Effectiveness of a Retrospective Drug Utilization Review on Potentially Unsafe Opioid and Central Nervous System Combination Therapy

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ABSTRACT

BACKGROUND: Drug overdose deaths are the leading cause of unintentional death in the United States, and opioid-related mortality is the primary contributor (75.2%). Among opioid-related mortalities, opioids are most commonly taken with benzodiazepines (30.1%) and antidepressants (13.4%). The utility of a retrospective drug utilization review (DUR) program initiated by a commercial health plan for members taking potentially unsafe opioid and central nervous system (CNS) combination therapy is currently unknown.

OBJECTIVE: To determine the effectiveness of a retrospective DUR program on potentially unsafe opioid and CNS combination therapy.

METHODS: This research is a pre-post study utilizing pharmacy claims data from 2.6 million commercially insured members enrolled in a health plan in the Midwest. Members were required to be at least aged 18 years as of August 30, 2013, and continuously enrolled from May 2, 2013, through February 15, 2014. Members with 1 or more paid claims for an opioid at least 200 morphine equivalent dose (MED) daily and a concurrent supply of another opioid, benzodiazepine, or antidepressant from May 2, 2013, through August 30, 2013 (120-day preintervention period) were targeted for the retrospective DUR program. These exclusion criteria were applied: members belonging to commercial groups requiring permission on claims data analyses, missing or invalid prescriber information, or presence of pharmacy claims indicating human immunodeficiency virus or acquired immunodeficiency syndrome during the 2 years prior to the pre-intervention period. Prescribers of high-dose opioids received a mailing (intervention) containing a member-specific letter, medication profile, and satisfaction survey to determine the prescriber-perceived clinical value of the program. To assess the effectiveness of the retrospective DUR program, criteria was reapplied to identify members still meeting criteria 120 days postintervention (February 15, 2014). Paired samples t-test was used to compare pre-post results.

RESULTS: Of 2,236,243 eligible members aged 18 years and older, 980 met DUR criteria. Prescribers for these members subsequently received a mailing regarding potentially unsafe opioid and CNS combination therapy. A total of 671 prescribers were sent a mailing regarding these 980 members. Among the 980 members meeting DUR criteria, distribution of prescriber specialty was family medicine (25.9%), physical medicine and rehabilitation (14.4%), internal medicine (13.0%), pain (9.2%), anesthesiology (7.0%), other (8.8%), and unknown (21.7%). High-dose opioids most commonly identified by the DUR were oxycodone extended release (27.6%), morphine sulfate extended release (17.7%), and fentanyl patch (13.1%). After reapplying DUR criteria to identify members still meeting criteria 120 days after the DUR, 528 members remained, representing a 28.1% reduction in high-risk opioid use. Survey response rate was 23.6% (231 of 980 surveys returned). The majority (62.3%) of respondents reported that this retrospective DUR program was useful in their daily practice.

CONCLUSIONS: A 28.1% reduction in potentially unsafe opioid and CNS combination therapy was observed after implementing a retrospective DUR program targeting high-risk opioid use. Among members remaining high risk after the DUR, the change in total unique opioids and total daily MED was nonsignificant. Members remaining at high risk after the DUR can be targeted for further interventions such as care management and member education regarding fraud, waste, and abuse. A majority of prescribers (90.5%) self-report using their states' prescription monitoring programs when prescribing controlled substances.

J Manag Care Spec Pharm. 2015;21(10):938-44

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What is already known about this subject

- From 1990 to 2010, drug overdose deaths increased from 3.4 per 100,000 to 12.4 per 100,000, an increase of approximately 300%.
- Opioids are primarily responsible for the increase in drug overdose mortality, accounting for 75.2% of cases.
- Among opioid-related mortalities, opioids are most commonly taken with benzodiazepines (30.1%) and antidepressants (13.4%).

What this study adds

- A commercial health plan implemented a retrospective drug utilization review (DUR) program targeting high-risk opioid use and observed a 28.1% reduction in such utilization.
- Among a commercially insured population, high dose opioids most commonly identified by a retrospective DUR program were oxycodone extended release (27.6%), morphine sulfate extended release (17.7%), and fentanyl patch (13.1%).
- The majority (90.5%) of prescribers self-reported using their states' prescription monitoring programs when treating patients with controlled substances.

Drug overdose deaths are the leading cause of unintentional death in the United States and increased for the eleventh straight year in 2010.^{1,2} From 1990 to 2010, drug overdose deaths increased from 3.4 per 100,000 to 12.4 per 100,000, an increase of approximately 300%.^{3,4} Opioids are the most common drug class involved in drug overdose deaths, with patients taking opioids in three fourths of cases.¹ Doses greater than 100 morphine equivalent dose (MED) daily are associated with 11 times greater risk for opioid-related overdose death.⁵ Additionally, concomitant use of benzodiazepines

FIGURE 1 Study Time Line

and antidepressants are most often involved in opioid-related mortalities, 30.1% and 13.4%, respectively.⁶

The Centers for Disease Control and Prevention (CDC) classify drug overdose as an epidemic.⁷ To combat the drug overdose epidemic, the CDC recommends the following: prescription drug monitoring programs (PDMPs), patient review and restriction programs, health care provider accountability, laws to prevent prescription drug abuse and diversion, and better access to substance abuse treatment. Retrospective drug utilization review (DUR) programs are a mechanism to monitor prescription claims information and have been successful in many different patient populations.⁸ However, the value of a retrospective DUR program for potentially unsafe opioid and central nervous system (CNS) combination therapy is unknown. A retrospective DUR program can identify members on potentially unsafe opioid and CNS combination therapy and contact their prescribers to reassess therapy and determine if dose reductions, discontinuation of potentially unsafe agents, or substitution for less dangerous medications are necessary. Third-party payers' pharmacy and medical costs could decrease, since these members tend to be on multiple medications and high utilizers of medical resources.⁹⁻¹² Hansen et al. (2011) reported that nonmedical use of prescription opioids costs the U.S. economy \$53.4 billion, mainly due to lost productivity (\$42 billion), followed by criminal justice costs (\$8.2 billion), drug abuse treatment (\$2.2 billion), and medical complications (\$944 million).¹³

The objective of this study was to determine the effectiveness of a retrospective DUR program among members whose claims history suggested potentially unsafe opioid and CNS combination therapy. This DUR identified members who were taking high doses of opioid analgesics concomitantly with other opioid analgesics, benzodiazepines, or antidepressants and encouraged their prescribers to reassess combination therapy.

Methods

This pre-post study utilized pharmacy claims data from 2.6 million commercially insured members enrolled in a Midwest Blue Cross Blue Shield plan. To be eligible for analysis, members were required to be at least aged 18 years as of August 30, 2013, and continuously enrolled from May 2, 2013, through February 15, 2014. The study timeline is shown in Figure 1.

Pharmacy claims were queried to identify members with an opioid claim at least 200 morphine equivalent dose (MED) daily and a concurrent supply of another opioid, benzodiazepine, or antidepressant from May 2, 2013, through August 30, 2013 (120-day preintervention period). Opioid, benzodiazepine, and antidepressant claims were identified using American Hospital Formulary System (AHFS) pharmacologic therapeutic classification codes (28:08.08 Opiate Agonists, 28:08.12 Opiate Partial Agonists, 28.24.08 Benzodiazepines, 28:12.0 Benzodiazepines, and 28:16.04 Antidepressants).

The following exclusion criteria were applied: members belonging to commercial groups requiring permission on claims data analyses, missing or invalid prescriber information, presence of pharmacy claims indicating malignancy, or human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) during the 2 years prior to the pre-intervention period. HIV and cancer drugs were identified by AHFS codes 8:18.08 Antiretrovirals and 10:00 Antineoplastics, respectively. Claims for days' supply less than 20 were excluded to capture chronic therapy because these members were at highest risk for opioid overdose.

Identified members were targeted for the retrospective DUR program. The DUR involved a provider-directed intervention for the most recent prescriber of a high-dose opioid for the identified member. In October 2013, prescribers received a mailing via the U.S. Postal Service, containing a member-specific letter, medication profile, and satisfaction survey to

FIGURE 2 Member Selection

AIDS = acquired immune deficiency syndrome; HIV = human immunodeficiency virus; MED = morphine equivalent dose; mg = milligram.

determine the prescriber-perceived clinical value of the program (see the Appendix, available in online article). Prescribers were asked to reevaluate the members' pain management therapies. The questionnaire survey was developed by researchers and reviewed internally by a medical director (physician) and pharmacy clinical director (pharmacist) for clarity and brevity. Revisions were made based on recommendations. The survey included multiple choice and free response questions. Participation was voluntary with no incentives offered to respondents, and surveys were returned via fax.

Criteria were reapplied to identify members still meeting criteria 120 days postintervention (February 15, 2014) to assess the effectiveness of the retrospective DUR program. A 120-day preintervention and postintervention time period was selected to capture 90-day fills. Members were categorized based on

their combination therapies. For example, opioid/antidepressant indicated that a member took at least 1 opioid and at least 1 antidepressant. Categories were as follows: (a) opioid/opioid, (b) opioid/benzodiazepine, (c) opioid/antidepressant, and (d) opioid/benzodiazepine/antidepressant. Statistical testing data for member characteristics are presented as means with standard deviations or frequencies with percentages. Paired samples t-test was used to compare differences from preintervention to postintervention. A *P* value of <0.05 was used to determine statistical significance.

Results

Figure 2 shows the flow of members in the study. From the 2,236,243 eligible members aged 18 years and older, 980 met DUR criteria. Among the 980 members meeting

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FIGURE 3 Members Taking Potentially Unsafe Opioid and CNS Combination Therapy

^aOf the 980 members meeting DUR, 246 members discontinued Blue Cross Blue Shield pharmacy insurance and were excluded from postintervention analysis. CNS=central nervous system; DUR=drug utilization review.

TABLE 1 Demographics, Opioid Exposure, and Category of Combination Therapy, N=528^{a,b}

Demographics			
Age in years, mean ± SD	52.8 ± 10.9		
Male, n (%)	276 (52.3)		
Level of opioid exposure			
	Preintervention	Postintervention	P Value
Total unique opioids, mean ± SD	1.8 ± 0.7	1.8 ± 0.6	0.213
Total morphine equivalents per day, mean ± SD	395.3 ± 315.2	396.5 ± 344.2	0.847
Category of combination therapy, n (%)			
	Preintervention	Postintervention	P Value
Opioid/opioid	168 (31.8)	172 (32.6)	<0.001
Opioid/benzodiazepine	112 (21.2)	115 (21.8)	<0.001
Opioid/antidepressant	165 (31.3)	148 (28.0)	<0.001
Opioid/benzodiazepine/antidepressant	83 (15.7)	93 (17.6)	<0.001

^aMembers are classified into a category by having at least 1 drug in each class (e.g., opioid/antidepressant indicates member is taking at least 1 opioid and at least 1 antidepressant).

^bThese members remain high risk after the DUR intervention, representing opportunities for interventions such as care management and member education regarding fraud, waste, and abuse.

DUR=drug utilization review; SD=standard deviation.

DUR criteria, distribution of prescriber specialty was family medicine (25.9%), physical medicine and rehabilitation (14.4%), internal medicine (13.0%), pain (9.2%), anesthesiology (7.0%), other (8.8%), and unknown (21.7%). High-dose opioids most commonly identified by the DUR were oxycodone extended release (27.6%), morphine sulfate extended release (17.7%), and fentanyl patch (13.1%). A total of 200 MED daily was considered a high dose, according to the American Pain Society and American Academy of Pain Medicine.^{14,15} The study sample consisted of 528 members aged 18 years and older, who were continuously enrolled from May 2, 2013, through February 15, 2014, with an opioid claim of at least 200 MED daily and a concurrent supply of another opioid, benzodiazepine, or antidepressant during the preintervention and postintervention periods. Although 980 members were targeted for the retrospective DUR program, 246 members discontinued the Blue Cross Blue Shield pharmacy insurance and were excluded from postintervention analysis.

Members meeting DUR criteria pre- and postintervention were the focus of this study's analysis, since they represented the highest-risk members taking opioid and CNS combination therapy. A total of 206 members no longer met DUR criteria in the postintervention period, representing a 28.1% reduction in high-risk opioid use (Figure 3). Of the 206 members who were no longer high risk, 66 (32.0%) were opioid/antidepressant; 58 (28.2%) were opioid/opioid; 47 (22.8%) were opioid/

benzodiazepine/antidepressant; and 35 (17.0%) were opioid/benzodiazepine. A total of 246 members were lost to follow-up because they discontinued pharmacy coverage during the postintervention period.

Average member age was 52.8 years, and 52.3% of the study cohort was male (Table 1). The average number of unique opioids was 1.8 for the preintervention and postintervention periods ($P=0.213$). Change in average total MED per day was nonsignificant (395.3 vs. 396.5, $P=0.847$). Among these high-risk members, the level of opioid exposure remained unchanged and did not increase. Table 1 shows member distribution among the different combination therapy categories during the preintervention and postintervention periods. All categories had a small increase except the opioid/antidepressant category, which experienced a decrease.

Survey Results

The survey was sent to 671 unique prescribers managing pain therapy for the 980 members targeted for the retrospective DUR program. Of this number, 231 surveys were returned, representing a response rate of 23.6%. Table 2 shows the survey results. The majority (70.6%) of responses indicate that no change to pain management therapy was made, but 8.5% of responses indicate that opioid dose was decreased, and 14.0% indicated some other change. For responses indicating some

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TABLE 2 Survey Results

1. Based on the information you received, did you change your patient's pain management therapy?^a		
Response (n = 235)	n	(%)
Yes, decreased the patient's opioid dose.	20	(8.5)
Yes, discontinued drug(s) that interacted with the patient's opioid.	1	(0.4)
Yes, discontinued opioid and switched to a different agent.	1	(0.4)
Yes, other	33	(14.0)
No	166	(70.6)
No response	14	(6.0)
2. Do you routinely use your state's prescription monitoring program (PMP) to see what controlled substances your patient is obtaining from pharmacies?		
Response (n = 231)	n	(%)
Yes	209	(90.5)
No	9	(3.9)
No response	13	(5.6)
3. How useful was the information you received?		
Response (n = 231)	n	(%)
Very useful	33	(14.3)
Useful	61	(26.4)
Somewhat useful	50	(21.6)
Not useful	64	(27.7)
No response	23	(10.0)
4. Please indicate your specialty^a		
Response (n = 248)	n	(%)
Pain specialist	91	(36.7)
Internal medicine	37	(14.9)
Family medicine	63	(25.4)
Neurologist	11	(4.4)
Hospitalist	0	(0.0)
Physician assistant	3	(1.2)
Nurse practitioner	11	(4.4)
Other	19	(7.7)
No response	13	(5.2)

^aPrescribers were allowed to choose more than 1 answer.

other change was made, 30.3% respondents planned to address therapy with members or perform a urine screen; 27.3% provided specific clinical rationale for therapy; and 24.2% discontinued a medication or reported making a therapeutic change. Most survey respondents (90.5%) reported routine use of their states' prescription monitoring programs when prescribing a controlled substance, and 62.3% reported that the information received was useful. Pain specialists (36.7%) were most common among survey respondents, followed by family medicine (25.4%) and internal medicine (14.9%).

Discussion

This study showed that a retrospective DUR program targeting commercially insured members can result in a 28.1% decrease in potentially unsafe opioid and CNS combination therapy. High-dose opioids most commonly identified by the DUR were oxycodone extended release (27.6%), morphine sulfate

extended release (17.7%), and fentanyl patch (13.1%). Such findings are consistent with the MassHealth DUR program in Massachusetts, which identified the necessity for a management strategy regarding long-acting opioid analgesics (oxycodone extended release, morphine sulfate extended release, fentanyl, and methadone).¹⁶ As a result of the MassHealth DUR program, a prior authorization was implemented for all high-dose, long-acting opioid analgesics.

A targeted retrospective DUR program can be one of many different approaches that collectively address the opioid mortality epidemic. Additional strategies include lock-in programs in which controlled substance claims of a high-risk member is reimbursed only if a specific prescriber and pharmacy is used.¹⁷ Such strategy is more common among Medicaid plans, and lock-in programs could potentially benefit the highest-risk members still meeting our DUR criteria postintervention. Connecticut's DUR Board observed a savings of \$3.7 million and \$2.4 million in 2009 and 2011, respectively, when examining results of its retrospective DUR programs and lock-in programs combined.¹⁸

Among the 980 members meeting DUR criteria in our study, distribution of prescriber specialty was family medicine (25.9%), physical medicine and rehabilitation (14.4%), internal medicine (13.0%), pain (9.2%), anesthesiology (7.0%), other (8.8%), and unknown (21.7%). Our retrospective DUR program may serve as a selection tool for prescribers who may benefit from academic detailing, as well as identify members that can be targeted for care management and member education regarding fraud, waste, and abuse. Although pain specialists were managing pain therapy for 9.2% of members targeted for the DUR, they were the largest group among survey respondents (36.7%). Pain specialists were very responsive regarding a retrospective DUR program targeting high-risk opioid use.

Our retrospective DUR program identified members taking potentially unsafe opioid and CNS combination therapy. Interactions of such drug combinations can potentially result in respiratory depression and drug overdose death. The literature has shown that drug interactions involving opioids are associated with higher health care costs.⁹ Pergolizzi et al. (2014) found that monthly health care costs were significantly greater by \$609 among patients exposed to a potential drug-drug interaction of clinical significance compared with those not exposed.¹⁹ Summers et al. (2011) found significantly higher (\$667) average 6-month health care costs among patients exposed to opioid drug interactions compared with patients without such drug interactions.²⁰ Although these studies focused on opioid drug interactions related to the cytochrome P450 pathway, such findings provide insight on costs associated with opioid drug interactions.

In addition to retrospective DUR programs that can identify potentially unsafe opioid and CNS combination therapy, prescribers and pharmacists can utilize PDMPs, which identify controlled substances that members are obtaining from

pharmacies. Health care professionals are able to determine if a member is receiving potentially unsafe drug combinations that otherwise may be unknown. Academic detailing efforts can be employed to encourage prescribers to use these resources when prescribing controlled substances. Our survey results showed that 90.9% of respondents reported routine use of their state's PDMP when prescribing a controlled substance. Prescribers are utilizing PDMPs to appropriately manage their patients.

Limitations

The current study is not without limitations. First, the study used pharmacy claims data, which do not provide information regarding adherence or whether the member is actually taking the medication. Patient-specific characteristics captured by medical claims were not included, which could potentially illuminate factors that may be driving therapy change. Second, data are limited to a commercial population in the U.S. Midwest; therefore, findings may not be generalizable to Medicare/Medicaid populations or other geographic regions. Third, members often elect to pay cash for controlled substances, and this study was not able to capture cash transactions not billed through insurance. Fourth, response bias may be present among survey respondents, since the intervention and survey were administered by the health plan providing reimbursement to physicians. Fifth, there was no direct comparison group. Rather, the control was the historical claims experience of each member. The 28.1% decrease in potentially unsafe opioid use cannot be attributed solely to the intervention; the decrease may have occurred because of other factors that may impact opioid use, including disease severity and concomitant alcohol use. This limitation is inherent to pre-post study designs, but pre-post design in this study was used because the intervention was implemented to all members meeting criteria for potentially unsafe drug therapy in the health plan's commercial population. Lastly, survey response rate was 23.6%. Future research in this area should focus on the patient and prescriber factors that are predictive of positive postintervention changes to opioid therapy.

Conclusions

Commercial health plans can reduce risk of adverse effects and death associated with high-dose opioid analgesics used in combination with other CNS sedating agents. A 28.1% reduction in potentially unsafe opioid and CNS combination therapy was observed after implementing a retrospective DUR program targeting high-risk opioid use. Because the drug overdose epidemic is the leading cause of unintentional death in the United States, managed care organizations are well positioned to use multiple strategies such as care management and academic detailing, as well as member education regarding fraud, waste, and abuse, as follow-up to a retrospective DUR program for a comprehensive approach to further manage and reduce high-risk opioid use.

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DISCLOSURES

The authors have no financial interest or affiliation with any company, product, or service listed in this article. The source of funding for this research was Blue Cross Blue Shield of Michigan.

Study concept and design were primarily contributed by Wesolowicz and Tungol Lin, with assistance from Qureshi and Liu. Data were collected by Qureshi and Tungol Lin and interpreted by Qureshi, Tungol Lin, and Liu. The manuscript was written and revised by Qureshi and Tungol Lin.

ACKNOWLEDGMENTS

The authors thank Andrew Bugelli, Sandra Logan, and Deepa Meenakshi-Sundaram at Blue Cross Blue Shield of Michigan for performing data extraction and manipulation to create analysis datasets based on research protocols provided by the authors.

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APPENDIX Satisfaction Survey for Providers

1. Based on the information you received, did you change your patient's pain management therapy?
☐ Yes, decreased the patient's opioid dose.
☐ Yes, discontinued drug(s) that interacted with the patient's opioid.
☐ Yes, discontinued opioid and switched to a different agent.
☐ Yes, other (please specify): _____
☐ No
2. Do you routinely use your state's prescription monitoring program (PMP) to see what controlled substances your patient is obtaining from pharmacies?
☐ Yes
☐ No
3. How useful was the information you received? (1 = very useful, 2 = useful, 3 = somewhat useful, 4 = not useful)
1 2 3 4
4. Please indicate your specialty:
☐ Pain specialist
☐ Internal medicine
☐ Family medicine
☐ Neurologist
☐ Hospitalist
☐ Physician's assistant
☐ Nurse practitioner
☐ Other (please specify): _____
5. Comments: _____