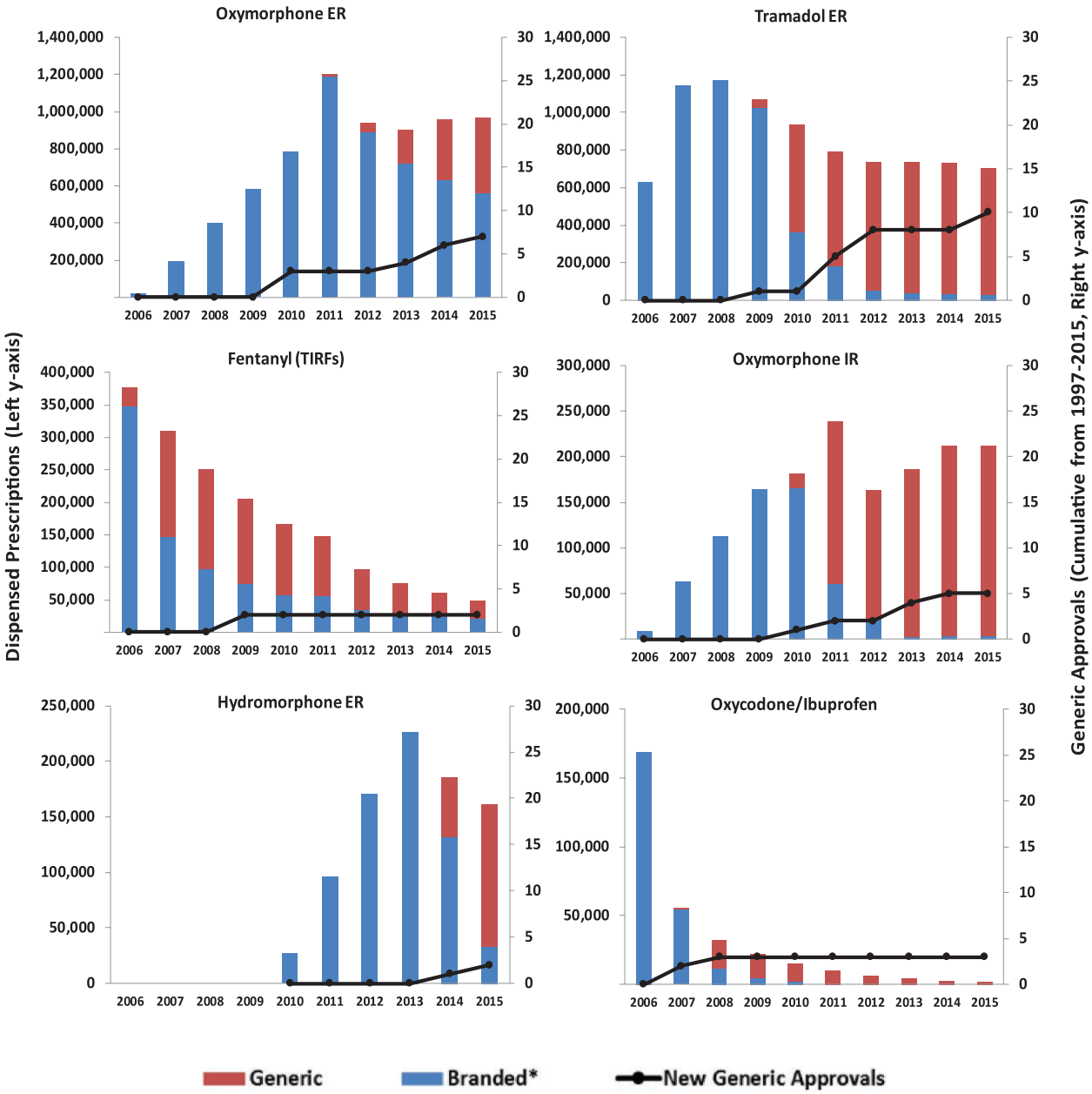


Fig. 6. Cumulative number of U.S. Food and Drug Administration generic approvals (*right axis, line graph*) and the nationally estimated annual number of prescriptions dispensed (*left axis, bar graph*) from U.S. outpatient retail pharmacies for opioid analgesics with "newly marketed generics," stratified by brand (brand and branded generic) and generic products from 2006 through 2015. Source: IQVIA, National Prescription Audit. *Branded: All trade name products including Brand and Branded Generic products. **Newly marketed generics: Generic versions for opioid analgesics, where the generics were dispensed for the first time during 2006–2015. Excludes injectable formulations, opioid-containing cough/cold products, and opioid-containing medication assistance therapy products. Oral solid products for Transmucosal Immediate-Release Fentanyl (TIRFs) were included. Brand TIRF products include Abstral, Actiq, Fentora, Onsolis (does not include sprays). Brand product of hydromorphone ER includes Exalgo. Brand products of tramadol include Ultram ER, Conzip, and Ryzolt. ER = extended-release formulation; IR = immediate-release formulation.

warranted to fully understand the complex factors contributing to the differences in prescribing pattern changes.

Although this study provides a broad overview of opioid analgesic utilization, we were not able to specifically address the impact of our findings on opioid abuse, misuse, addiction, and deaths. The opioid epidemic is a complex and multifactorial phenomenon associated with both legal and illicit sources (*e.g.*, heroin and illicit fentanyl) of opioids.[3] Several factors make attribution of overdoses and deaths particularly difficult. For example, the opioid data in our analyses relate to prescriptions obtained legally through retail pharmacies. However, drugs such as heroin may be laced with other drugs such as fentanyl; death

certificate data do not capture whether the source of the drug attributed as the cause of death due to overdose is legal or illicit.

The observational and descriptive design of this study also limits our ability to infer causal relationships between regulatory approvals or other interventions and opioid analgesic dispensing patterns. However, observational trends in the data provide a robust, national-level understanding of prescribing patterns. More granular analyses for specific populations or locations may not be generalizable and may reflect local interventions. Although the definitions of "brand" and "generic" used in the analysis of prescription data do not exactly align with U.S. Food and Drug Administration definitions based on new drug application or abbreviated new drug application approval, the overall impact of this difference in the analyses of the opioid analgesic product market appears to be minimal. In addition, we did not examine the role that promotional efforts may have played in increased prescribing of opioids, particularly earlier in the study period. The marketing and promotion of prescription opioid analgesics and their effects on increased prescribing have been the subject of investigations and legal actions.[30–32] Finally, we were unable to control for potential confounders such as drug pricing, and our results cannot be generalized to other drug classes.

There has been a dramatic increase in prescriptions dispensed for opioid analgesics since 1997. However, despite an increased number of opioid analgesic approvals in recent years, prescriptions dispensed in the outpatient setting declined since 2012. The current opioid analgesic market appears to be an ecosystem in which the introduction of new products, brand or generic, is more likely to lead to substitutions between products than increased dispensing. Our examination of dispensed prescription patterns shows a shifting and complex market where multiple factors likely influence prescribing, and the approval of new products alone may not be sufficient to be a primary driver of increased prescribing.

Acknowledgments

The authors would like to thank Rajdeep Gill, Pharm.D.; Corinne Woods, R.Ph., M.P.H.; at the U.S. Food and Drug Administration, Silver Spring, Maryland, for their excellent research assistance with IQVIA data. The authors would also like to thank Judy Staffa, Ph.D., R.Ph.; Sharon Hertz, M.D.; Judith A. Racoosin, M.D., M.P.H.; Douglas C. Throckmorton, M.D, at the U.S. Food and Drug Administration, and Christopher M. Jones, Pharm.D., M.P.H., from the Office of the Assistant Secretary for Planning and Evaluation in the U.S. Department of Health and Human Services, Washington, D.C., for providing helpful comments and feedback on the manuscript.

Research Support

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. This study was carried out as part of the authors' official duties at the U.S. Food and Drug Administration, Silver Spring, Maryland. However, the views expressed in this manuscript are the authors' own, and do not reflect the official positions of the U.S. Food and Drug Administration.

Competing Interests

The authors declare no competing interests.

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References

1. U.S. Department of Health and Human Services: Opioid abuse in the US and HHS actions to address opioid-drug related overdoses and deaths. Available at: https://aspe.hhs.gov/sites/default/files/pdf/107956/ib_OpioidInitiative.pdf. Accessed July 15, 2016
2. Substance Abuse and Mental Health Services Administration: Center for Behavioral Health Statistics and Quality. Results from the 2013 National Survey on Drug Use and Health: Summary of national findings. Available at: http://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs2013/NSDUH-DetTabs2013.htm#tab7.2b. Accessed July 15, 2016
3. Centers for Disease Control and Prevention: Trends in deaths involving heroin and synthetic opioids excluding methadone, and law enforcement drug product reports, by census region — United States, 2006–2015. Available at: https://www.cdc.gov/mmwr/volumes/66/wr/mm6634a2.htm?s_cid=mm6634a2_w. Accessed September 27, 2017
4. U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion: National action plan for adverse drug event prevention. 2014. Available at: http://health.gov/hcq/pdfs/ADE-Action-Plan-508c.pdf. Accessed April 4, 2016
5. The White House Office of the Press Secretary: President Donald J. Trump is taking action on drug addiction and the opioid crisis. The White House. October 26, 2017. Available at: https://www.whitehouse.gov/the-press-office/2017/10/26/president-donald-j-trump-taking-action-drug-addiction-and-opioid-crisis. Accessed October 28, 2017
6. Centers for Disease Control and Prevention: Vital signs: overdoses of prescription opioid pain relievers---United States, 1999--2008. MMWR Morb Mortal Wkly Rep 2011; 60:1487
7. CONGRESS.GOV. S.3163 – A bill to designate the calendar decade beginning on January 1, 2001, as the "Decade of Pain Control and Research". Available at: http://thomas.loc.gov/cgi-bin/query/z?c106:S.3163.IS. Accessed July 11, 2016
8. The Joint Commission: Joint Commission Statement on Pain Management. Available at: https://www.jointcommission.org/joint_commission_statement_on_pain_management/. Accessed August 8, 2016
9. Siddons A: Proposed opioid drugs illustrate quandary for FDA. CQ News. June 9, 2016. Available at: http://www.cq.com/doc/4905643?4. Accessed June 23, 2016
10. Letter to Secretary Burwell from the FED Up! Rally Steering Committee. Available at: http://feduprally.org/wp-content/uploads/2014/09/Burwell-Letter-completed-with-signature-Final.pdf. Accessed July 27, 2016
11. McCarthy M: FDA is urged to reverse its approval of new pain drug Zohydro ER. BMJ 2014; 348:g1894
12. U.S. Food and Drug Administration: Drugs@FDA: FDA approved drug products. Available at: https://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Accessed June 10, 2016
13. U.S. Food and Drug Administration: Development and approval process (drugs). Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/. Accessed June 10, 2016

14. U.S. Food and Drug Administration: Generic drugs. Available at: http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm144456.htm. Accessed June 10, 2016
15. U.S. Food and Drug Administration: Drugs@FDA: FDA approved drug products. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=PERCOCET. Accessed June 10, 2016
16. U.S. Food and Drug Administration: Drugs@FDA: FDA approved drug products. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=VICODIN. Accessed June 10, 2016
17. U.S. Food and Drug Administration: FDA list of authorized generic drugs. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm126389.htm. Accessed June 11, 2016
18. National Center for Injury Prevention and Control: CDC conversion reference table. A compilation of opioid analgesic formulations with morphine milligram equivalent conversion factors, 2014 version. Atlanta, GA: Centers for Disease Control and Prevention. Available at: http://www.pdmpassist.org/pdf/BJA_performance_measure_aid_MME_conversion.pdf. Accessed June 11, 2016
19. U.S. Census Bureau, Population Division: Intercensal estimates of the resident population by sex and age for the United States: April 1, 2000 to July 1, 2010 and annual estimates of the resident population for the United States, regions, states, and Puerto Rico: April 1, 2010 to July 1, 2015 (NST-EST2015-01). December 2015. Available at: https://www.researchgate.net/publication/228232752_Pharmaceutical_Use_Following_Generic_Entry_Paying_Less_and_Buying_Less. Accessed July 1, 2016
20. Saha A, Grabowski H, Brinbaum H, Greenberg P, Bizan O: Generic competition in the US pharmaceutical industry. Int J Econ Bus 2006; 13:15–38. Available at: https://dukespace.lib.duke.edu/dspace/bitstream/handle/10161/6726/Generic%20Competition.pdf?sequence=1. Accessed July 10, 2016
21. Huckfeldt PJ, Knittel CR: Pharmaceutical use following generic entry: Paying less and buying less (No. w17046). National Bureau of Economic Research. 2011. Available at: https://www.researchgate.net/publication/228232752_Pharmaceutical_Use_Following_Generic_Entry_Paying_Less_and_Buying_Less. Accessed July 12, 2016
22. Epidemic: Responding to America's prescription drug abuse crisis. Available at: https://www.whitehouse.gov/sites/default/files/ondcp/policy-and-research/rx_abuse_plan.pdf. Accessed July 10, 2016
23. Opioid abuse in the US and HHS actions to address opioid-drug related overdoses and deaths. Available at: https://aspe.hhs.gov/sites/default/files/pdf/107956/ib_OpioidInitiative.pdf. Accessed July 11, 2016
24. National Pain Strategy: A comprehensive population health-level strategy for pain. Available at: http://iprcc.nih.gov/docs/DraftHHSNationalPainStrategy.pdf. Accessed July 10, 2016
25. Information regarding the CDC Guideline Prescribing Opioids for Chronic Pain. Available at: http://www.cdc.gov/drugoverdose/prescribing/guideline.html. Accessed July 10, 2016
26. National Institutes of Health: The Interagency Pain Research Coordinating Committee. Federal Pain Research Strategy. Available at: http://iprcc.nih.gov/FPRS/FPRS.htm. Accessed July 15, 2016
27. U.S. Food and Drug Administration: Fact sheet: FDA opioids action plan. Available at: http://www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm484714.htm. Accessed July 10, 2016
28. Drug Enforcement Administration, Department of Justice: Schedules of controlled substances: Rescheduling of hydrocodone combination products from schedule III to schedule II: Final rule. Fed Regist 2014; 79:49661–82
29. Jones CM, Lurie PG, Throckmorton DC: Effect of US Drug Enforcement Administration's rescheduling of hydrocodone combination analgesic products on opioid analgesic prescribing. JAMA Intern Med 2016; 176:399–402
30. Van Zee A: The promotion and marketing of OxyContin: Commercial triumph, public health tragedy. Am J Public Health 2009; 99:221–7
31. Keefe PR: The family that built an empire of pain. The New Yorker. November 2, 2017. Available at: https://www.newyorker.com/magazine/2017/10/30/the-family-that-built-an-empire-of-pain. Accessed November 10, 2017
32. Garrison J: Nashville sues opioid manufacturers to recoup costs of fighting epidemic. Tennessean. December 23, 2017. Available at: http://www.tennessean.com/story/news/2017/12/23/nashville-sues-opioid-manufacturers-recoup-costs-fighting-epidemic/978861001/. Accessed December 29, 2017

Appendix 1.

Table A1. Opioid Analgesics by Active Moiety

Acetaminophen/butalbital/caffeine/codeine
Acetaminophen/caffeine/dihydrocodeine
Acetaminophen/codeine
Acetaminophen/hydrocodone
Acetaminophen/oxycodone
Acetaminophen/pentazocine
Acetaminophen/propoxyphene
Acetaminophen/tramadol
Acetylsalicylic acid/butalbital/caffeine/codeine
Acetylsalicylic acid/caffeine/dihydrocodeine
Acetylsalicylic acid/caffeine/propoxyphene
Acetylsalicylic acid/codeine
Acetylsalicylic acid/hydrocodone
Acetylsalicylic acid/oxycodone
Acetylsalicylic acid/pentazocine
Buprenorphine (Butrans, Purdue, USA)
Butorphanol
Codeine
Fentanyl
Hydrocodone
Hydrocodone/ibuprofen
Hydromorphone
Ibuprofen/oxycodone
Levorphanol
Meperidine
Methadone
Morphine
Morphine/naltrexone
Naloxone/pentazocine
Oxycodone
Oxymorphone
Propoxyphene
Tapentadol
Tramadol

Appendix 2.

Table A2. New Drug Application Approvals for Opioid Analgesics, 1997 through 2015

Drug	Active Moieties	Application Type	Approval Date	IQVIA Prescription Classification	Application Holder
Nucynta	Tapentadol HCL	Type 1 new molecular entity	Nov 2008	Trade name (brand)	Depo NF SUB, LLC (USA)
Actiq	Fentanyl citrate	Type 3 new dosage form	Nov 1998	Trade name (brand)	Cephalon, Inc. (USA)
Roxicodone	Oxycodone HCL	Type 3 new dosage form	Aug 2000	Trade name (brand)	Mallinckrodt, Inc. (USA)
Avinza	Morphine sulfate (ER)	Type 3 new dosage form (withdrawn Nov 2015)	Mar 2002	Trade name (brand)	Pfizer, Inc. (USA)
Rybix ODT	Tramadol HCL	Type 3 new dosage form (withdrawn Nov 2016)	May 2005	Trade name (brand)	Shionogi, Inc. (USA)
Ultram ER	Tramadol HCL	Type 3 new dosage form	Sep 2005	Trade name (brand)	Valent Pharmaceuticals North America, LLC (USA)
Palladone	Hydromorphone HCL (ER)	Type 3 new dosage form (withdrawn Nov 2016)	Sep 2014	Trade name (brand)	Rhodes Pharmaceuticals, LP (USA)
Exalgo	Hydromorphone HCL	Type 3 new dosage form	Mar 2010	Trade name (brand)	Mallinckrodt, Inc. (USA)
Butrans	Buprenorphine	Type 3 new dosage form	Jun 2010	Trade name (brand)	Purdue Pharma LP (USA)
Abstral	Fentanyl citrate	Type 3 new dosage form	Jan 2011	Trade name (brand)	Sentynl Therapeutics, Inc. (USA)
Morphine sulfate oral solution	Morphine sulfate	Type 3 new dosage form	Jun 2011	No trade name (generic)	Multiple
Lazanda	Fentanyl citrate	Type 3 new dosage form	Jun 2011	Trade name (brand)	Elefsee Pharma (USA)
Nucynta ER	Tapentadol HCL	Type 3 new dosage form	Aug 2011	Trade name (brand)	Depo NF SUB, LLC (USA)
Subsys	Fentanyl	Type 3 new dosage form	Jan 2012	Trade name (brand)	Insys Development Company, Inc. (USA)
Nucynta oral solution	Tapentadol	Type 3 new dosage form	Oct 2012	Trade name (brand)	Depo NF SUB, LLC (USA)
Zohydro ER	Hydrocodone bitartrate	Type 3 new dosage form	Oct 2013	Trade name (brand)	Pernix Ireland Pain Limited (USA)
Xartemis XR	Oxycodone; acetaminophen	Type 3 new dosage form	Mar 2014	Trade name (brand)	Mallinckrodt, Inc. (USA)
Hysingla ER	Hydrocodone bitartrate	Type 3 new dosage form	Nov 2014	Trade name (brand)	Purdue Pharma LP (USA)
Belbuca	Buprenorphine	Type 3 new dosage form	Oct 2015	Trade name (brand)	BioDelivery Sciences International, Inc. (USA)
Ionsys	Fentanyl HCL	Type 3 new dosage form	May 2006	Trade name (brand)	The Medicines Company (USA)
Opana*	Oxymorphone HCL	Type 3 new dosage form	Jun 2006	Trade name (brand)	Endo Pharmaceuticals, Inc. (USA)
Opana ER	Oxymorphone HCL	Type 3 new dosage form	Jun 2006	Trade name (brand)	Endo Pharmaceuticals, Inc. (USA)
Fentora	Fentanyl citrate	Type 3 new dosage form	Sep 2006	Trade name (brand)	Cephalon, Inc. (USA)
Onsolis	Fentanyl citrate	Type 3 new dosage form	Jul 2009	Trade name (brand)	BioDelivery Sciences International, Inc. (USA)
Vicoprofen	Hydrocodone; ibuprofen	Type 4 new combination	Sep 1997	Trade name (brand)	AbbVie, Inc. (USA)
Ultracet	Tramadol; acetaminophen	Type 4 new combination	Aug 2001	Trade name (brand)	Janssen Pharmaceuticals, Inc. (USA)

(*Continued*)

Table A2. (Continued)

Drug	Active Moieties	Application Type	Approval Date	IQVIA Prescription Classification	Application Holder
Embeda	Morphine; naltrexone	Type 4 new combination	Aug 2009	Trade name (brand)	Alpharma Pharmaceuticals, LLC (USA)
Targiniq ER	Oxycodone HCL; naloxone	Type 4 new combination	Jul 2014	Trade name (brand)	Purdue Pharma LP (USA)
Combunox	Oxycodone; ibuprofen	Type 4 new combination (withdrawn Nov 2016)	Nov 2014	Trade name (brand)	Forest Research Institute, Inc. (USA)
OxyContin reformulation	Oxycodone HCL	Type 5 new formulation or new manufacturer	Apr 2010	Trade name (brand)	Purdue Pharma LP (USA)
Conzip	Tramadol HCL	Type 5 new formulation or new manufacturer	May 2010	Trade name (brand)	Cipher Pharmaceuticals, Inc. (USA)
(Oxecta) Oxaydo	Oxycodone HCL	Type 5 new formulation or new manufacturer	Jun 2011	Trade name (brand)	Egalet US Inc. (USA)
Codeine sulfate oral solution	Codeine sulfate	Type 5 new formulation or new manufacturer	Jun 2011	No trade name (generic)	Multiple
Opana ER reformulation	Oxymorphone HCL	Type 5 new formulation or new manufacturer	Dec 2011	Trade name (brand)	Endo Pharmaceuticals, Inc. (USA)
Morphabond	Morphine sulfate	Type 5 new formulation or new manufacturer	Oct 2015	Trade name (brand)	Daiichi Sankyo, Inc. (USA)
Morphine sulfate IR tablets	Morphine sulfate	Type 7 drug already marketed without an approved New Drug Application	Mar 2008	No trade name (generic)	Multiple
Morphine sulfate oral solution	Morphine sulfate	Type 7 drug already marketed without an approved New Drug Application	Mar 2008	No trade name (generic)	Multiple
Codeine sulfate	Codeine sulfate	Type 7 drug already marketed without an approved New Drug Application	Jul 2009	No trade name (generic)	Multiple
Oxycodone HCL tablet	Oxycodone HCL	Type 7 drug already marketed without an approved New Drug Application	Oct 2010	No trade name (generic)	Multiple
Oxycodone HCL oral solution	Oxycodone HCL	Type 7 drug already marketed without an approved New Drug Application	Oct 2010	No trade name (generic)	Multiple
Oxycodone HCL oral solution	Oxycodone HCL	Type 7 drug already marketed without an approved New Drug Application	Jan 2012	No trade name (generic)	Multiple

*The original new drug application for Opana ER approved in 2006 is no longer marketed, but the new drug application was not withdrawn by the applicant. Therefore, generic products referencing the original new drug application as oxymorphone ER are still marketed. †Original application for OxyContin new drug application 20553 approved in 1995 was withdrawn by the applicant and officially published as withdrawn in the Federal Register effective August 2013.

ER = extended-release formulation; HCL= hydrochloric acid; IR = immediate-release formulation; ODT = orally-dissolving tablet; XR = extended-release formulation.

Appendix 3.

Table A3. Nationally Estimated Annual Number of Prescriptions Dispensed for the Top 10 Newly Approved Opioid Analgesic Brand Products and All Other Newly Approved Opioid Analgesic Brand Products* in the U.S. Outpatient Retail Pharmacy Setting from 1997 through 2015

Year	OxyContin (Oxycodone ER)	Butrans (Buprenorphine)	Opana ER (Oxymorphone)	Opana (Oxymorphone)	Nucynta (Tapentadol)	Nucynta ER (Tapentadol)	Hysingla ER (Hydrocodone)	Zohydro ER (Hydrocodone)	Subsys (Fentanyl)	Ultracet (Tramadol/ Acetaminophen)	All Other Newly Branded Products*
1997	923,841	—	—	—	—	—	—	—	—	—	—
1998	1,911,883	—	—	—	—	—	—	—	—	—	1,738,762
1999	3,504,827	—	—	—	—	—	—	—	—	—	2,705,477
2000	5,932,981	—	—	—	—	—	—	—	—	—	3,593,011
2001	7,075,767	—	—	—	—	—	—	—	—	367,314	3,919,289
2002	7,147,458	—	—	—	—	—	—	—	—	4,082,239	3,669,265
2003	7,553,728	—	—	—	—	—	—	—	—	5,126,026	2,147,874
2004	6,987,793	—	—	—	—	—	—	—	—	5,649,863	1,576,742
2005	4,458,230	—	—	—	—	—	—	—	—	2,384,471	1,473,406
2006	1,492,308	—	21,375	8,923	—	—	—	—	—	193,123	1,766,002
2007	1,870,454	—	196,975	62,408	—	—	—	—	—	112,689	1,860,588
2008	4,905,290	—	400,138	113,167	—	—	—	—	—	71,824	1,867,432
2009	5,990,029	—	582,710	165,094	133,239	—	—	—	—	50,197	1,565,718
2010	5,984,113	—	786,827	165,779	534,145	—	—	—	—	37,873	680,099
2011	5,691,037	266,332	1,190,852	60,554	920,757	37,531	—	—	—	29,843	498,359
2012	5,143,187	431,793	886,085	21,096	785,444	242,059	—	—	4,225	21,150	310,830
2013	4,865,206	497,697	721,070	2,338	598,517	259,294	—	—	19,481	16,755	236,815
2014	4,692,132	613,086	631,482	3,393	518,041	264,048	—	35,093	34,885	13,036	161,103
2015	4,227,208	643,634	560,441	3,669	489,059	289,459	85,934	64,023	40,539	9,285	75,943

Source: IQVIA, National Prescription Audit. Individual brand products represent the brand opioid analgesics dispensed in 2015 that were introduced into the market from 1997 through 2015. Only brand utilization is shown—the information does not include generic utilization. Opana ER includes the original formulation (approved 2006) and reformulation (approved 2011). OxyContin includes original formulation (approved 1995) and reformulation (approved 2010). Utilization excludes injectable formulations, opioid-containing cough/cold products, and opioid-containing medication assistance therapy products.

*All Other Newly Branded Products includes all brand opioid analgesic products approved between 1997 through 2015 that are not individually shown.

ER = extended-release formulation.