Dear Editor,

We are writing to discuss the paper entitled "Patient-Reported Utilization Patterns of Fentanyl Transdermal System and Oxycodone Hydrochloride Controlled-Release Among Patients With Chronic Nonmalignant Pain" in the May/June 2003 issue of the *Journal of Managed Care Pharmacy*.¹

We credit the authors in their task of collecting information on chronic pain patients via survey method, as this type of study in chronic nonmalignant pain patients has never been conducted. The results, although intriguing, were based on a single survey with no follow-up survey assessments.

It is interesting to note that the only values that were significant in the multivariate analyses were gender (more females in the fentanyl transdermal system group) and duration on medication (those taking oxycodone hydrochloride controlled-release were taking the medication longer than those on the fentanyl transdermal system). We have several questions and comments that we would like the authors to address in order to provide the readers with a more complete understanding of the results:

1. We recommend providing a complete version of the survey to the readership. The pieces of the survey provided in the article do not permit the reader to make a full assessment of the questions asked. A full version of the survey should be made available so the reader can make a more complete and objective assessments of the findings. Additionally, a complete version of the survey could be helpful to other health care workers interested in this data.
2. We recommend collecting pain scores from a valid and reliable scale when surveying pain patients. This survey examined duration of adequate pain relief based on recall without using a pain scale. We feel the primary endpoint of interest for pain patients should be pain control as measured by a valid reliable instrument.
3. This study focused on pain clinics. It should be noted that patients referred to such practices often are not representative of the general population that has a pain complaint. Thus, there is substantial ascertainment bias in this study, which may reduce the generalizability of the results to a typical primary care setting.
4. Why were differences within the 2 groups not accounted for in the beginning of the analysis? The 2 groups compared appear to be different with regard to gender (more females in the fentanyl transdermal system group), time on therapy (those taking oxycodone hydrochloride controlled-release were taking the medication longer than those on the fentanyl transdermal system), and use of supplemental analgesia (the oxycodone hydrochloride controlled-release group were taking significantly less). There was no control for potential confounding in this analysis.
5. Why was nonparametric analyses employed, and why did the results (morphine equivalents of controlled-release oxycodone was significantly less than the transdermal fentanyl system) change dramatically after controlling for patient

characteristics (morphine equivalents of the transdermal fentanyl system was less than controlled-release oxycodone)?

6. In conducting the multivariate analyses, it was mentioned that the sample selection was not normally distributed and therefore the bootstrapping method (repeated samples drawn from a smaller sample to estimate the empirical distribution) was instituted. Why was a complete presentation of the distribution results not available in the manuscript? A complete presentation of the distribution results would assist the readers in understanding what was not normally distributed and would allow the reader to make the judgment if moving on to bootstrapping is appropriate. We feel bootstrapping was not necessary since the population of surveyed patients was 437 for the oxycodone hydrochloride controlled-release group and 253 for the fentanyl transdermal system group.
7. In tables 3 and 4, the mean, standard deviation, and median were provided, which are very helpful in understanding the distribution; however, more information on distribution would be helpful to the reader. We request the authors to provide a minimum and maximum value when the standard deviation is greater than the mean and provide the mode when it is not equal to the median. Providing this information will help the reader assess the distribution within each group.
8. A sensitivity analyses was performed on the morphine equivalents for transdermal fentanyl system but not for controlled-release oxycodone. We request that either a sensitivity analyses be conducted for both agents or a single morphine equivalent dosage be selected for the transdermal fentanyl system. The current approach induces bias on the effective dose of both the transdermal fentanyl system and the controlled-release oxycodone tablet. Whereby the transdermal fentanyl system is given the opportunity to be more or less effective, the controlled-release oxycodone tablet is not given this opportunity.

The method for data collection in these chronic pain patients is unique and provides beneficial information that cannot be captured through either a retrospective database analyses or a randomized clinical trial. We appreciate the publication of this information and hope to have our questions answered by the authors.

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REFERENCES

1. Ackerman SJ, Mordin M, Reblando J, et al. Patient-reported utilization patterns of fentanyl transdermal system and oxycodone hydrochloride controlled-release among patients with chronic nonmalignant pain. *J Managed Care Pharm*. 2003;9(3):223-31.

The Authors Respond

We welcome and encourage thoughtful critique of prospective, observational, multicenter studies. The respondent's letter raises several points about our methods, which we attempt to clarify below.

This patient-reported utilization study¹ was conducted to assess the actual daily use of fentanyl transdermal system (transdermal fentanyl) and oxycodone hydrochloride (HCl) controlled-release among patients with chronic nonmalignant pain and to compare these patterns to standard dose administration guidelines recommended in the manufacturers' prescribing information (PI). The focus of this investigation was patient-reported utilization patterns, not pain control. As such, the patient-reported utilization survey (from which questions were included in the manuscript) inquired about the duration of adequate pain relief by using time intervals (refer to Tables 3 and 4) that could then be compared with the standard dose administration guidelines as recommended in the manufacturers' PI. We agree that studies in which the primary outcome measure is pain control should include a validated pain-related instrument.

Seifeldin and Grossman are correct in that this survey was administered to patients with chronic nonmalignant pain referred to clinics that specialize in pain management. As we previously noted in the manuscript, the results of this study may not be generalizable to either malignant pain patients or patients who seek medical care in other settings.

To better describe the distributions, below we have provided the minimum and maximum values for variables where the standard deviation exceeded the mean; we also have provided the mode for variables where the median did not equal the mode. Among oxycodone HCl controlled-release patients, the interval between administrations was 7.8 hours, on average, while the mode was 6 hours (median 7 hours). The mode for daily dose of oxycodone HCl controlled-release was 60 mg (median 80 mg), and the minimum and maximum values were 10 mg and 2,400 mg, respectively. Among fentanyl transdermal system patients, the number of days the current patch will be worn was 2.5, on average, while the mode was 2 days (median 2.5 days). The mode for daily dose of transdermal fentanyl was 50 mcg/hour (median 75 mcg/hour).

Several points raised by the Seifeldin and Grossman are based on a misunderstanding of our methods.

Both unadjusted (Table 5) and adjusted (Table 6) analyses were performed. By definition, the unadjusted analysis did not control for potential confounding factors, whereas the adjusted analysis did control for demographic and clinical characteristics that differed between groups. A patient characteristic that is associated with both the treatment (transdermal fentanyl or oxycodone HCl controlled-release) and the outcome (daily oral morphine equivalents) would be considered a confounding factor and could influence the results and inferences, as we observed in this study.

Because the manufacturer's PI for transdermal fentanyl pro-

vides a range of oral morphine equivalents (Table 1),² in the "base case" analysis, the average of the range for each dosage strength of transdermal fentanyl was used to calculate daily oral morphine equivalents (Table 5). In addition, sensitivity analyses were conducted by varying the oral morphine equivalents for each dosage strength of transdermal fentanyl between the low and high values (Table 5). A priori, we selected the "base case" oral morphine equivalents of transdermal fentanyl for use in the multivariate analysis, which adjusted for demographic and clinical characteristics that differed between groups.

A nonparametric "bootstrapping" approach was used to estimate the mean difference in daily oral morphine equivalents from oxycodone HCl controlled-release compared with transdermal fentanyl because the dependent variable—oral morphine equivalents—was skewed. Bootstrapping involves "resampling" the data many times (i.e., repetitive computations) to generate an empirical estimate of the entire sampling distribution.³ A nonparametric bootstrapping procedure allowed development of an *asymmetric* 95% confidence interval around the mean difference in daily oral morphine equivalents between groups. A parametric bootstrapping approach may have inappropriately developed a *symmetric* 95% confidence interval. The nonparametric bootstrapping approach also permitted estimation of the probability that the daily oral morphine equivalents from oxycodone HCl controlled-release exceeded the daily morphine equivalents from transdermal fentanyl. The probability that oxycodone HCl controlled-release patients had higher oral morphine equivalents was 82.6%, which suggests a trend toward higher oral morphine equivalents per day in the oxycodone HCl controlled-release group (Table 6).

While the respondents raise certain valid points, we stand by the central finding of our study: transdermal fentanyl and oxycodone HCl controlled-release both appear to be used by patients in a manner that is inconsistent with the standard recommendation in the manufacturers' PI; however, the difference between patient-reported utilization (i.e., average interval between oxycodone HCl controlled-release administrations or number of days the current transdermal fentanyl patch will be worn) and the standard recommendations in the manufacturers' PI (i.e., every 12 hours for oxycodone HCl controlled-release and every 72 hours for transdermal fentanyl) is more pronounced with oxycodone HCl controlled-release. Among oxycodone HCl controlled-release patients, only 18% of patients were observed to exhibit every-12 hour administration patterns (Table 3), whereas 41% of transdermal fentanyl patients reported wearing the patch for at least 3 days (Table 4).

These findings contradict a statement in a previous letter to the Editor⁴ that stated, "No information exists in the OxyContin package insert with regard to tablet quantity restrictions" While that is true, and the oxycodone HCl controlled-release package insert permits asymmetric dosing, there are instructions that indicate oxycodone HCl controlled-release tablets should be taken every 12 hours. Despite the different measures of utiliza-

tion used in this study versus the prescription pattern study reported by Malkin et al.,⁵ which was based on a claims database analysis using California Medicaid (Medi-Cal) data, the findings are consistent; that is, oxycodone HCl controlled-release is *prescribed*, on average, and *taken*, on average, more frequently than every 12 hours, thereby supporting the validity of the our conclusions.⁶ Our study results also suggest that a pharmacoeconomic evaluation based solely on the PI dosing recommendations may lead to an inaccurate assessment of the true costs of these agents.

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REFERENCES

1. Ackerman SJ, Mordin M, Reblando J, et al. Patient-reported utilization patterns of fentanyl transdermal system and oxycodone hydrochloride controlled-release among patients with chronic nonmalignant pain. *J Managed Care Pharm.* 2003;9(3):223-31.
2. *Physicians' Desk Reference*, 54th ed. Montvale, NJ: Medical Economics Company; 2002.
3. Mooney CZ, Duval RD. *Bootstrapping: A Nonparametric Approach to Statistical Inference*. Newbury Park, California: Sage Publications, Inc.; 1993.
4. Seifeldin R, Grossman P, Luo R. Limitations of fentanyl/oxycodone database analyses [letter to the editor]. *J Managed Care Pharm.* 2002;8(4):301-02.
5. Malkin JD, Ackerman SJ, Schein J, et al. Cost and utilization patterns of fentanyl transdermal system and oxycodone hydrochloride controlled-release in a California Medicaid population. *J Managed Care Pharm.* 2002;8(2):132-40.
6. Curtiss FR. Searching for drug benefit benchmarks—cost per day of therapy [editorial]. *J Managed Care Pharm.* 2002;8(1):54-55.