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Trends in the use and abuse of branded and generic extended release oxycodone and fentanyl products in the United States

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Abstract

Background: A great deal of previous work on the pharmacoeconomics of alcohol, tobacco and illicit drug abuse indicates that as cost decreases, abuse increases and vice versa. The application of these cost principles to the abuse of prescribed medications is largely unknown. In this paper we assessed whether the introduction of generic products in the U.S. increased the therapeutic use and illicit abuse of extended release oxycodone products and the fentanyl patch.
Methods: As an index of therapeutic use, we purchased prescription data for each of the ZIP codes in which we had corresponding abuse data. To gather information about prescription drug abuse, we elicited cases with quarterly questionnaires completed by a key informant network.
Results: The introduction of generic extended release (ER) oxycodone and fentanyl patch did not significantly change the total prescriptions written for these products, but markedly altered the composition of sales: branded sales dropped precipitously over a very short time and this was compensated for by a corresponding increase in sales of generics. Surprisingly, the introduction of generic products did not increase the abuse of ER oxycodone or fentanyl products; the branded version was the drug of choice for at least 2 years.
Conclusions: Our data suggest that drug costs alone do not increase the overall likelihood that a prescription opioid analgesic will be used therapeutically or abused. However, while generics are rapidly endorsed by insurance companies as a prescribed entity, abuse of the branded versions of ER oxycodone and fentanyl remains predominant for some time.

Keywords: Opioids; Oxycodone; Fentanyl; Generics; Prescription drug abuse; Pharmacoeconomics

1. Introduction

A great deal of previous work from the United States, Canada, Europe and Asia on the pharmacoeconomics of drug abuse indicates that as cost decreases, abuse increases and vice versa (Plamper et al., 2006; Hyland et al., 2005; Zhang et al., 2006; Caulkins, 2001; Hyatt and Rhodes, 1995; Petry, 2001; Sloan et al., 1994). These data were derived mostly from the use of tobacco and alcohol and the applicability of these models to prescribed drugs with abuse potential has never been assessed to our knowledge, with the exception of a single study we carried out with the non-scheduled opioid analgesic tramadol. We documented that the introduction of generic tramadol, which was far cheaper (<50%) than the branded product – Ultram (Ortho-McNeil Pharmaceutical) – had no discernable effect on its therapeutic use or rates of abuse (Cicero et al., 2005a). Since tramadol products (immediate release [IR] and extended release [ER] preparations and tramadol-acetaminophen containing products) were non-scheduled opioid drugs and their use was already extensive, it is possible that their market share may have already been so high that cheaper versions would not have had a measurable effect. Furthermore, tramadol products have very low rates of abuse, and command a very small street price—less than US$ 1–2 per tablet (Cicero et al., 2005a), such that price probably did not inhibit or encourage its use. Thus, we felt that our results with tramadol did not conclusively invalidate the intuitive assumption that cheaper generic drugs would lead to more use and abuse.

Unlike tramadol, oxycodone and fentanyl products, which have very high abuse rates and command very high prices in the illicit market (Cicero et al., 2005c), would seem to be perfect prescription opioid analgesics to more definitively

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assess the hypothesis that decreased costs will drive up both the use and abuse of opioid analgesics. Most importantly, we had an unprecedented opportunity to track total persons prescribed oxycodone and fentanyl products and the corresponding rates of abuse, both before and after the introduction of generics.

The concept that lowering the price of prescription drugs with abuse liability will increase their therapeutic use has never been tested, but there is a significant world-wide literature on the influence of price on the use of prescribed medications. For example, it has been shown across the world (e.g. Europe, North America and Japan) that price limits the therapeutic use of 15 different non-opioid classes of therapeutic agents to a very significant extent (Monnet et al., 2005; Huskamp et al., 2005; Paterson et al., 2006; Walker and Willey, 2004; Taira et al., 2003; Smith, 1993; Wadland et al., 2005; Campo et al., 2005; DeWitt et al., 2006; Federman et al., 2001; Goldman et al., 2004). All of these studies showed dramatic increases (up to 30%) in the use of prescribed drugs when prices dropped. Based on our previous experience with tramadol in which we found no such trend (Cicero et al., 2005a), it can be hypothesized that the use of analgesics may be price insensitive. However, this represents an N of only one with an unusual drug that is not scheduled, and, as a result, is prescribed more readily by physicians than scheduled drugs (Cicero et al., 1999, 2005a; Adams et al., 2006). In the current studies we were able to examine in much greater detail the intuitively obvious hypothesis that price will influence both the use and abuse of opioid analgesics, much as it does for other prescription, therapeutically useful drugs.

2. Methods

2.1. Patients using prescribed opioids

To calculate the therapeutic use of opioid analgesics, we purchased data from Verispan Inc. (Yardley, Pennsylvania) for each of the 3-digit ZIP codes for each quarter in which we had abuse data and calculated the average number of persons who filled a prescription, dubbed Unique Recipients of Dispensed Drugs (URDDs). This data base does not count the same patient more than once during each quarterly reporting period and, hence, the term URDDs best describes the denominator. We purchased URDDs for all oxycodone products including the branded version from the 4th quarter of 2003 through the 3rd quarter of 2006. In the case of the fentanyl patch, a breakdown of branded and generic forms was available for only the last two calendar quarters—the 2nd and 3rd quarters of 2006.

2.2. Key informant questionnaires

To gather information about prescription drug abuse we employed a key informant network consisting of 351 drug abuse experts, mainly treatment specialists, located in 217 of the nation's 973 three-digit ZIP codes. This informant network, which has been fully described in earlier reports (Cicero et al., 2005a; Cicero and Inciardi, 2005b), has previously been shown to be sufficiently sensitive to identify abuse of generic versions of branded drugs as they become available. The validity, reliability and limitations of the key informant network as a source of cases of abuse has been discussed in-depth elsewhere (Cicero et al., 1999, 2005a; Cicero and Inciardi, 2005b). A quarterly questionnaire asked whether the informant had direct, first hand knowledge and evidence of abuse or dependence which satisfied DSM-IV criteria (American Psychiatric Association, 1994) for ER oxycodone products and that the informant could distinguish with certainty whether the branded or generic drugs were utilized.

2.3. Cases of abuse

To standardize our results, we expressed rates of abuse as cases/100,000 population in the reporting ZIP codes for each quarter. This corrected for both differences in the number of ZIP codes and large population differences between ZIP codes.

2.4. Patient/subject confidentiality

The protocol was approved by the Washington University Institutional Review Board (IRB).

3. Results

3.1. Patient exposure

Fig. 1 shows the average number of URDDs for hydrocodone, ER oxycodone [branded OxyContin® and all generics], and the fentanyl patch (branded Duragesic and the generic products) during the 3-year period from quarter 4, 2003 through the end of quarter 3, 2006 in the ZIP codes reporting each quarter. The use of hydrocodone and fentanyl increased slowly but steadily over the 3 years we studied it, as was true for most opioid drugs over this time period (Cicero et al., 2007), but ER oxycodone use remained relatively flat. The introduction of generic ER oxycodone and fentanyl products did not significantly change the total use of these products.

3.2. Branded versus generic sales compositions

As shown in Fig. 2, the composition of the prescriptions filled for ER oxycodone (panel A) changed dramatically over this period; sales for branded oxycodone products dropped slightly with the introduction of a single dosage form from one company and then decreased precipitously in the last quarter of 2005 through quarter 3 of 2006 corresponding to the introduction of a large number of generics. As a mirror image, sales for generics rose in direct proportion to the loss of branded sales such

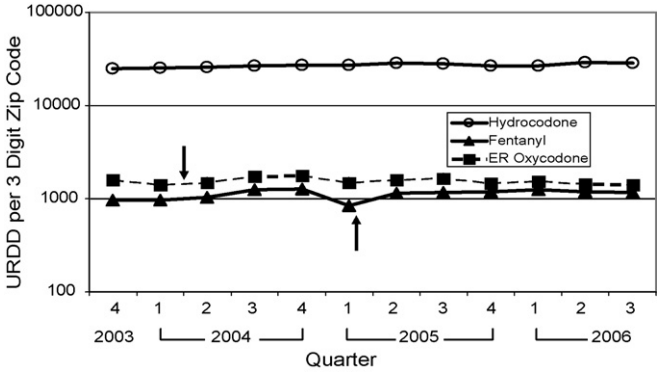

Fig. 1. The average number of Unique Recipients of Dispensed Drug (URDDs) for all ER oxycodone (OxyContin® and all generic extended release forms), the fentanyl patch (parent compound – Duragesic and all generic versions) and all hydrocodone products. The arrow indicates the introduction of generic formulations of oxycodone in 2004 and fentanyl in 2005.

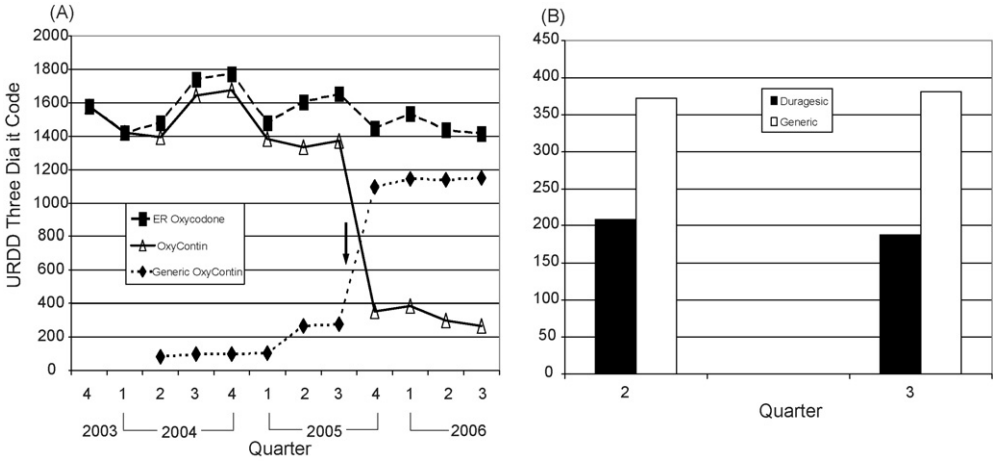

Fig. 2. (A) The average URDDs per 3-digit ZIP code for all oxycodone products and a breakdown into the generic and branded version (OxyContin®). (B) The breakdown of the branded (Duragesic) and generic fentanyl patch for the 2nd and 3rd quarter of 2006, the only data which were available.

that total usage remained the same. We were only able to obtain data for the 2nd and 3rd quarters of 2006 for fentanyl (Fig. 2B), but the same pattern as seen with oxycodone was evident: the generic constituted 67% of the total use compared to the branded version in quarter 2, and this increased to 70% in quarter 3 of 2006.

3.3. Cost of branded and generic forms of ER oxycodone and the fentanyl patch

The cost of the branded versions of ER oxycodone and the fentanyl patch, OxyContin® and Duragesic, respectively, compared to the generics are shown in Table 1 for two local (St. Louis, Missouri) pharmacies, one part of a large national retail chain, and one part of a large national discount chain. As can be seen, the generic fentanyl was on average 35–45% cheaper than the branded version and both the branded and generic patches were much cheaper in the discount chain than in the retail chain. The same was observed with oxycodone except there was no difference between stores and in both cases the generic was only 20% cheaper than OxyContin®. As is shown, the price of both the branded and generic versions varied from one drug store to another and from month to month (data not shown).

Table 1
Cost of branded and generic formulations of oxycodon and fentanyl

	Branded ($)	Generic ($)	Cheaper (%)
Oxycodone[a]			
Retail pharmacy	358.79	290.39	−20
Discount chain	351.46	289.68	−18
Fentanyl[b]			
Retail pharmacy	283.99	182.95	−35.58
Discount chain	257.88	138.68	−46.22

OxyContin® is the branded version of ER oxycodone; Duragesic is the branded version of the fentanyl patch; date: January 11, 2007.
[a] 100 tablets, 40 mg.
[b] Five patches, 75 mg.

3.4. Number of abuse cases

Fig. 3 shows the mean number of abuse cases/100,000 population of ER oxycodone, fentanyl and hydrocodone products from quarter 4, 2003 through quarter 3, 2006. Upon the introduction of the generic form there was no increase in overall abuse cases of ER oxycodone and fentanyl products for the initial 5–6 quarters, but after that there was a gradual increase in abuse, particularly for fentanyl. Interestingly, the abuse of hydrocodone also increased over the study period and, as a result, there were no statistically significant differences in the rates of increase in abuse for all these drugs. As shown in Fig. 4A, although abuse of branded ER oxycodone declined somewhat after the introduction of generic products, the branded drug remained the overwhelming drug of choice for the remainder of the study by a ratio of 10–1. Although we only have data on the breakdown of generic and branded fentanyl for the 2nd and 3rd quarters of 2006 (Fig. 4B), precisely the same 10–1 ratio existed over 12 months after the introduction of the generic.

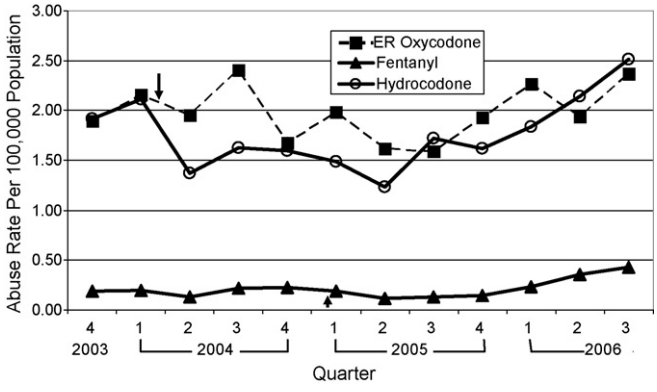

Fig. 3. The average rates of abuse, expressed as the number of cases of abuse/100,000 persons for all ER oxycodone (OxyContin® and all generic ER forms), fentanyl (Duragesic and all generic versions), and all hydrocodone products. The arrows indicate the date of introduction of generic oxycodone and fentanyl products.

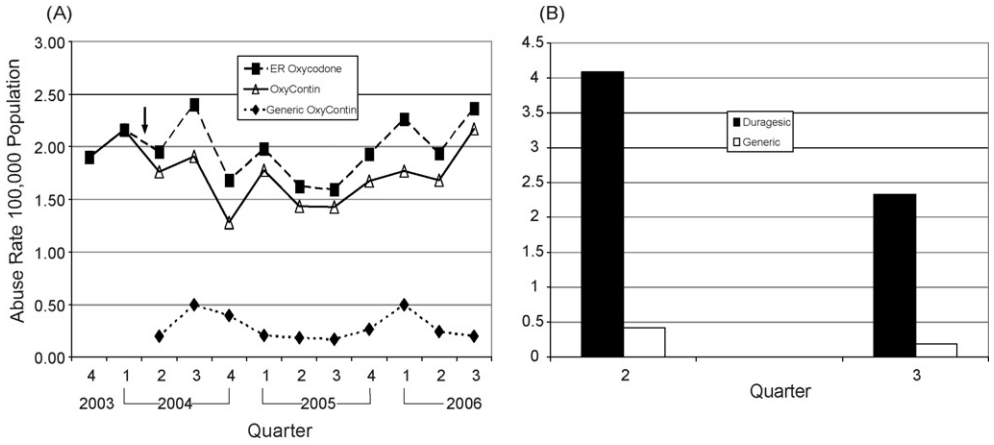

Fig. 4. (A) The average rate of abuse, expressed as the numbers of cases of abuse/100,000 persons for all oxycodone products and the branded and generic version. (B) The average rate of abuse, expressed as the numbers of cases of abuse/100,000 persons, for branded and generic fentanyl for the 2nd and 3rd quarters of 2006, the only data which were available.

4. Discussion

We found that the number of people filling prescriptions for ER oxycodone and fentanyl products did not increase markedly with the availability of cheaper generic versions, even at costs savings of over 45% in the case of fentanyl. These data suggest that drug costs alone do not increase the overall likelihood that a prescription opioid analgesic will be prescribed, but, as shown by our data, it does seem to determine whether a brand name or generic is provided as a prescription. These results are surprising in view of extensive literature which suggests that medically appropriate drug utilization is limited to a significant extent by the costs of the medications (Monnet et al., 2005; Huskamp et al., 2005; Paterson et al., 2006; Walker and Willey, 2004; Taira et al., 2003; Smith, 1993; Wadland et al., 2005; Campo et al., 2005; DeWitt et al., 2006; Federman et al., 2001; Goldman et al., 2004). Thus, as cost decreases, therapeutic use increases, by as much as 30%. One interpretation of our data is that this may not be true for opioid analgesics since these prior analyses were based on widely used non-analgesics, such as antibiotics and cardiovascular medications. We hypothesize that the medically appropriate use of opioid analgesics is restrained by factors unrelated to costs, such as fear of their abuse liability (Adams et al., 2006), and, as a result, cheaper generics do not increase overall use. However, it should also be noted that ER oxycodone products have been the subject of intense media and regulatory scrutiny and it is possible that the failure of a generic to increase sales may be, in part, due to the reluctance of physicians to prescribe the extended release product formulations. This, of course, does not apply in the case of fentanyl. Our hypothesis that cost is not a limiting factor in the use of opioid analgesics needs to be evaluated more extensively in additional studies, such as focused studies on physicians' prescribing practices regarding their use of generic drugs, including opioids.

Our results also do not support the hypothesis that overall abuse of opioid analgesics – oxycodone and fentanyl products – would rise significantly with the availability of cheaper generics, as has been observed previously for tobacco, alcohol and illicit drugs (Monnet et al., 2005; Huskamp et al., 2005; Paterson et al., 2006; Walker and Willey, 2004; Taira et al., 2003; Smith, 1993; Wadland et al., 2005; Campo et al., 2005; DeWitt et al., 2006; Federman et al., 2001; Goldman et al., 2004). The present data, coupled with prior work with tramadol (Cicero et al., 2005a), suggest that this relationship may not exist for prescription opioid analgesics. It is unclear why this apparent difference exists between illicit drugs and prescribed opioid medications. It may be noteworthy that after the first 12–18 months, there appeared to be an upward trend in the abuse of oxycodone and, particularly, fentanyl, although the increase was not significantly greater than that observed with the protypic opioid, hydrocodone. However, these data may reflect increased penetration of the generic into the illicit market and/or more acceptance of the generic as a substitute for the branded version, but this remains to be determined by continuous tracking.

A limitation in our studies is that we have no way of tracing the source of drugs available through drug dealers or other forms of diversion since the illicit market for these drugs is unique to specific areas of the country. Thus, it is possible that, by whatever mechanisms, only branded drugs are available and that this could explain in part our results. However, we have shown that doctors' prescriptions are used by 40–50% of all prescription opioid abusers, including at least some dealers (Cicero et al., 2005a, 2007) as a major source of the drug. Thus, the documented shift in physicians prescribing practices (or a pharmacist's decision) from the branded to generic product should result in an almost immediate availability of the cheaper generic on the street. It would appear that in spite of immediate availability, selection of the branded version persists for some time. These data suggest either that the price of a preferred prescription drug entity is irrelevant to abusers of that drug, or more likely that there is significant "brand loyalty" amongst addicts which has been suggested in our earlier reports with tramadol (Cicero et al., 2005a; Cicero and Inciardi, 2005b). That is, given the choice, they will pick the familiar branded drug over a generic. From qualitative information gleaned from interviews with abusers, it would appear that this reflects a fairly obvious perspective: if

one is willing to expend limited resources for a drug, there is some comfort in knowing that the product being offered is the real thing. Since generics look very different than the formulation normally purchased, this may dissuade use until it can be documented that the generic is bioequivalent in terms of those factors, such as mood altering effects, which drive abuse. Thus, the most logical interpretation of the data described in this paper on therapeutic use and illicit abuse is that cost drives insurance companies or self-payers to use the generic almost immediately for therapeutic purposes, whereas illicit users are more reticent to purchase a generic until it is validated that it is bioequivalent. We are currently exploring the latter possibility in a longitudinal study of 2500 prescription drug abusers seeking treatment for their abuse or dependence.

There are other obvious limitations to our approach. This is a limited convenience sample of individuals who enter a treatment center for abuse or are participating in a research program in which abuse is being studied. Moreover, we stressed that informants needed to be certain whether a generic or branded product was used, but there may be some imprecision in this regard. However, our results are almost identical to a prior study in which we found that arrestees charged with illegal possession of prescription opioids showed an overwhelming preference for the branded version of oxycodone in terms of theft or otherwise illicitly obtained oxycodone products (Inciardi et al., 2006). In addition, in a recent report analyzing poison control data (Bailey et al., 2006) it was shown that the introduction of the generic did not seem to increase the number of calls for all oxycodone products. Although these data have limited relevance to abuse, they do support our findings that the widespread availability of generics does not seem to reflect an overall increase in the use and abuse of ER oxycodone and fentanyl products.

Finally, a limitation in our approach is that the denominator – amount of drug prescribed – is very difficult to know with certainty since total sales by pharmacies cannot realistically ever be known with certainty. However, there are two databases, Versipan and IMS Health, Inc. which track patients who fill prescriptions or total prescriptions filled, respectively, and provide national estimates for all drugs. Both procedures are built on complex proprietary sampling techniques of several thousand pharmacies (>35,000 for Versipan) around the country, selected to be representative of all geographical areas (urban, rural, suburban), type of business (hospital or community based), customer base and so forth. From these samples, IMS estimates the total number of prescriptions filled, while Versipan, by excluding people who refill existing prescriptions, estimates the total number of unique people who fill a prescription. There are pros and cons to both methods. IMS provides total volume of sales, but fails to provide information on number of patients. Thus, patients refilling an existing prescription can be counted multiple times, meaning that a relatively small number of individuals, such as cancer patients and others in severe chronic pain, can lead to an overestimation of the unique number of patients who use the drug. Versipan, on the other hand, excludes individuals refilling a prescription in a certain time frame (quarterly in our case) and, thus, provides an excellent estimate of the number of patients using particular drugs, but underestimates the volume of prescriptions. We selected Versipan data for two reasons: first, our goal in all of these studies was to examine the risk-benefit ratios of opioid analgesics and, hence, the number of patients using a drug is the most appropriate measure; second, we felt that the use of a cheaper generic was a choice that was uniquely made by a patient and his/her insurance company. Thus, on balance Versipan and the identification of patients seemed the most logical choice. It should be noted that we previously (Cicero et al., 1999, 2005a) found that tramadol refills represented somewhere in the area of 20% of all prescriptions which held constant over time. Hence, even had we used IMS data, the relative trends and our conclusions would have been identical to those reported here since the refill rates for all drug formulations were constant.

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