Assessment of a Retrospective Drug Utilization Review Alert Letter Program

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Abstract

• Objective: To assess the impact of a drug utilization review (DUR) alert letter program on metformin discontinuation rates in patients with a metformin claim and an absolute contraindication to metformin therapy.

• Patients and setting: Members enrolled in a private health plan and their affiliated pharmacy benefits manager in the U.S. Midwest.

• Intervention: Members with a metformin claim and a metformin absolute contraindication diagnosis (ie, heart failure, renal insufficiency, or metabolic acidosis) had a letter sent to their physician that contained patient-specific information about the safety risks of metformin therapy. 16,575 patients who had a metformin claim but no documented contraindications comprised the comparison group.

• Results: 712 (3.7%) of members with a metformin claim had an absolute metformin medical contraindication. 566 members had letters sent to their physicians. At 9 months, 37.3% had discontinued metformin as compared with 20% of patients in the comparison group ($P < 0.001$). The rate of metformin discontinuation over the 9-month follow-up period was 84% higher in the intervention group (hazard ratio 1.84 [95% confidence interval, 1.62–2.09]; $P < 0.0001$).

• Conclusion: This focused DUR alert letter intervention demonstrated a statistically significant 84% associated decrease in metformin use among patients at risk for a life-threatening adverse reaction to metformin. DUR programs that provide actionable information to physicians can decrease inappropriate prescribing and reduce health care expenditures.

The Omnibus Budget Reconciliation Act of 1990 mandated state Medicaid programs to provide claims-based retrospective drug utilization review (DUR) [1]. Following passage of this act, most managed care organizations and pharmacy benefit managers (PBMs) also developed retrospective DUR programs. Retrospective DUR uses pharmacy claims data to identify potentially inappropriate pharmacotherapy [2]. The goal of DUR is to prevent or minimize inappropriate prescribing, thereby reducing unnecessary therapy and medication errors along with their associated morbidity and costs [1,3].

When members exposed to potentially inappropriate prescribing are identified through DUR, the health plan typically sends an alert letter notifying the physician of the problem and requesting a change in therapy [2]. Medicaid retrospective DUR programs that use single-intervention alert letters focusing on a specific drug or group of drugs have been successful in reducing rates of unnecessary pharmacotherapy [4–7]. In these programs, the state Medicaid offices identified patients receiving potentially unnecessary medications and sent alert letters to physicians specifying the patient at risk and asking the physician to consider making a change in therapy.

We developed a DUR letter intervention for metformin following the publication of a study showing that 22% of randomly sampled patients prescribed metformin possessed a medical condition considered an absolute contraindication to the medication [8]. Metformin has an absolute contraindication in patients with congestive heart failure requiring pharmacologic treatment, renal dysfunction, or acute or chronic metabolic acidosis because these conditions are associated with increased risk for development of life-threatening lactic acidosis [9]. There were 47 confirmed cases of lactic acidosis associated with metformin use during the first 14 months after the drug’s United States release [10]. The mortality rate in these cases was 43%, and 91% of the patients had a relative or absolute contraindication to metformin.

The goal of our DUR alert letter intervention was to reduce the number of members taking metformin concurrent...
with a metformin absolute contraindication. In this paper, we describe the intervention and report on its effect on metformin prescribing in high-risk patients.

**Methods**

**Patients and Setting**

The population studied was all 1.08 million members of a large Blue Cross plan in the U.S. Midwest receiving pharmaceutical benefits through a single PBM. All members were screened for a metformin claim submitted between 1 January 2002 and 22 May 2002. A metformin claim was defined as a generic product identifier (GPI; First Databank [Medispan], Indianapolis, IN) code beginning with 272500, 279970, or 279980. The days’ supply submitted with each claim was multiplied by 1.1, increasing the effectual days’ supply by 10% to adjust for missed doses (eg, 30-day supply would be adjusted to 30 x 1.1 = 33 days of potential exposure). The prescription fill date and effectual days’ supply were used to determine if the member had a supply of metformin medication on 10 June 2002, the day the alert letter was sent.

Members with a metformin claim during the analysis period were screened for diagnoses that are an absolute contraindication for metformin: heart failure, renal insufficiency, or metabolic acidosis. Medical claims for the period May 2001 to April 2002 were searched for ICD-9 coded diagnoses in the primary fields of heart failure (428.XX), renal failure (585.XX), or acidosis (as a proxy for metabolic acidosis, 276.2). Patients with a diagnosis code for heart failure also were required to have at least 1 claim for digoxin (GPI beginning with 312000), a diuretic (GPI beginning with 37), or an angiotensin-converting enzyme inhibitor (GPI beginning with 36100 or 36991502 or 36991802) between January 2002 and May 2002. Patients with a metformin claim and a metformin absolute contraindication diagnosis comprised the intervention group. Patients with a metformin claim and none of the contraindication diagnoses comprised the control group.

**Intervention**

We developed a 1-page physician alert letter that summarized the metformin contraindications and risks associated with prescribing metformin. The letters identified the specific patient at risk and included his/her metformin prescription records and medical claims indicating he/she has one or more of the diagnoses that are an absolute contraindication to receiving metformin. The letter recommended that the physician consider the risk-benefit associated with metformin therapy. The letter also recommended that in cases where the physician wanted the patient to continue metformin therapy, the physician should document the member’s understanding of the risks and benefits within the patient’s medical record. The physician alert letter was sent on health plan letterhead and was signed by the pharmacy program director. Alert letters contained a telephone number and address for questions and comments.

**Measures and Analysis**

The primary outcome was metformin discontinuation rates at 9 months. Statistical comparison was done using the Kaplan-Meier method and analyzed with SAS 8.2 (SAS Institute, Cary, NC). Metformin discontinuation was defined as no new metformin claims to the end of follow-up after the adjusted days’ supply of metformin ran out. Statistical significance was set at \( P < 0.05 \). In the Kaplan-Meier analysis method, the subject is required to be taking metformin on day 1. Therefore, only patients with a metformin claim indicating possession of metformin on 10 June 2002, the day the alert letter was sent to physicians, were included in the analysis. Using enrollment files, patients who disenrolled were censored on disenrollment date.

For all members with a metformin claim during the study period following the alert letter mailing, medical data were assessed for acidosis claims. Because lactic acidosis does not have a specific ICD-9 code, the general acidosis ICD-9 code of 276.2 was used as a proxy. In addition, a Current Procedural Terminology (CPT) code for lactate laboratory charge 83605 was required to be considered a lactic acidosis event. We required the ICD-9 event to have occurred within 10 days of the lactate CPT claim to enhance the accuracy of potential lactic acidosis event classification.

**Results**

19,135 members with a metformin claim were identified, and 712 (3.7%) of these had an absolute metformin medical contraindication. 116 (16.3%) were excluded due to lack of metformin supply on the date the letter was sent and 30 (4.2%) due to inability to identify the metformin prescriber from the pharmacy claim record. Thus, 566 members had metformin alert letters sent to their physicians. 18,423 members had a metformin claim but did not have a metformin alert letters sent to their physicians. 18,423 members had a metformin claim but did not have a metformin medical contraindication. Of these, 1848 (10%) were excluded due to lack of metformin supply on the alert letter date. Thus, 16,575 members comprised the comparison group.

At 9 months’ follow-up, 533 intervention group members and 15,280 comparison group members were still enrolled in the health plan. The metformin discontinuation rate at 9-months was significantly lower in the intervention group (199/533 [37.3%]) compared with the comparison group (3056/15,280 [20.0%]) \( (P < 0.001) \). The rate of discontinuation was 84% higher in the intervention group (hazard ratio, 1.84 [95% confidence interval, 1.62-2.09]; \( P < 0.001 \)) (Figure). The largest divergence between the groups was seen during the initial 60 days postintervention. This was followed by a similar attrition rate in both groups during the subsequent 210 days.
Prescriber feedback was not formally solicited; however, 17 response letters were received (Table). The most common comment involved an administrative issue, such as the patient no longer or never being under the physician’s care.

We found no potential lactic acidosis events among the intervention group during the follow-up period. One potential metformin lactic acid event was found in the comparison group.

Administrative costs associated with the metformin alert letter totaled $1436.40, which included the costs of a clinical pharmacist to create the physician letter and administer the program, an analyst to identify the patients and prescribers, an administrative assistant, and materials (envelopes, paper, letter, postage).

Discussion

Although the contraindications to metformin use are clear and have been known for years [9,10], more than 3% of patients with a metformin claim in this DUR program had an absolute medical contraindication. Our physician alert letter intervention incorporating patient-specific medical and pharmacy claim history was associated with a statistically significant reduction in metformin claims among high-risk patients. Discontinuation rates were 84% higher in the intervention group as compared with the comparison group.

We believe our study is one of the first to analyze a private PBM’s retrospective DUR alert letter program. In addition, the intervention in our study was unique because it integrated both pharmacy and medical claims, and it addressed the use of a metformin in patients with an absolute medical contraindication (ie, safety). Studies of retrospective DUR focusing on this group of patients have not been previously reported.

The limitations of this study include the use of administrative pharmacy and medical claims. Such data may contain miscoding, and when using this data one assumes accurate diagnosis as well as medication compliance. This study design assumed that the 2 groups had comparable discontinuation rates prior to the intervention. However, data validating this assumption were not generated and are not presented. Other factors that could have contributed to discontinuation differences between the groups include divergent rates of adverse events and efficacy, which we were unable to assess with claims data. In addition, the publication by Horlen et al [8] may have had an impact on the prescribing behavior of the physicians in this study. However, we sent the alert letter within 1 month of this publication, and the medical literature suggests that a such a publication does not affect prescribing.

Table. Summary of Physician Feedback

<table>
<thead>
<tr>
<th>Response Category</th>
<th>No. of Letters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient was no longer or never had been under</td>
<td>7</td>
</tr>
<tr>
<td>prescriber care</td>
<td></td>
</tr>
<tr>
<td>Patient no longer has metformin contraindication or</td>
<td>5</td>
</tr>
<tr>
<td>is no longer on metformin</td>
<td></td>
</tr>
<tr>
<td>Criticism of using claims data to identify patients</td>
<td>2</td>
</tr>
<tr>
<td>and prescribers</td>
<td></td>
</tr>
<tr>
<td>Request to send alert letter to specialist who</td>
<td>1</td>
</tr>
<tr>
<td>originally prescribed metformin</td>
<td></td>
</tr>
<tr>
<td>Reviewed patient’s case and although contraindication</td>
<td>1</td>
</tr>
<tr>
<td>to metformin exists prescriber believes benefits</td>
<td></td>
</tr>
<tr>
<td>outweigh risks</td>
<td></td>
</tr>
<tr>
<td>Compliment on alert letter, thanking health plan</td>
<td>1</td>
</tr>
<tr>
<td>for sending it</td>
<td></td>
</tr>
</tbody>
</table>

Figure. The hazard ratio of metformin discontinuation in the intervention group compared to the comparison group was 1.84 (95% confidence interval, 1.62–2.09; P < 0.0001). The decrease in number at risk over time reflects the fact that 1295 comparison and 33 intervention members left the health plan during the 9-month follow-up.
behavior for many months or years [11]. Our analysis measured a decrease in metformin use within 60 days of the letter. Finally, the lack of randomization precludes us from drawing a direct cause-and-effect conclusion with this analysis. We selected a quasi-experimental study design due to the medical concern of withholding safety information from physicians when a known life-threatening risk exists.

The potential for retrospective DUR to prevent or minimize inappropriate prescribing has been questioned since the mandated Medicaid DUR program was implemented [12,13]. A study of multiple states’ Medicaid retrospective DUR programs was unable to identify an effect, and the authors concluded that policy makers should consider withdrawing the legislative mandate for retrospective DUR [14]. However, there was an extremely high false-positive alert rate in this study. Of the 612,892 high-risk alerts reviewed by pharmacists, 98.3% of them lacked clinical significance [14,15]. The authors were unable to measure an effect in the remaining alerts because they were not able to identify the specific patients associated with the alerts. In addition, these state programs involved many individual alerts, and the data on the individual alerts were pooled for global analysis. Pooling may have caused a dilution of the impact of effective alerts. If a focused analysis of each individual alert had been done, the authors may have come to a different conclusion. A high-rate of false-positive alerts also was seen in a study of a private-sector PBM DUR program [16]. Conversely, small single-intervention retrospective DUR programs have been found to reduce inappropriate pharmacotherapy [4–7]. Our findings are consistent with previous studies of focused programs, suggesting that global programs should be reassessed to identify the individual interventions that are effective and eliminate those that are driving the high false-positive alert rate.

The largest divergence in metformin discontinuation between intervention and comparison groups occurred during the first 60 days after the alert letters were sent, suggesting physicians who did take action as a result of the letter did so early. This finding suggests that the mailing should be repeated approximately 60 days after the initial mailing to potentially increase the metformin discontinuation rate.

Approximately two thirds of metformin members at high risk for life-threatening lactic acidosis still had a supply of metformin 9 months after the alert letter was sent. One reason a large number of members with an absolute contraindication to metformin remained on the drug may be that the medical community does not express clear consensus on the risk of lactic acidosis associated with metformin. Recent publications and reviews of metformin-associated lactic acidosis have suggested the risk may be negligible [17,18]. However, these analyses note that the metformin had been “prescribed under study conditions, taking into account contraindications” [18]. In addition, the American Diabetes Association has reaffirmed the contraindications to metformin use [19].

We calculated the projected savings from the intervention. The current estimate of lactic acidosis risk among metformin users with an extremely low rate of absolute contraindication is 1 case per 2272 patient-years exposure [20]. Although the definitive rate of lactic acidosis among patients with an absolute contraindication is unknown, an estimated 20-fold higher risk is reasonable [10]. Thus, one can estimate a rate of 1 lactic acidosis case per 114 (range, 57–228) patient-years of metformin exposure in high-risk patients [9,10]. To estimate the number of potential lactic acid events avoided, we multiplied the absolute difference in metformin discontinuation rates between the intervention and comparison groups by the number of members who received physician alert letters. The higher metformin discontinuation rate in the intervention group resulted in 98 patient-years less of metformin exposure among members with an absolute contraindication to metformin (ie, [37.4% intervention rate – 20.0% comparison rate] × 566 intervention patients). The 98 years less of metformin exposure suggests that 0.86 (range, 0.43–1.72) lactic acidosis events were avoided in this program, based on the estimated rate of 1 event per 114 patient-years of metformin exposure.

We estimated the cost of a lactic acidosis event to be $7119.50, the charges directly associated with the probable lactic acidosis event identified in the one patient in the comparison group with a probable lactic acidosis claim. Using these cost data and the projected events avoided, we estimate this metformin alert letter resulted in a potential cost avoidance of $6122.77 (range, $3061.39–$12,245.54) per year for the 566 intervention patients.

This focused retrospective DUR alert letter intervention incorporating medical and pharmacy data was associated with an 84% decrease in metformin use among patients at risk for a life-threatening adverse reaction to metformin. This program was created at minimal cost and with a projected medical cost savings. These findings and those of other focused interventions suggest that retrospective DUR programs that provide actionable information to physicians can decrease inappropriate prescribing and reduce health care expenditures.

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Funding/support: All funding for this project was provided internally by Prime Therapeutics, Inc., a pharmacy benefits manager.

References

1. Medicaid program; Drug Use Review program and electronic claims management system for outpatient drug claims–HCFA. Interim final rule with comment period. Fed Regist 1992;57: