Limitations of Fentanyl/Oxycodone Database Analysis

Dear Editor,

This letter is in response to the article by Malkin et al., “Cost and Utilization Patterns of Fentanyl Transdermal System and Oxycodone Hydrochloride Controlled-Release in a California Medicaid Population,” which was published in the March/April 2002 issue of the Journal of Managed Care Pharmacy.1

The authors are to be commended for attempting to examine patterns of pharmacy utilization and associated costs in the California Medicaid (Medi-Cal) program among persons receiving fentanyl transdermal system (Duragesic, Janssen Pharmaceutical Products) or oxycodone hydrochloride controlled-release (OxyContin, Purdue Pharma), and to compare pharmacy claims to dose administration guidelines for these drugs; they are correct in noting that information of this nature is quite limited in the published literature. Unfortunately, however, the methods employed by Malkin and colleagues are so seriously flawed as to render their conclusions utterly worthless. Problems with the study include:

(1) The authors limited their attention to persons in a Medi-Cal database who were enrolled in the fee-for-service portion of this program; they constitute only about 60% of total Medi-Cal enrollment. Malkin et al. provide no justification for excluding from their study all persons who were enrolled in the managed care portion of this program, and its impact on their findings is unknown and potentially significant.

(2) While not central to their analysis or conclusions, their designation of prescriptions as being for the treatment of malignant pain based on the presence of a cancer diagnosis on a single medical claim within the prior 12 months seems highly questionable and prone to significant error. Their findings with respect to the breakout of prescriptions for the treatment of malignant versus nonmalignant pain should therefore be regarded with some skepticism.

(3) Of significant concern is the central role that the authors have accorded information from the days-supplied field on pharmacy claims for fentanyl transdermal system or oxycodone hydrochloride controlled-release. In fact, their entire line of argument and conclusions are dependent upon the accuracy of this information, as they use this measure (i.e., days of drug supplied) to calculate average daily dosage as well as average daily, monthly, and annual costs. It therefore is troubling that the days-supplied field is optional and need not be completed by the pharmacist to receive payment from Medi-Cal. The authors note that this information was missing for substantial numbers of patients.

(4) Even among those for whom data were not missing in the days-supplied field, however, the information may be unreliable and bear little correspondence to the actual number of therapy-days that patients received—and by implication, to their average daily dosage or daily cost of therapy. What evidence is there that this might be the case? Unfortunately, Malkin et al. do not report any information on the frequency distribution of therapy-days supplied that would allow the reader to gauge the accuracy of these data.

Therefore, to address this issue, we looked at another large integrated claims database (Protocare Sciences), which has similar fields to those of the Medi-Cal database, to assess the reliability of information on therapy-days supplied. Similar to the methods employed by Malkin et al., we identified all patients who had received either fentanyl transdermal system (n=3,770) or oxycodone hydrochloride controlled-release (n=10,079) between January 1, 1998 and June 30, 2000. Despite the fact that both of these medications are indicated for the treatment of chronic pain, therapy-days supplied was 10 or less for more than 10% of all claims. Even more disconcerting, however, is the fact that these prescriptions had substantially higher average daily dosages than those where the reported number of therapy-days supplied was greater. While one can well imagine that some patients might receive either of these medications for a relatively brief period of time (e.g., following surgery), the fact that patients with relatively few therapy-days supplied had much higher average daily dosages suggests that the former measure may be under-reported for many patients and hence quite unreliable. As noted above, if this information is inaccurate, then so too are average daily dosages and costs that the authors calculate using this measure.

(5) The authors’ basecase assumption that oxycodone hydrochloride controlled-release patients should take only one tablet at each dosing is invalid. Malkin et al. are simply wrong when they state (p. 133) that this is “recommended in the manufacturer’s prescribing information.” The package insert for OxyContin, in fact, provides no guidance as to the appropriate number of tablets that patients should take either per dose or per day. There is thus no basis for the authors’ assumption that patients should take at most two OxyContin tablets daily. Furthermore, for many total daily dosages of OxyContin that patients often receive, it is impossible to do this with only two tablets per day. For example, a 60 mg dose can only be taken as three 20 mg tablets or six 10 mg tablets. The authors’ conclusion that the average prescription for oxycodone hydrochloride controlled-release exceeds the recommended number of tablets per day by 70% is thus clearly wrong. While the authors relax their two-tablet-per-day assumption in a sensitivity analysis, the fact remains that their principal conclusions—and the ones presumably that readers will remember—all follow from this obvious misstatement of fact.

(6) The authors report that OxyContin therapy costs approximately $25 more on average each month than Duragesic therapy. This “finding,” however, is based on the estimated cost per day of therapy (which they calculate by dividing the cost of each pharmacy claim by the number of therapy-days supplied) multiplied times~30 (i.e., the number of days in a month). As noted above, however, if the number of therapy-days is under-reported on some prescriptions, an upward bias would be imparted to the estimated daily and monthly costs of therapy. Little significance should therefore be accorded to the comparison of monthly therapy costs that the authors report.
Finally, it should be noted that in calculating savings to the Medi-Cal program from switching patients from oxycodone hydrochloride controlled-release to fentanyl transdermal system, the authors use the conversion information that is provided in the package insert for Duragesic. In fact, had they used the conversion information that is provided by the manufacturer of OxyContin, they would have arrived at distinctly different projections and hence conclusions. For example, using the Duragesic package insert, the authors assumed that patients receiving OxyContin 30 mg q12h should be started on a 25 mg/hr fentanyl transdermal patch. The Duragesic package insert, however, specifically states that the "recommended initial...dose (when converting from other opioids)...is conservative, and 50% of patients are likely to require a dose increase after initial application..." In contrast, the package insert for OxyContin advises clinicians that the appropriate conversion when going from fentanyl transdermal system 25 mg/hr to OxyContin is 10 mg q12h. This conversion schedule means that for a patient receiving Duragesic at a prescribed dosage of 75 mg/hr, the appropriate conversion dose to OxyContin would be 30 mg q12h. Not surprisingly, the authors' findings would have changed substantially had they used the latter rather than the former conversion schedule. Given the discrepancy between these two package inserts (both of which have been approved by the U.S. Food and Drug Administration), it would have been more honest and balanced had the authors performed their calculations using both alternative conversion schedules.

In summary, while Malkin et al. are to be commended for their attempt to examine pharmacy claims for patients receiving fentanyl transdermal system or oxycodone hydrochloride controlled-release in the Medi-Cal program, their methods are so seriously flawed and biased as to render their conclusions completely groundless.

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DISCLOSURE

Dr. Oster disclosed that he has received research funding from Purdue Pharma.

REFERENCES


Dear Editor,

We are writing in regard to “Cost and Utilization Patterns of Fentanyl Transdermal System and Oxycodone Hydrochloride Controlled-Release in a California Medicaid Population” published in the March/April 2002 issue.1 We will refer to it as the “Study.” This article clearly demonstrates the potential value of using administrative databases for investigation purposes; however, it also demonstrates limitations and potential pitfalls in conducting database analyses.

- The Study conducted the analysis only on the fee-for-service (FFS) portion of the Medi-Cal database, which was 61.3% of 1997 Medi-Cal enrollment. Based on 1997 and 2000 HCFA figures, only 52.18% and 44.3% of the U.S. Medicaid population were enrolled in FFS programs.2 These results suggest that the Study cannot be extrapolated and results are solely those found in the FFS portion of the Medi-Cal dataset.

- The Study extrapolated FFS findings to the managed care portion of the Medi-Cal population (Table 3: “Total cost per year across all Medi-Cal patients”). Multiple studies show FFS patients have poorer health status and different demographics than managed care patients.3,4 Reported extrapolated findings are invalid, and, as a result, the Study reported findings will be different than actual results due to population selection bias.

- The Study uses the “Days supplied” field as the primary driver in this analysis. “The days supply field is not a mandatory field in the Medi-Cal database, and missing values were coded as zero.” Interestingly, while the authors acknowledge the poor quality of the data field, they continue to use the field to determine “mean number of units dispensed per days supplied” and eliminate claims from the analyses (4.2% of the fentanyl transdermal system prescription sample and 2.3% of the oxycodone HCL controlled-release prescription sample). Use of a nondiagnostic field to base primary results is one of the most reckless ways to conduct and analyze a database analysis.

- Figures listed in Table 3 of the Study are not transparent. First column, third row, the mean cost per month of the 25 mg/hr transdermal fentanyl system is $129.04. If multiplied, $129.04 by 12, a total annual cost of $1,548.48 will be obtained. “The total cost per year across all Medi-Cal patients” is $0.6 million. When $0.6 million is divided by the annual cost, $1548.48, results in 387.47 patients who received the 25 mg/hr fentanyl transdermal system. This number cannot be correct since the sample size of the 25 mg/hr fentanyl transdermal is 16,275. This inconsistency affects all of Table 3 results.

- In Figure 1, the Study suggests that oxycodone HCL controlled-release users “exceed the recommended number of tablets per day.” No information exists in the OxyContin package insert with regard to tablet quantity restrictions. Additionally, both Roth et al5 and Caldwell et al6 have reported between 29%-36.8% of patients require asymmetric dosing when using oxycodone HCL controlled-release. The authors fail to address this phenomenon in their analysis.

- The Study conducted a sensitivity analysis using mean number of tablets per dosing (Table 4). The “mean number of tablets per
The Authors’ Respond

We welcome and encourage thoughtful critique of retrospective database studies. While the respondents’ letters did raise certain valid points, they also distorted or misunderstood several other points. We will attempt to clarify these issues.

Both respondents were concerned with the use of the days-supply field in this study. Seifeldin et al. said that use of a non-mandatory field (i.e., referring to the days-supply field) is “one of the most reckless ways to conduct and analyze a database analysis,” and Oster said that “this information was missing for substantial numbers of patients.” In actuality, the days-supply field was present in 97 percent of claims, so it is unlikely that the absence of data in this field skewed our findings in a meaningful way. As stated in the Methods section (p. 133): “A total of 101,773 fentanyl transdermal system and oxycodone HCl controlled-release prescriptions were identified, accounting for 18,271 patients. The days-supply field is not a mandatory field in the Medi-Cal database and missing values were coded as zero. We excluded 2,414 fentanyl transdermal system prescriptions (4.2% of our sample) and 1,015 oxycodone HCl controlled-release prescriptions (2.3% of our sample) where days-supply was missing.”

The respondent letters are correct when they allude to the importance we attributed to the days-supply field of pharmacy claims in order to identify daily dosage. Oster further states that this information “may be unreliable and bear little correspondence to the actual number of therapy days that patients received—and by implication, to their average daily dosages or daily cost of therapy.” Although previous studies have reported a high degree of reliability and validity of prescription drug data, it is appropriate to critically examine the fields upon which analyses of administrative data are based and to confirm that key fields are valid. Others have proposed days supply as a fundamental benchmark measure of utilization in pharmacy benefit management.

In order to elucidate on the relationship between the way in which a drug is prescribed and how it is actually taken by patients, Janssen Pharmaceutica recently commissioned a multisite survey of 691 patients (253 fentanyl transdermal system patients and 438 oxycodone HCl controlled-release patients). Although we are reluctant to cite new, as-yet unpublished data because the methods and results have not yet been subjected to peer review, we make an exception in this case because of the respondents’ strong concerns about our reliance on the days-supply field in the Medi-Cal database. The results are highly consistent with the findings of Malkin et al.: the median patient in the Janssen-commissioned survey who received fentanyl transdermal system reported wearing his or her current patch for 2.5 days; for oxycodone HCl controlled-release, the median patient reported taking one oxycodone HCl controlled-release tablet per dosing, with three dosings per day. In short, the patient-reported data were extremely consistent with both the assumptions and the findings reported in the claims-based study that is the subject of the respondents’ criticism. These results will be submitted to a peer-reviewed journal, and we believe they will add significant clarification to the utilization patterns associated with these two long-acting opioids.

Drs. Seifeldin, Grossman, and Luo are employees of Purdue Pharma.

REFERENCES


7. OxyContin [package insert]. Stamford, CT, Purdue Pharma L.P.
Regarding which conversion guidelines to use to determine equianalgesic dosing, particularly in the absence of a “gold standard,” Oster is correct when he noted that we would have gotten different results if we had used conversion information provided by the manufacturer of oxycodone HCl controlled-release. Our approach would have been more balanced had we relied on conversion information provided by manufacturers of both of the products we examined.

Both respondent letters are correct when they note that our study included only patients enrolled in the fee-for-service portion of Medi-Cal and that, therefore, our results should not be generalized to Medicaid programs with formulary policies that differ from those of Medi-Cal. This is a limitation that we pointed out in our article (e.g., “the results of this study may not be generalizable to either private health plans or Medicaid programs with formulary policies that differ from those of Medi-Cal” (pp. 138-39), and “Our findings underscore the need for additional studies to better understand the pharmacy claims in large patient populations, such as managed care” (p. 140).

The other points raised by the respondents either distort what we wrote or are based on a misunderstanding of our methods.

Both respondent letters assert that we mischaracterized the prescribing information for oxycodone HCl controlled-release with respect to the number and timing of dosings per day. Oster says we stated that our assumption that patients take only one tablet at each dosing is “recommended in the manufacturer’s prescribing information” (p. 133). Here is what we actually wrote:

“We examined the dosage, number of units dispensed, and days supplied for each prescription. We then computed the mean number of units dispensed per days supplied (mean units per prescription divided by the mean days supply per prescription), and compared this to the mean number of units dispensed per day recommended in the manufacturer’s prescribing information. When performing this comparison for oxycodone HCl controlled-release, we assumed that patients consume only one tablet at each dosing. We performed a sensitivity analysis taking into account the possibility that some patients consume more than one tablet per dosing (for example, two tablets at night and one tablet in the morning).”

Seifeldin et al. state that we did not address the phenomenon known as asymmetric dosing. Yet we did so in the quotation above and subsequently:

Manufacturer’s prescribing information for oxycodone HCl controlled-release indicates that some patients may benefit from asymmetric dosing (a different dose given in the morning than in the evening), tailored to their pain pattern. The extent to which actual use exceeds recommended use is sensitive to our assumption that patients take only one tablet per dosing. However, under a broad range of plausible assumptions about the number of tablets taken at each dosing, oxycodone HCl controlled-release is taken more frequently than is recommended by the manufacturer’s prescribing information (pp. 135, 137).

In short, we disagree with the respondents’ contention that we mischaracterized the manufacturer’s prescribing information. We clearly described our base case assumption—namely, that patients consume only one oxycodone HCl controlled-release tablet at each dosing—but considered a range of reasonable alternatives. Our conclusion—that oxycodone HCl controlled-release use exceeds the twice-a-day dosing—is robust to a broad range of plausible assumptions about the number of tablets that patients take at each dosing.

Seifeldin et al. go on to say that our sensitivity analyses about the number of dosings per day “do not make sense” because we appear to be assuming that many patients break or crush oxycodone HCl controlled-release tablets. No such assumption was implicitly or explicitly made. When we assumed a mean number of tablets per dosing of 1.1, this does not mean that every patient takes 1.1 tablets per dosing. It means that 9 patients take 1 tablet per dosing and 1 patient takes 2 tablets per dosing. This is explained clearly on p. 137 of our article.

Seifeldin et al. state that the figures in Table 3 are not transparent. As we noted in our methods section (p. 133), the cost per year was derived as the mean cost per prescription times the number of prescriptions per year. Thus, the $0.6 million annual cost of 25 _g/hr fentanyl transdermal system is simply the number of 25 _g/hr prescriptions per year (16,275 x 12/32) times the mean cost of each prescription ($92.63). (Deflating the number of prescriptions by 12/32 is necessary because the dataset covers 32 months rather than 12.)

In short, while the respondents raise certain valid issues, we stand by the central finding of our study: fentanyl transdermal system and oxycodone HCl controlled-release both appear to be used in a manner that is inconsistent with manufacturers’ prescribing information. However, the difference between “real-world” prescription patterns and the manufacturers’ PI recommendation is more acute with oxycodone HCl controlled-release tablets. This difference has cost implications and is supported by the cross-sectional survey of actual patient utilization patterns.

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REFERENCE

Correction
In the May/June 2002 Journal of Managed Care Pharmacy, author Hema Viswanathan’s e-mail (page 211) was incorrect. She can be reached at hema1@pharmacy.purdue.edu. In the same article in Table 1 (page 213), the generic name of Corex was misspelled; the correct name is chlorpheniramine maleate.