The Prevalence of Opioid-Related Major Potential Drug-Drug Interactions and Their Impact on Health Care Costs in Chronic Pain Patients

ABSTRACT

BACKGROUND: Literature has shown that chronic pain patients prescribed opioids are at an increased risk for experiencing drug-drug interactions as a result of polypharmacy. In addition, chronic, noncancer pain patients who experience drug-drug interactions have been shown to have greater health care utilization and costs. However, no study has focused on the health economics of major clinically significant drug-drug interactions associated with long-acting opioids.

OBJECTIVES: To (a) estimate the prevalence of major drug-drug interactions among patients prescribed a long-acting opioid and (b) evaluate the potential impact of major drug-drug interactions on health care costs.

METHODS: This study was a retrospective cohort analysis using claims data from the MarketScan Commercial Claims and Encounter Database between 2008 and 2010. Patients with at least 1 prescription for a long-acting opioid for ≥ 30 days were placed into cohorts according to the expected clinical impact of the potential drug-drug interaction: major versus none. Propensity score matching was used to mitigate differences in baseline characteristics between the cohorts. Health care costs were based on payments for all covered health care services, which consisted of inpatient and outpatient medical, emergency department, and outpatient prescription costs.

RESULTS: Among 57,752 chronic, noncancer pain patients who met all inclusion and exclusion criteria, 5.7% (3,302) were exposed to a potential major drug-drug interaction. The costs associated with a potential interaction versus no potential interaction were significantly more after baseline characteristics of the cohorts were normalized by propensity score matching. Monthly health care costs in the 90-day post-index period were significantly greater ($3,366 vs. $2,757, a $609 difference) in patients exposed to a potential drug-drug interaction of major clinical significance, compared with those not exposed to a drug-drug interaction. The higher health care costs were mainly driven by outpatient and inpatient medical costs.

CONCLUSIONS: Exposure to potential drug-drug interactions may result in unnecessary and unintended health care costs. Physicians should be made aware of commonly administered cytochrome P450 (CYP450) metabolized drugs in the chronic pain patient and consider prescribing non-CYP450 metabolized opioid and nonopioid analgesics. Managed care’s use of utilization management tools to avoid these exposures may reduce costs.

What is already known about this subject

- A significant population of chronic pain opioid users, especially those with chronic low back pain and osteoarthritis, are exposed to potential drug-drug interactions.
- The economic burden associated with drug-drug interactions in chronic pain patients is substantial. Previous published reports have indicated that patients who have chronic low back pain or osteoarthritis, and who are prescribed an opioid, have increased overall health care costs (medical plus prescription payments at 6 months) of approximately $250-$575 and $1,000-$1,200, respectively, depending on age.

What this study adds

- A relatively small proportion of chronic, noncancer pain patients (5.7%) prescribed long-acting opioids may be exposed to potential drug-drug interactions that can have major clinical impact.
- Exposure to these major drug-drug interactions is associated with an increased monthly cost of $609 in the 90-day post-index period.

Persistent pain impacts 116 million adults and costs $560-$635 billion annually in United States. Multimodal management strategies that use both nonpharmacological and pharmacological interventions are commonly employed in the practice of pain management. Furthermore, chronic noncancer pain (CNCP) patients, who commonly present with comorbidities or related medical conditions, require rational polypharmacy for the specific disease management. When multiple drugs administered concomitantly are metabolized and modulated by the same enzymatic system—such as cytochrome P450 (CYP450)—through induction or inhibition, a pharmacokinetic drug-drug interaction (pDDI) can occur. The clinical expression of this interaction may be undetectable or may lead to a clinically relevant event whose manifestations can vary in severity and be difficult to predict. Chronic opioid users are at an increased risk of experiencing such pDDIs. According to guidelines issued jointly by the American Pain Society and the American Academy of Pain Medicine, chronic opioid therapy...
Drug-drug interactions may also impact hospitals’ economic performance in terms of a longer length of hospital stay, higher operating expenses, and decreased profits. While the global incidence of pDDIs is not known, a sharp increase in prevalence was noted among seniors from 1992 to 2005, with a prevalence of 19.2% in those aged > 70 years. Previous research has reported a 27% prevalence of pDDIs among ambulatory chronic low back pain patients using CYP450 opioid analogic drugs and 26% in patients with osteoarthritis. Among patients using opioids, regardless of diagnosis, the mean 6-month health care costs after pDDIs were significantly higher versus matched patients without pDDIs (difference of $667). Thus, pDDIs seem to lead to side effects that incur increased health care costs. The high prevalence of pDDIs suggests that opioid product selection should include considerations of CYP450 metabolism, but the relatively high prevalence of these interactions may hinder utilization management efforts.

There are many isoenzyme pathways within the CYP450 system, and the most relevant ones related to opioids are 3A inhibition, 3A induction, and 2D6 inhibition. For example, an opioid metabolized via the 3A pathway may not interact with a concomitant drug metabolized via the 2D6 pathway. More importantly, the significance of the clinical impact of these interactions could vary depending on the particular opioid/precipitant drug combination. Some studies have been published on the topic of CYP450-related pDDIs between opioids and precipitant drugs. However, one major limitation associated with these studies was that the pDDI was simply defined as a concurrent exposure between an opioid metabolized through the CYP450 system and a precipitant drug (inducer or inhibitor), which was also metabolized through the CYP450 system.

In this study, we focus on the chronic use of long-acting opioids (LAOs), since their longer-term exposures to pDDIs may provide information for a population most clinically impacted by economic consequences. First, we looked at the prevalence of pDDIs among chronic LAO users to understand the scope of the problem in these patients. Second, we evaluated the composition of these pDDIs related to the enzyme system involved. Finally, we identified the costs for patients with pDDIs who may be expected to experience adverse drug reactions (ADRs) of major clinical significance, compared with a matched sample of patients whose concomitant exposures are without the potential for ADRs of major clinical significance. Our purpose was to provide data that would guide or influence decisions regarding utilization management efforts related to LAO products in chronic use.

### Methods
This study was a retrospective cohort analysis using health care claims derived from the MarketScan Commercial Claims and Encounter Database, which represents the health care experiences of approximately 110 million lives. Data include enrollment, medical (inpatient and outpatient), and prescription (outpatient) records integrated from all providers of care. For the study period from years 2008 to 2010, data were collected from 150+ large employers (200+ carriers) and 20+ regional health plans with annual enrollment around 40 million. The covered patients include active employees, early retirees, continuing insurance beneficiaries, and their dependents insured by employer-sponsored plans (i.e., non-Medicare eligible). The MarketScan commercial database is representative of the commercially insured population in the United States and has been published widely in a variety of therapeutic areas focusing on epidemiology and outcomes research.

The MarketScan commercial database used in this study is de-identified and fully compliant with the Health Insurance Portability and Accountability Act of 1996; thus, this study was exempt from the review and approval of an institutional review board.

### Opioids, CYP450 Precipitant Drugs, and CYP450 Pathways
Based on a recently published article by Overholser and Foster (2011), we developed an algorithm to identify pDDIs and classified them as having potential to cause ADRs of major clinical significance (pDDI-Major). The 9 most commonly prescribed opioids are displayed by their CYP450 pathways and potential to cause ADRs of major clinical significance (Table 1). These were matched against 19 precipitant drugs (Table 1) that can affect the absorption, distribution, metabolism, and/or elimination of various opioids and cause major pDDIs, depending on the CYP450 isoenzyme pathways (note that 2 of these 19, mibefradil and troglitazone, were withdrawn from the U.S. market. For example, fluconazole, as a precipitant drug, could lead to a pDDI–Major when exposed to oxycodone, or a moderate pDDI when exposed to hydrocodone (not included in this analysis), but does not lead to a pDDI when exposed to morphine (fluconazole does not affect the absorption, distribution, metabolism, and/or elimination of morphine).
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Patient Selection

Patients who had at least 1 prescription for a LAO analgesic ≥ 30 days between 2008 and 2010 were first identified. The first of these LAOs was used to establish the opioid index date. To qualify patients as initiating LAOs, a minimum of 6 months continuous enrollment was required prior to the opioid index date; 6 months continuous enrollment after the opioid index date was also required as the minimum follow-up time. Patients were excluded if they met any of the following criteria: did not have both medical and prescription coverage for the entire study period; were involved with a health maintenance organization (HMO) or point of service (POS) with capitation during the study period; were aged < 18 years at the LAO index date; had a cancer diagnosis during the study period; or had a pregnancy diagnosis during the study period.

All patients were required to have concomitant prescriptions for opioids and precipitant drugs after the opioid index date. If these overlaps did not have the potential to cause pDDI–Major, the patients were allocated into either (a) pDDI–None cohort (concomitant exposure to medications with no potential to cause drug-drug-interaction [e.g., morphine and fluoxetine]) or (b) pDDI–Moderate cohorts (e.g., oxycodone and fluoxetine, data not reported). Furthermore, to estimate the incremental costs associated with pDDI–Major, patients categorized in the pDDI–None cohort were required to have a concomitant exposure between an opioid (hydromorphone, morphine, or oxymorphone) and 1 of the 19 precipitant drugs identified for pDDI–Major. While analyses were also performed on the cohort of patients exposed to pDDI–Moderate, only comparisons of pDDI–Major to pDDI–None are included in this report. Only pDDI–Major was included because of its greater impact on cost and potential for intervention by different stakeholders.

Baseline and Observation Periods

The index date for the pDDI–Major patients was the first date of an overlap between an opioid and a precipitant drug that interact via the same CYP450 pathway; the index date for the pDDI–None patients was the first date of an overlap between an opioid and a precipitant drug that do not interact via the CYP450 pathway. The baseline period covered a duration of 180 days before the index date and the observation period covered a duration of 90 days, starting at the index date.

Baseline Patient Characteristics

Patient demographics included age, gender, region, health plan, type of insurance, and continuous enrollment days. The Charlson comorbidity index (CCI) was derived based on Deyo’s adaptation with several procedure codes that reflect Romano’s adaptation.24-26 Individual categories under the CCI index were also tabulated, such as diabetes, myocardial infarction, and peripheral vascular disease. Health care costs were also derived for the baseline period.

The number of distinct opioids and distinct days on opioids were derived for each patient. All opioids were converted into morphine equivalent doses and summed for the baseline period.

Outcome Measures

Among those patients initiating ≥ 30 days of LAOs (chronic opioid users), prevalence of pDDI–Majors was estimated. Also, we summarized the composition of these pDDI–Majors in terms of the CYP450 pathway (3A or 2D6), the type of interaction (inhibition or induction), and the type of opioid drugs and precipitant drugs. Inhibition was defined as those precipitants capable of reducing the enzyme activity of one or more isoforms of the CYP450 pathway, while induction was defined as those precipitants capable of increasing the activity of the CYP450 pathway.

CYP450 Isoenzyme Pathways

<table>
<thead>
<tr>
<th>Opioids</th>
<th>3A Inhibition</th>
<th>3A Induction</th>
<th>2D6 Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Yes</td>
<td>Yes</td>
<td>–</td>
</tr>
<tr>
<td>Methadone</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Oxycodone</td>
<td>Yes</td>
<td>Yes</td>
<td>–</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Morphine</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Tramadol</td>
<td>–</td>
<td>–</td>
<td>–</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Precipitant drugs</th>
<th>3A Inhibition</th>
<th>3A Induction</th>
<th>2D6 Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Yes</td>
<td>–</td>
<td>Yes</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Fluoxetine</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
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<tr>
<td>Itraconazole</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Ketoconazole</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Mibefradil</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
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<tr>
<td>Paroxetine</td>
<td>–</td>
<td>Yes</td>
<td>–</td>
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<tr>
<td>Phenytoin</td>
<td>–</td>
<td>Yes</td>
<td>–</td>
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<tr>
<td>Quinidine</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
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<tr>
<td>Rifampin</td>
<td>–</td>
<td>Yes</td>
<td>–</td>
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<tr>
<td>Ritonavir</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Terbinafine</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
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<tr>
<td>Thiopentalazine</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
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<tr>
<td>Troglitazone</td>
<td>–</td>
<td>Yes</td>
<td>–</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Yes</td>
<td>–</td>
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</tr>
</tbody>
</table>

*Dashes indicate “No”.

CYP450 = cytochrome P450.
Health care costs were derived based on payments for all covered health care services during the 90-day observation period, regardless of diagnosis, and consisted of inpatient medical, outpatient medical, emergency department, and outpatient prescription costs. Prescription costs were captured for both opioid and nonopioid prescriptions. All costs were standardized to a monthly basis and adjusted to 2010 dollars using the Consumer Price Index for Medical Care and expressed in U.S. dollars (U.S. Bureau of Labor Statistics). The impact of pDDI–Major on health care costs was measured as the excess (incremental difference) between the pDDI–Major and pDDI–None cohorts.

Statistical Analysis
Continuous variables were summarized using sample means and compared using the Student's t-test between matched cohorts. Categorical variables were summarized using the sample size and proportions, with the comparison between cohorts based on the Pearson chi-square test. Statistical significance was assessed with a 2-sided 0.05 level. Unless otherwise stated, all confidence intervals were 95% 2-sided. Baseline characteristics were also compared using standardized mean differences, which are not influenced by sample size and are useful for comparing cohorts in large observational studies. A value of 0.1 standard deviation or less indicates a negligible difference in means between groups. All statistical analyses and summaries were performed and produced using SAS software package 9.2 (Cary, NC).

Propensity score matching was used to mitigate the potential impact of selection bias. Such bias was estimated using a logistic regression with the cohort designation pDDI–Major as the dependent variable. A number of baseline covariates were included in the model: age; gender; region; plan type; CCI scores; prescription group and class counts (as provided in the Red Book drug dictionary); number of precipitant drugs; opioid days and morphine equivalent doses; inpatient, outpatient, and prescription costs; and health care resource utilization in various categories. Because the definition of our cohorts is based on the concurrent exposure of opioids and precipitant drugs, we also included the use of precipitant drugs in the observation period in the model. Lastly, the opioid experience at the start of the observational period (LAO, short-acting opioid, or both) was also included in the matching.

Since cost end points tend to be influenced by extreme outliers and have a skewed, long right-tail distribution, we first removed patients whose baseline or observational costs exceeded the 99th percentile and then analyzed cost using a generalized linear model. The negative binomial distribution with a log link was used in our study to estimate the ratio of the mean cost and served as the basis for significance of the comparison. The gamma distribution was explored, but we chose the negative binomial because it offers a more flexible variance-mean structure. The modified Park test was used to confirm the selection of the negative binomial model. The incremental cost difference was based on the least-squares means from a linear regression model.
Results

The sample selection steps are displayed in Table 2. A total of 280,689 patients had at least 1 prescription for ≥30 days of a LAO between July 1, 2008, and June 30, 2010, and 57,752 patients met all the inclusion and exclusion criteria. There were 2,278 and 984 patients eligible for the comparative analysis between pDDI–Major and pDDI–None cohorts, respectively.

After propensity score matching (Table 3), baseline characteristics that had a large difference, as determined by the standardized mean difference > 0.1, were similar between the cohorts. Before matching, the mean baseline monthly overall cost was $5,909 and $3,790 for the pDDI–Major and pDDI–None cohorts, respectively, with a standardized mean difference of 0.19. After propensity score matching, the mean baseline monthly overall cost was $3,681 and $3,572 for the pDDI–Major and pDDI–None cohorts, respectively, with a standardized mean difference of 0.02. The other important patient baseline characteristic, CCI, was 0.6 and 0.4 (standardized mean difference 0.17) before the matching and 0.4 (standardized mean difference 0.01) for both cohorts after the matching.

Prevalence and Composition of pDDI–Major

Based on the final sample of 57,752 patients, the prevalence in the 90 days after the LAO index date for pDDI–Major was 5.7% (3,302 patients). Among these patients, 69% (2,278) had no occurrence of pDDI–Major in the baseline (due to LAOs < 30 days or SAOs) and had a morphine equivalent dose >0.

These 2,278 patients were the basis of the pDDI–Major cohort before the propensity score matching. Among 2,278 patients, 97.7% had only 1 type of pDDI. In terms of the CYP450 pathway involved, 83.3% of the patients had a pDDI caused by 3A inhibition, followed by 11.9% caused by 2D6 inhibition, and 7.2% caused by 3A induction. The composition of the pDDIs that were responsible for the pDDI–Majors is displayed in Figure 1. Oxycodone was the leading opioid in these pDDI pairs, accounting for 57.3% of the patients. Opioids that followed included fentanyl (32.9%), methadone (18.3%), and codeine (1.8%). The most common precipitant drugs were fluconazole (34.5%), diltiazem (14.0%), clarithromycin (11.4%), and verapamil (10.9%). In the 90-day observation period, the average duration of concomitant use of opioids and precipitant drugs via interacting CYP450 pathways was 25.4 days; the average of duration was 18.6, 2.4, and 4.8 days for the 3A inhibition, 3A induction, and 2D6 inhibition pathways, respectively.

Health Care Cost Comparison Between pDDI–Major and pDDI–None Cohorts

Based on the 99th percentile cutoff and the propensity score matched cohorts, the estimated mean monthly overall health care costs for the 90-day observation period from the multivariate linear model were $3,366 and $2,757 for the pDDI–Major and pDDI–None cohorts, respectively. The monthly health care cost difference (the incremental impact of pDDI–Major on health care cost) was estimated to be $609 during the 90-day period (Table 4). The generalized linear model provided a similar result, with an estimated cost ratio of 1.232 ($P<0.0001$). The difference in the monthly health care cost was mainly driven by outpatient medical cost (difference $257, ratio 1.219, $P=0.004$) and the inpatient medical cost (difference $289, $P=0.1146$; Table 4). The costs of emergency room (ER) and

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**TABLE 3** Selected Patient Characteristics: pDDI–Major Versus pDDI–None

<table>
<thead>
<tr>
<th>Cohorts Before Matching</th>
<th>Propensity Score Matched Cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pDDI–Major (n = 2,278)</td>
</tr>
<tr>
<td></td>
<td>pDDI–None (n = 984)</td>
</tr>
<tr>
<td>Age in years (mean, SD)</td>
<td>48.9 (10.5)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>32.40</td>
</tr>
<tr>
<td>Rx therapeutic classes, baseline (mean, SD)</td>
<td>11.5 (5.7)</td>
</tr>
<tr>
<td>Charlson score, baseline (mean, SD)</td>
<td>0.6 (1.1)</td>
</tr>
<tr>
<td>Overall monthly cost ($), baseline (mean, SD)</td>
<td>5,909 (12,574.3)</td>
</tr>
</tbody>
</table>

*T = t-test; W = Wilcoxon rank-sum test; C = chi-square test.
pDDI = pharmacokinetic drug-drug interaction; SD = standard deviation; Rx = prescription; STMD = standardized mean difference.
The Prevalence of Opioid-Related Major Potential Drug-Drug Interactions and Their Impact on Health Care Costs in Chronic Pain Patients

The monthly overall health care cost difference based on the 95th percentile cutoff was estimated to be $296 with a cost ratio of 1.165 ($296/257 = 1.165; P = 0.003), which was mainly driven by outpatient medical cost (difference $120, ratio 1.164, $120/103 = 1.164; P = 0.03); inpatient medical cost (difference $101, ratio 1.248, $101/81 = 1.248; P = 0.2665); and ER cost (difference $50, ratio 1.019, $50/49 = 1.019; P = 0.012).

Outpatient prescription drugs were comparable between the 2 cohorts. The monthly overall health care cost difference based on the 95th percentile cutoff was estimated to be $296 with a cost ratio of 1.165 ($296/257 = 1.165; P = 0.003), which was mainly driven by outpatient medical cost (difference $120, ratio 1.164, $120/103 = 1.164; P = 0.03); inpatient medical cost (difference $101, ratio 1.248, $101/81 = 1.248; P = 0.2665); and ER cost (difference $50, ratio 1.019, $50/49 = 1.019; P = 0.012).

FIGURE 1 Distribution of Opioid and Precipitant Combinations for pDDI–Major Patients (N = 2,278)

preDDI = pharmacokinetic drug-drug interaction.
The Prevalence of Opioid-Related Major Potential Drug-Drug Interactions and Their Impact on Health Care Costs in Chronic Pain Patients

**Discussion**

Using previous work as a guide, this retrospective database analysis focused attention on improving the comparison between drug-drug exposures with the potential to have major clinical impact versus exposures without such potential.\(^{16,17,20,21}\) These studies comparing costs of exposures, regardless of the clinical importance, could have confounding effects and potentially result in improper estimation of the impact of pDDIs on health care costs. To mitigate this potential, the current study used strict inclusion criteria to focus on patients expected to be most affected by pDDIs (pDDI–Major) as well as obtain patient cohorts that were very similar in terms of baseline characteristics. By comparing pDDI–Major to pDDI–None exposures, a more accurate evaluation of the impact of opioid-related pDDIs on health care costs was accessed.

To accurately compare the patient cohorts, confounding factors present at baseline, which initially contributed to a significant difference in overall monthly cost between pDDI–Major and pDDI–None cohorts (\(P < 0.001\)), were mitigated by propensity score matching. Similar to previous work, a number of covariates were included to make the cohorts comparable. Although the propensity score matching did not yield perfect results, the baseline comparisons in terms of overall monthly costs were not significantly different between pDDI–Major and pDDI–None cohorts. In addition, we further improved upon previous work by controlling for exposure to various precipitant/concomitant drugs in the 90-day observation period (Figure 2). This control allowed us to focus on drugs that were comparable in terms of the nature of CYP450 exposures (pDDI–Major, pDDI–None). Therefore, cost differences between the 2 groups are the result of similar potential precipitant drugs, but involving a different opioid and the potential for a significant clinical impact from the pDDI.

It has been conservatively estimated that approximately 27% of chronic opioid users are exposed to pDDIs.\(^{18}\) For a majority of patients, this type of drug-drug exposure will not result in a pDDI–Major, as the prevalence of such exposures from our study was about 5.7%. While the prevalence of pDDI–Major may seem small (1 in 18), these patients required substantially more resources than pDDI–None patients. The cost difference between the pDDI–Major group and the pDDI–None group was shown to be $609 per month during the 90-day observation period. Given the small number of patients affected and the large cost impact, these results suggest that interventions may be manageable, feasible, and important.

There are sparse data in the literature regarding the prevalence, severity, and cost implications of pDDIs involving opioids. The true incidence of pDDIs is very difficult to quantify, and many go unrecognized and unreported. Our current results are consistent with previous work conducted by our group evaluating potential exposure to pDDIs. Retrospective evaluations of a large medical claims database indicate that patients using chronic opioids metabolized by the CYP450 system are frequently exposed to potentially interacting drugs. In
these studies, the exposure of patients with chronic low back pain and osteoarthritis treated with opioids to potential pDDIs was approximately 30%.\textsuperscript{16,17} In patients with osteoarthritis taking a CYP450 metabolized opioid, the risk of exposure to a potentially interacting drug was higher in females and increased with age and the number of medications at baseline before receiving an opioid.\textsuperscript{18} These data are in agreement with our current results and suggest that many chronic users of opioids are at high risk for potential pDDIs.

Physicians should be made aware of the concurrent medications a patient is taking prior to opioid prescription. In cases where CYP450 precipitant drugs are being taken, physicians may consider using a multimodal pain treatment approach that may incorporate both pharmacological and nonpharmacological treatments. Pharmacological treatments may include opioids and nonopioids that are not primarily metabolized through the CYP450 system. A prescription for one of these analgesics does not guarantee the patient will not experience a pDDI, but patients taking non-CYP450 metabolized analgesics are more likely to avoid a pDDI. Based on current guidelines, physicians should also reevaluate patients to determine whether opioid treatment is necessary, especially in light of an always changing regulatory environment regarding extended release and long-acting opioids.\textsuperscript{4,33} In addition, the health care industry continues to rely heavily upon technology to help support practitioners during the prescribing process. Computerized physician order entry (CPOE) systems, pharmacy dispensing systems, bar-coded medication administration, electronic medication reconciliation, and electronic personal health records are all being implemented to reduce the risks associated with medication errors.\textsuperscript{34} Even though these systems are in place and are meant to help detect pDDIs (among other tasks), 5.7% of patients taking LAOs still experience pDDI–Majors. Clinical alerts affecting only 5.7% of LAO users would not seem to significantly contribute to practitioner burden, an issue commonly cited as a problem using electronic messaging in CPOE and dispensing systems.
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Limitations
There are a number of limitations with the study. First, for the purposes of our evaluation, we assumed that all patients complied with medical advice and took their prescription medications as directed; we could observe only the dispensing of a prescription, not actual consumption. Second, we could not determine whether the prescribing physician performed appropriate laboratory monitoring or instructed the patient to change the dosage or type of medication in an effort to avoid an adverse interaction. Some of the patients may have changed their medications as a result of a physician consultation or hospital visit. Third, over-the-counter medications and prescription drugs paid for out of pocket were not captured in the database, although they may have contributed to CYP450 exposures. Fourth, given the observational nature of the study, there could be both observed and unobserved confounders that may have an impact on our results. The use of propensity score helps to mitigate the potential selection bias but may not be sufficient if the effects caused by unobserved confounders are significant. However, given the potential harm based on the available clinical evidence, it is unethical to randomize patients to drugs with potential adverse interactions in common clinical practice. Retrospective database analysis may help to identify signals and generate hypotheses in this regard. Fifth, patients who have a pDDI may not experience a clinically recognized adverse reaction, may experience a DDI of subclinical significance, or may not seek medical help even with a clinically significant DDI. In addition, direct correlation of a DDI was not possible because of the retrospective nature of the study, and ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification) codes were not available to provide a direct correlation. Therefore, associated clinical events were assessed as claims for services that represented potential adverse drug experiences. Finally, all potential precipitant drugs were not included for analysis. Only those well known and supported by literature to cause a major DDI were included, regardless of their overall utilization rate.

Conclusions
Reducing costs and improving quality of care is the key function in managed care, and identifying opportunities for improvement is a necessary step to achieving this goal. An area often overlooked is resource use associated with exposures carrying the potential to cause pDDIs. Based on the final sample of 57,752 CNCP patients using LAOs, the prevalence of pDDI–Major was 5.7% in the 90-day observation period. The estimated mean monthly overall health care costs from the multivariate linear model were $3,366 and $2,757 for the pDDI–Major and pDDI–None cohorts, respectively, a $609 difference. Among CNCP patients chronically taking LAO analgesics, the exposure to concomitant medications with the potential to cause ADRs of major clinical significance related to CYP450 metabolism is costly and worthy of efforts to avoid such exposure.

DISCLOSURES
This research was supported by Endo Pharmaceuticals Inc., in Malvern, Pennsylvania. Pergolizzi has served as an advisory board member, consultant, and speaker for Endo Pharmaceuticals Inc. Foster, Overholser, Sowinski, and Taylor have served as consultants for Endo. Ma is an employee of Endo, and Summers is a former employee of Endo.

All authors participated equally in originating and designing this study, collecting and interpreting data, and writing and revising the manuscript.

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