ABSTRACT

BACKGROUND: Management of opioid dependence is associated with many challenges such as the misuse of prescribed treatment and lack of medication adherence that can affect the clinical outcome of the patient. Buprenorphine-naloxone was approved by the U.S. Food and Drug Administration in October 2002 as the first outpatient treatment indicated for opioid dependence. There is only 1 report in the literature on the effectiveness of buprenorphine-naloxone in a real-world setting and no reports on persistence and cost obtained from administrative claims data.

OBJECTIVES: To determine (1) the length and cost of therapy with oral buprenorphine-naloxone, and (2) the cost avoidance for opioid dependence as measured by opioid utilization and opioid drug cost obtained from pharmacy claim records.

METHODS: The patients for this drug use evaluation (DUE) were identified from a New Jersey managed care organization (MCO) with approximately 1.8 million members with pharmacy benefits who (a) were continuously enrolled from October 1, 2004, through September 30, 2006; (b) had their first buprenorphine-naloxone pharmacy claim during the fixed 6-month initiation period (April 1, 2005, through September 30, 2005); and (c) had at least 1 opioid pharmacy claim in the 6-month pre period preceding the 6-month initiation period. The outcome measures included the number of opioid pharmacy claims, daily dose, days supply, and cost defined as opioid ingredient cost. Member cost share and net plan cost (after subtraction of member cost share) were also measured. The measurement periods for opioid use and cost were the fixed calendar periods for 6 months from October 1, 2004, through March 31, 2005, and for 12 months from October 1, 2005, through September 30, 2006. Persistence in the 12-month post period was defined as a gap of 30 days or less between depletion of the days supply for the preceding pharmacy claim for buprenorphine-naloxone and the date of service (refill date) for the succeeding pharmacy claim for buprenorphine-naloxone.

RESULTS: Of the 160 new buprenorphine-naloxone users with continuous pharmacy enrollment for the 2-year period ending September 30, 2006, 84 patients (52.5%) had at least 1 opioid pharmacy claim in the 6-month pre period from October 1, 2004, through March 31, 2005, and were included in this DUE. In the 12-month post period from October 1, 2005, through September 30, 2006, the median length of therapy with buprenorphine-naloxone was 1 month, and the mean length of therapy was 3.5 months. Only 40 patients (47.6%) had a pharmacy claim for buprenorphine-naloxone at month 1 in the 12-month post period. Persistence was 27.4% (n = 23) at 6 months (March 2006) and 20.2% (n = 17) at 12 months (September 2006) in the post period. A total of 24 study patients (28.6%) had no opioid pharmacy claims other than buprenorphine-naloxone in the 12-month post period. Utilization of opioids decreased by 18.8%, from 1.49 opioid pharmacy claims per patient per month (PPPM) in the pre period to 1.21 claims PPPM in the post period (P = 0.031). Excluding the 0.42 buprenorphine-naloxone claims PPPM, opioid utilization decreased by 47.0%, from 1.49 claims PPPM to 0.79 claims PPPM (P < 0.001) in the 12-month post period. Before subtraction of member cost share, the actual drug cost of opioids including buprenorphine-naloxone appeared to be 26.9% lower ($156.24 PPPM) in the post period compared with $213.74 PPPM in the pre period, but the difference was not statistically significant (P = 0.254). Excluding the cost of the buprenorphine-naloxone, actual opioid drug cost decreased 66.5% from $213.74 PPPM pre period to $71.65 PPPM post period (P = 0.047).

CONCLUSIONS: Approximately one half of the patients who had a new claim for buprenorphine-naloxone were excluded from this study because there was no utilization of prescription opioids in the 6 months prior to initiation. For patients with documented use of prescription opioids prior to initiation, treatment with buprenorphine-naloxone was associated with a reduction in opioid utilization and cost in the first year of follow-up. Persistence was only 27% at 6 months and 20% at 12 months, and there were no drug cost savings in the follow-up period when the actual cost of the buprenorphine-naloxone therapy was included.

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What is already known about this subject

- In a multicenter, double-blind, randomized placebo-controlled trial, 17.8% of urine samples for opiate-addicted persons were negative for opiates after 4 weeks of treatment with 16 mg of buprenorphine and 4 mg naloxone per day compared with 5.8% for placebo (P < 0.001). The open-label follow-up safety study over 52 weeks found 35% to 67% of urine samples negative for opiates. Another randomized 24-week trial without placebo-control reported about 6 weeks as the mean maximum duration of continuous abstinence from illicit opioids and 40% to 44% opioid-negative urine samples.
- There are many clinical trials of the efficacy of buprenorphine and buprenorphine-naloxone, but there is no retrospective drug use evaluation observational study published in the peer-reviewed literature that evaluates the relationship of buprenorphine-naloxone use for opioid dependence and the utilization and costs of prescription opioids.

Note: An editorial on the subject of this article appears on pages 195-97 of this issue.
A n estimated 5.2 million people aged 12 years or older abused pain relievers in 2006. Insured members who are opioid abusers are associated with 8.7 times higher mean annual direct health care cost than non-abusers ($15,884 versus $1,830, respectively). Since the implementation of the Drug Addiction Treatment Act of 2000 (DATA 2000), physicians have been able to treat opioid addiction in the outpatient setting. Methadone for treatment of opioid addiction is limited to certified opioid treatment programs (i.e., in designated “clinics”) by federal regulations. The combination of buprenorphine and naloxone in a sublingual tablet (Suboxone) is indicated for the treatment of opioid dependence and is preferred as maintenance therapy for most patients.

Buprenorphine-naloxone may be used by certified physicians in the outpatient setting for maintenance therapy, whereas methadone when used for opioid addiction in detoxification or maintenance programs is limited to certified opioid treatment programs. When treating opioid addiction with buprenorphine, there are 3 stages for maintenance therapy: (1) the induction phase occurs in an observed setting 12 to 24 hours after the patient has not used opioids; (2) the stabilization phase occurs when the patient experiences "no withdrawal symptoms, is experiencing minimal or no side effects, and no longer has uncontrollable cravings for opioid agonists"; and (3) the maintenance phase refers to when the patient is on steady doses of a buprenorphine-containing regimen. The length of therapy for the maintenance phase is individualized and may be infinite.

Buprenorphine is a partial agonist at the mu-opioid receptor, and its abuse potential is lower than that of a full agonist. Naloxone, a pure narcotic antagonist, has no clinically significant effects sublingually, but when administered intravenously, it produces an antagonist action. The combination of buprenorphine and naloxone is desirable in a population prone to abuse, because the presence of naloxone deters illicit use by injection of both buprenorphine and other opioids. To avoid precipitation of withdrawal, buprenorphine (Subutex) is preferred for use during initial therapy because it contains no naloxone. Following induction, buprenorphine-naloxone is preferred when its use includes unsupervised administration. Therefore, buprenorphine-naloxone, not buprenorphine, was chosen to include for this drug use evaluation (DUE) for maintenance therapy.

Under the federal Office of National Drug Control Policy Reauthorization Act of 2006 (ONDCPRA), the limitation on the number of patients a physician may treat with buprenorphine-naloxone for opioid dependence increased from 30 patients per prescriber to 100 patients. DATA 2000 requires physicians to undergo a training session or be accredited as an addiction specialist in order to treat opioid dependence in the outpatient setting. With more physicians and patients gaining experience with buprenorphine-naloxone, post-marketing analyses are possible. The recommended target dose of buprenorphine per the prescribing information is 16 mg per day, with the range of 4 mg to 24 mg per day, depending on the individual. The wholesale acquisition cost (WAC) per tablet in 2007 was $2.52 for the 2 mg to 0.5 mg buprenorphine-naloxone dose form and $4.45 for the 8 mg to 2 mg dose form.

Clinical trials have shown that buprenorphine treatment is at least as effective as moderate doses of methadone and more effective than clonidine to treat opioid addiction. In a multicenter, double-blind, randomized placebo-controlled trial, 17.8% of urine samples for opiate-addicted persons were negative for opiates after 4 weeks of treatment with 16 mg of buprenorphine with 4 mg naloxone per day compared with 5.8% for placebo (P<0.001). The open-label follow-up safety study (n=461, of whom 268 were from the double-blind trial) up to 52 weeks found 35% to 67% of urine samples negative for opiates. Another randomized 24-week trial without placebo control reported that the mean maximum duration of continuous abstinence from illicit opioids was about 6 weeks and 40% to 44% of opioid urine samples were negative.

Although there are clinical trials of buprenorphine-naloxone, there has not been a published retrospective DUE of opioid...
utilization associated with buprenorphine-naloxone intervention in a real-world setting. Clinical trials occur in a controlled environment, whereas a DUE can shed light on the use of drugs in the environment most important to clinicians and managed care health plans.

The objective of this retrospective DUE was to characterize the utilization patterns and associated costs of members using buprenorphine-naloxone for prescription opioid dependence by reporting (a) utilization defined as opioid pharmacy claims and opioid tablets dispensed, (b) savings defined as reduction in opioid pharmacy claims and opioid drug cost, and (c) persistence with therapy defined as a gap of no more than 1 month, starting from October 1, 2005. Review by an institutional review board was not sought because this DUE and the summary results involved no personal health information that was traceable to an individual health plan member.

Methods

Retrospective analysis identified members from a managed care organization with continuous commercial pharmacy benefit enrollment for 2 years (October 1, 2004, to September 30, 2006). The managed care organization is located in New Jersey and during the study period had approximately 1.8 million commercial pharmacy members, including health maintenance organization, point-of-service, preferred provider organization, direct access, medical savings account, and traditional indemnity plans. Opioid pharmacy claims were identified using Medi-Span Generic Product Identifier codes beginning with 6510 (narcotic agonists), 6520 (narcotic partial agonists), 6540 (narcotic antagonists), and 6599 (narcotic combinations). A first pharmacy claim was defined as no use of buprenorphine-naloxone in the preceding 6 months. Members who had their first buprenorphine-naloxone claim during the initiation period (April 1, 2005, through September 30, 2005) and had at least 1 opioid pharmacy claim 6 months before initiation were included in the present study (Figure 1).

The follow-up analyses focused on (1) opioid utilization and cost 6 months before and 12 months after the 6-month initiation period, and (2) buprenorphine-naloxone persistence and dose 12 months after the initiation period. The following outcomes were calculated for opioid utilization pre and post index: number of pharmacy claims, days supply, and cost defined as total drug ingredient cost; member cost share; and net plan cost after subtraction of member cost share. The type of opioid product was also assessed, including the number of units (i.e., tablets, capsules, etc.) before and after initiation of buprenorphine-naloxone therapy.

Persistence was assessed for 12 months following the 6-month initiation period for buprenorphine-naloxone, defined as a gap of not more than 1 month in buprenorphine-naloxone therapy (i.e., the patient was defined as non-persistent when there was a gap of 30 days or more between the depletion of the days supply in the preceding claim and the date of service (fill date) of the following claim). Duration of therapy was counted as the number of months (claims) of buprenorphine-naloxone commencing in October 2006.

The dose of buprenorphine per day was calculated for each claim using the following formula: (number of tablets divided by days supply) multiplied by the strength of buprenorphine-naloxone filled. The statistical test used to calculate P values was a 1-tailed paired t-test. Because the 6-month pre period cannot be compared with the 12-months post period, statistical analyses were performed on the per-patient-per-month (PPPM) results.

Results

Of the 298 new users of buprenorphine-naloxone, 160 (53.7%) had continuous pharmacy benefit eligibility for the entire 2-year period of the study, and 84 (52.5%) of the 160 had prior use of an opioid pharmacy claim in the 6-month pre period (Figure 2). Of the 84 patients who met the inclusion and exclusion criteria, 62% were male, and 38% of patients were female. The mean age was 40.0 years (n=84, Figure 3).

The average ingredient cost of opioids decreased from $213.74 PPPM in the 6 months prior to the initiation period to
$71.65 PPPM in the 12 months after the 6-month initiation period ($P=0.047$, Table 1). When the cost of buprenorphine-naloxone was included, the average drug cost (before member cost share) for opioid pharmacy claims was $156.24 PPPM in the 12-month follow-up period, not significantly less than the pre period ($P=0.254$). The average number of opioid claims excluding buprenorphine-naloxone was lower in the follow-up period (0.79 PPPM) compared with the pre period (1.49 PPPM, $P<0.001$); when buprenorphine-naloxone is included in the comparison, the average number of opioid claims decreased after initiation of buprenorphine-naloxone (1.21 vs. 1.49 PPPM, $P=0.031$), but this lower opioid utilization did not translate into lower opioid drug cost ($156.24 vs. $213.74 PPPM, $P=0.254$).

The direct drug cost of the intervention, prior to subtraction of member cost share, was $477.93 per patient during the 6-month initiation period from October 1, 2004, through March 31, 2005 (Table 2). Because initiation of buprenorphine-naloxone therapy could have commenced at any time during the 6-month initiation period, the total cost understates the actual cost of a 180-day treatment initiation period for all patients, and the cost per patient overstates an initiation pharmacy claim for buprenorphine-naloxone treatment. Members paid $7,589 (18.7%) of the total allowed charge (i.e., managed care organization (MCO) cost + member cost) for buprenorphine-naloxone during the initiation period (Table 2).

There were 422 claims for buprenorphine-naloxone during the 12-months post period from October 1, 2005, through September 30, 2006, or 0.42 PPPM, of which 72% (304 claims) were for buprenorphine-naloxone 8 mg to 2 mg, while 118 claims were for the 2 mg to 0.5 mg strength (Table 3). Most members were within the recommended buprenorphine daily dose of 4 mg to 24 mg per day (Table 4). Of the total 281 claims written by prescribers with known medical specialty information in the database, 55.5% (156 claims) were from general/family practitioners or internal medicine, and 22.0% (62 claims) were from psychiatrists or physical medicine and rehabilitation specialists.

Excluding buprenorphine-naloxone use, there was an average 96.8 units PPPM of solid-dose opioid drug use in the 6 months in the pre period, which dropped by 43.9% to 54.3 units PPPM in the 12-months post period (Table 5). By opioid drug type, the largest reduction in use occurred with the fentanyl patch and oral transmucosal fentanyl (i.e., “lollipop”).

Of the 84 patients new to buprenorphine-naloxone therapy at some point in the 6-month period from October 1, 2004, through March 31, 2005, 59 patients (70.2%) had filled at least 1 pharmacy claim for buprenorphine-naloxone in the 12-months follow-up period from October 1, 2005, through September 30, 2006. Persistence, defined as a gap in therapy of no more than 30 days between exhaustion of the days supply and the actual subsequent refill date, was 47.6% (n=40) at month 1 of the 12-months follow-up period (Figure 4). Persistence, starting October 1, 2005, decreased to 27.4% (n=23) at month 6 (March 2006) and 20.2% (n=17) at 12 months (September 2006). The mean persistence over the follow-up period was 3.5 months, and the median length of therapy was 1 month.

### Discussion

Almost one half of the new users, 76 of 160 (47.5%), of buprenorphine-naloxone did not have an outpatient pharmacy claim for an opioid drug in the 6 months preceding the initiation period. This suggests that the real-world use of buprenorphine-naloxone often involves treatment of opioid dependence for illicit drug use. Another retrospective chart review of 30 opioid-dependent patients treated with buprenorphine-naloxone induction as inpatient, found that 93% had a history of heroin use, 33% had used prescribed opioids, and 27% had used both.13 The use of buprenorphine-naloxone for detoxification from illicit opiates has implications for assessment of the potential cost savings associated with interventions with buprenorphine-naloxone because...
the costs of illicit opioids are not captured in administrative claims databases.

Initiation of treatment with buprenorphine-naloxone in a sample of patients with at least 1 opioid pharmacy claim in the prior 6 months was associated with a decrease in the number of opioid claims PPPM from 1.49 to 1.21, with a reduction of 43.9% in the number of solid dosage forms from pre index to post index. Furthermore, 28 of the 84 members did not fill any opioid medication claims during the 12 months after initiation, therefore not incurring direct opioid pharmacy costs. The average opioid cost PPPM decreased by 66.5% in the 12-month period following new use of buprenorphine-naloxone, but these drug cost savings associated with reduced opioid utilization were not statistically significant after accounting for the direct drug cost of the intervention.

Persistence was low by our measure; the mean persistence was 3.5 months, and the median length of therapy was 1 month. One reason for the low numbers was that the persistence calculation did not account for gaps in therapy of more than 1 month. Patients with opioid addiction have frequent relapses.3 A patient
Opioid Drug Utilization and Cost Outcomes Associated With the Use of Buprenorphine-Naloxone in Patients With a History of Prescription Opioid Use

### TABLE 4

<table>
<thead>
<tr>
<th>Dose of Buprenorphine (mg per day) a</th>
<th>% of Total Pharmacy Claims b (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 4 mg</td>
<td>13.0% (55)</td>
</tr>
<tr>
<td>&gt; 4 mg to ≤ 8 mg</td>
<td>31.8% (134)</td>
</tr>
<tr>
<td>&gt; 8 mg to ≤ 16 mg</td>
<td>40.0% (169)</td>
</tr>
<tr>
<td>&gt; 16 mg to ≤ 24 mg</td>
<td>11.8% (50)</td>
</tr>
<tr>
<td>&gt; 24 mg to ≤ 32 mg</td>
<td>1.9% (8)</td>
</tr>
<tr>
<td>&gt; 32 mg to ≤ 48 mg</td>
<td>1.4% (6)</td>
</tr>
</tbody>
</table>

a The dose of buprenorphine per day for each pharmacy claim was calculated with the following formula: (# tablets divided by days supply) multiplied by the mg per tablet.

b Buprenorphine-naloxone is supplied in 2 strengths in sublingual dose form: 2 mg-0.5 mg and 8 mg-2 mg; 304 (72%) of the 422 claims for buprenorphine-naloxone during the 12-month post period were the 8 mg-2 mg strength, and 118 claims were the 2 mg-0.5 mg strength. Of the 281 claims (66.6%) written by prescribers with known medical specialty information in the database, 55.5% (156) were in general/family practice or internal medicine, and 22.0% (62) were psychiatrists or physical medicine and rehabilitation specialists.

### TABLE 5

**PPPM Utilization In Units of Top Opioid Products a 6-Months Pre Period and 12-Months Post Period (N = 84)**

<table>
<thead>
<tr>
<th>Opioid Type</th>
<th>6-Month Pre Period PPPM Quantity</th>
<th>12-Month Post Period PPPM Quantity</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone-acetaminophen</td>
<td>36.0 tablets</td>
<td>17.1 tablets</td>
<td>-52.5%</td>
</tr>
<tr>
<td>Hydrocodone-acetaminophen</td>
<td>26.3 tablets</td>
<td>9.1 tablets</td>
<td>-65.4%</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>15.4 tablets or capsules</td>
<td>13.2 tablets or capsules</td>
<td>-14.3%</td>
</tr>
<tr>
<td>Tramadol-acetaminophen</td>
<td>6.0 tablets</td>
<td>7.1 tablets</td>
<td>+18.3%</td>
</tr>
<tr>
<td>Hydrocodone-ibuprofen</td>
<td>2.5 tablets</td>
<td>2.6 tablets</td>
<td>+4.0%</td>
</tr>
<tr>
<td>Oral transmucosal fentanyl citrate</td>
<td>2.3 lozenges</td>
<td>0.03 lozenges</td>
<td>-98.7%</td>
</tr>
<tr>
<td>Methadone</td>
<td>1.8 tablets</td>
<td>1.8 tablets</td>
<td>0%</td>
</tr>
<tr>
<td>Buprenorphine oral b</td>
<td>1.1 tablets</td>
<td>1.3 tablets</td>
<td>+18.2%</td>
</tr>
<tr>
<td>Other opioids</td>
<td>5.4 tablets c</td>
<td>2.1 tablets d</td>
<td>-61.0%</td>
</tr>
<tr>
<td>Total solid dosage forms</td>
<td>96.8 patches</td>
<td>54.3 patches</td>
<td>-43.9%</td>
</tr>
<tr>
<td>Fentanyl patch</td>
<td>1.1 patches</td>
<td>0.03 patches</td>
<td>-97.3%</td>
</tr>
<tr>
<td>Buprenorphine ampule</td>
<td>0.06 mL</td>
<td>0 mL</td>
<td>-100.0%</td>
</tr>
</tbody>
</table>

a Pharmacy claims for opioid drugs identified by Medi-Span Generic Product Identifier (codes beginning with 6510 (narcotic agonists), 6520 (narcotic partial agonists), 6540 (narcotic antagonists), and 6599 (narcotic combinations). A first pharmacy claim for buprenorphine-naloxone was defined as no use in the preceding 6 months.

b Buprenorphine without naloxone.

c Actual results included pharmacy claims for acetaminophen-codeine tablets, butalbital-acetaminophen-cafeine-codeine capsules, hydromorphone tablets, morphine capsules, oxycodone-aspirin tablets, and propoxyphene N-acetaminophen tablets.

d Actual results included pharmacy claims for acetaminophen-codeine tablets, morphine capsules and tablets, oxycodone-ibuprofen tablets, propoxyphene N-acetaminophen tablets, butalbital-acetaminophen-cafeine-codeine capsules, hydromorphone tablets, meperidine tablets, oxycodone-aspirin tablets, pentazocine-acetaminophen tablets, and pentazocine-naloxone tablets.

PPPM = per patient per month.
in the present study could be counted as “discontinued” by the persistence measure but later restart therapy with buprenorphine-naloxone during the 12-month follow-up period. In addition, if a patient had continuous fills for scripts after the first 30 days of October 2005, the persistence was 0 days. Caldiero et al. reported that, in a retrospective chart review, patients had an average of 3.4 prior substance use treatments before receiving inpatient induction of buprenorphine maintenance.13 There are no reports in the literature for the incidence of buprenorphine-naloxone relapses and restarts.

Most patients received the recommended 4 mg to 24 mg of buprenorphine per day, commonly prescribed as buprenorphine-naloxone (8 mg to 2 mg), 2 tablets per day. Very few patients had pharmacy claims for buprenorphine doses >32 mg per day. There was no dispensing limit placed on buprenorphine-naloxone during this study. Effective May 2007, a dose limit of 120 tablets per month was implemented at this MCO, allowing for a maximum dose of 32 mg of buprenorphine per day.

Because there are no retrospective, observational studies reported in the literature that evaluate the relationship of buprenorphine-naloxone use for opioid dependence and utilization and costs of prescription opioids, comparisons cannot be made between the results of the present study and other attempts to measure effectiveness of this intervention. In 2007, Mintzer et al. reported that 54% of 99 patients treated in 2 primary care clinics were “sober” after 6 months of therapy with buprenorphine-naloxone as determined by global assessment of the treating physician, including the results of periodic urine tests.14 These patients in 2 primary care clinics had demographic characteristics at baseline (mean age of 33 years and 64% males) that were similar to the present analysis. The average time in treatment was 105 days.

Compared with the 54% “success” rate reported by Mintzer et al. at 6 months of follow-up, we found that only 1 of 2 patients who received buprenorphine-naloxone as a new patient had a follow-up claim for the drug at 1 month following the initial treatment period, and only 27% were persistent at 6 months. In fact, 71.4% of the patients included in the DUE had filled at least 1 pharmacy claim for an opioid other than the study drug during the follow-up period after initiation of buprenorphine-naloxone. The results reported by Mintzer et al. pertained to hands-on primary care where the caregivers followed the patients and encouraged participation in psychological support groups.

Fudula et al. conducted a double-blind, randomized, placebo-controlled efficacy trial, with an open-label safety extension, involving opiate-dependent patients who were assigned to office-based treatment with sublingual buprenorphine 16 mg in combination with naloxone (4 mg) per day versus buprenorphine alone (16 mg per day) or placebo (initial randomized treatment for 4 weeks, followed by 48 to 52 weeks of open-label therapy). The authors reported that the percentage of urine samples during the open-label phase that were negative for opiates ranged from 32.5% to 67.4% in multiple assessments conducted during 1 year of follow-up.11 These results suggest that patients with opioid dependence have variable results depending on the time of measurements in this dynamic disease.

Bell et al. randomized 119 subjects seeking treatment for heroin addiction to observed or unobserved doses of buprenorphine-naloxone for heroin dependence in outpatient drug treatment centers.15 The mean retention in treatment did not differ between treatments (P=0.84), and mean reduction in days of self-reported heroin use in the preceding month did not differ between the unobserved group (18.5 days) versus the observed group (22.0 days, P=0.13). At 3 months, 52% of 92 interviewed patients reported no use of heroin in the last month. The mean cost per treatment episode, including cost of medication; medical, counseling, and dispensing costs; other health care costs like hospital admissions, etc.; travel costs; and travel time, in Australian dollars was AU$1,663 in the unobserved group versus AU$2,138 in the observed group.

Limitations
No causal relationship between buprenorphine-naloxone treatment and change in opioid use can be inferred from this study because it is an observational study without a control group. Second, it is not possible to determine the use of illicit substances from a pharmacy claims database. Although 24 of the 84 members did not fill pharmacy opioid claims other than buprenorphine-naloxone in the 12-month follow-up period, a DUE of this type, based on analysis of pharmacy administrative claims, cannot assess illicit opioid utilization. Our study results suggest that there was a decline in prescription opioid claims, but whether patients were sober or obtained opioids from illegal sources is unknown.

Third, no medical claims were examined in this study. Without access to medical claims, it was not possible to examine the relationship between buprenorphine-naloxone use and total medical costs. For example, patients may have been receiving psychiatric care, and its effect on drug efficacy cannot be measured with this DUE.

Fourth, we used an unusual study design based on fixed calendar periods rather than the customary approach of following each patient for a given number of months following the date of the first claim for the intervention. This method was intended to simulate a real-world situation for this health plan to determine the prescription opiate utilization for the patients after a 6-month initiation period. The shortcoming of this method is the creation of a follow-up period longer than 12 months from the date of the first buprenorphine-naloxone claim. For example, a patient could have started buprenorphine-naloxone as early as April 2005 and stopped treatment after 5 months (in September 2005), and this patient was considered nonpersistent, with no follow-up claim for buprenorphine-naloxone. In other words, the length of buprenorphine-naloxone therapy in the initiation period could
have been as short as a few days or as long as 180 days prior to the start of the 12-month follow-up period. In fact, only 59 patients received buprenorphine-naloxone during follow-up. Therefore, our findings for mean utilization of and persistence with the intervention drug most likely underestimate what might be expected in an analysis that employed a running 12-month follow-up period following the first (initiation) buprenorphine-naloxone pharmacy claim.

Fifth, this study defined the initiation claim as the first claim for buprenorphine-naloxone during the calendar period from April 1, 2005, through September 30, 2005, with no prior use in the 6-month period from October 1, 2004, through March 31, 2005. However, some patients may have had utilization of buprenorphine alone, without naloxone. For the 84 patients included in the present study, utilization of buprenorphine alone was 1.1 tablets PPM in the 6-month pre period and 1.3 tablets PPM in the 12-month post period.

Sixth, the observed decrease in utilization of oral transmucosal fentanyl citrate contributed significantly to the lower total opioid cost in the post period. During the 24 months of study in this DUE, there was no prior authorization requirement for the use of oral transmucosal fentanyl citrate (e.g., use allowed for only the U.S. Food and Drug Administration-approved indication for cancer patients). A quantity limit of 120 transmucosal fentanyl “lollipops” per month was implemented prior to the study period on August 1, 2004, but this quantity limit would not have affected the pre versus post comparison in the present study.

Seventh, a dispensing (quantity) limit of 120 tablets per 30 days was placed on the following opioids in March 2005, the last month of the pre period: controlled-release oxycodone tablets, oxycodone-acetaminophen, tramadol, tramadol-acetaminophen, and hydrocodone-acetaminophen. The effect of this quantity limit on the use of these drugs has not been assessed but could have contributed to lower opioid utilization in the follow-up period from October 1, 2005, through September 30, 2006. However, the quantity limit imposed in March 2005 did not present a new limitation for Schedule II controlled substances such as controlled-release oxycodone, which were already subject to a dispensing limit of 120 dosage units or 30 days supply by New Jersey state regulations, except for patients with terminal illness, intractable pain, or residence in a long-term-care facility.

Conclusions

About one-half of the utilization of buprenorphine-naloxone in this managed care plan appeared to be associated with nonprescription opioid use. Initiation of treatment with combination buprenorphine-naloxone in patients with a history of prescription opioid use was associated with reduced prescription opioid utilization, but not direct pharmacy cost, after 12 months of follow-up. Using a definition of persistence as a gap of no more than 1 month between the date of exhaustion of the days supply and the next fill date, persistence with buprenorphine-naloxone was 27% at 6 months and 20% at 12 months of follow-up.
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