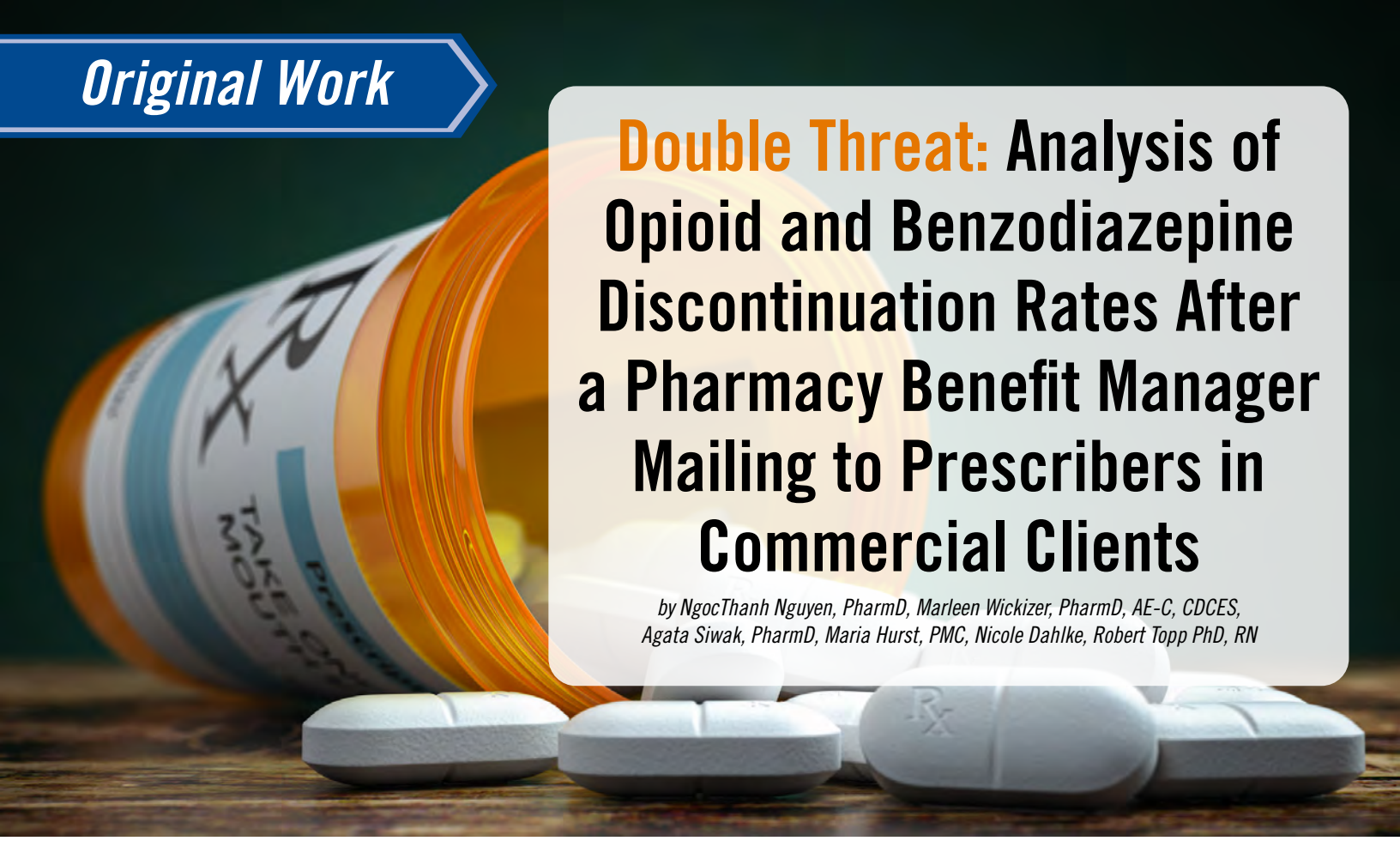
Original Work

Double Threat: Analysis of Opioid and Benzodiazepine Discontinuation Rates After a Pharmacy Benefit Manager Mailing to Prescribers in Commercial Clients

by NgocThanh Nguyen, PharmD, Marleen Wickizer, PharmD, AE-C, CDCES, Agata Siwak, PharmD, Maria Hurst, PMC, Nicole Dahlke, Robert Topp PhD, RN



Abstract

Objective: To determine the effect of prescriber mailings on the discontinuation of opioids and/or benzodiazepines among commercial health plan members who are prescribed these medications concurrently.

Methods: A retrospective analysis was conducted on members of two commercial health plans who had concurrent claims for both opioids and benzodiazepines for two of four months between March and June of 2019. Letters were mailed to the prescribers of members of one commercial health plan; this was the intervention group. The primary endpoint was the percentage of members with discontinuation of one or more opioids and/or benzodiazepines after the intervention. Secondary endpoints included morphine milligram equivalent (MME) for opioids, number of prescriptions, day supply, and quantity in each class.

Results: A higher percentage of the intervention group (52.8%) discontinued an opioid and/or benzodiazepine compared to the control group (41.4%). However, this difference was not statistically significant ($p=0.09$). Over the duration of the study, the intervention group experienced a significant decline ($p<0.05$) in all metrics of opioid prescriptions. This included the change in average MME compared to the control group (-10.5 vs. – 4.1, $p<0.05$). The intervention group significantly declined in all metrics of benzodiazepine prescriptions over the duration of the study compared to baseline and the control group.

Conclusion: Following prescriber mailings, opioid and benzodiazepine prescriptions were reduced among members concurrently prescribed these medications.

The increasing number of opioids being prescribed for chronic noncancer pain has contributed to the opioid epidemic, which has led to an increase in opioid misuse and abuse, illicit drug use, and overdose.[1-2] Hospitalizations due to opioid use increased by 64% between 2005 and 2014.[3-4] National overdose deaths related to prescription opioids steadily increased from 1999, with 3,442 deaths annually, to 17,029 deaths in 2017. A decline in opioid-related deaths was observed in 2019 with 14,139 deaths, but it increased again in 2020 with 16,416 deaths.[5] When taken concurrently, benzodiazepines and opioids together put patients at a higher risk for respiratory depression and fatal overdose.[6-8] Deaths related to drug overdose with concurrent use of opioids and benzodiazepines increased from 1,135 in 1999 to 11,537 in 2017, then declined to 9,711 in 2019. By 2020, drug overdoses involving opioids with benzodiazepines increased again to 12,290.[5,9] Due to these events, the Food and Drug Administration (FDA) has updated the labeling for both classes of medications to include a boxed warning that cites the serious risks—including risk of death—of taking

both classes of medications together.[10] To combat the opioid epidemic, the Centers for Disease Control and Prevention (CDC) has created guidelines outlining 12 steps for opioid prescribing.[11] These guidelines describe the steps for initiation or continuation of opioids for chronic pain, selection of opioids, opioid dosage, duration, follow-up, and termination. To reduce the risk of overdose, the 2016 CDC Opioid Prescribing Guidelines recommend avoiding concurrently prescribing opioids with benzodiazepines when possible.[10-11] Other ways to decrease the misuse of opioids include prescription drug monitoring programs, Drug Enforcement Administration (DEA) drug take-back days, reformulation of opioids to be tamper resistant, and access to treatment for opioid use disorder.[12-13] Overdose reversal agents, like naloxone, can be administered by the patient or patient's agent, are available as a prescription or dispensed by a pharmacist under a standing order depending on the state.

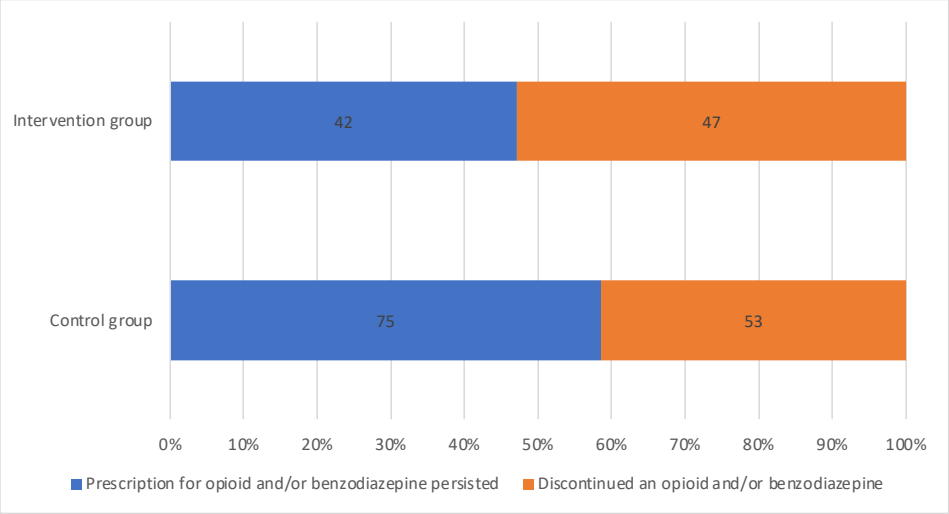
The Center for Medicaid and Children's Health Insurance Program (CHIP) released guidance to reduce opioid abuse and misuse through the implementation of the new Medicaid Drug Utilization Review (DUR).[14] The guidance includes prescription claim reviews at the point of sale, retrospective review, identification of processes to detect fraud and abuse, and mandatory DUR report updates. States are required to implement safety edits and claims review automated processes.

Pharmacy benefit managers (PBMs) are in a unique position in healthcare, because they have access to pharmacy claims data from multiple prescribers and from multiple pharmacies, allowing them to detect when a member is filling prescriptions for opioids and benzodiazepines concurrently. The Double Threat program is a retrospective DUR safety program used by Navitus Health Solutions, LLC, a PBM, to identify members who have concurrent claims of both an opioid and benzodiazepine. The internal application identifies members and generates their opioid and benzodiazepine medication profiles during a four-month timeframe. The goal of the Double Threat safety program is to promote safe, effective, and appropriate prescription drug use for all members and encourage coordinated care among the health care team. Limited data is available on the effects of a prescriber mailing as an intervention in reducing concurrent use of opioids and benzodiazepines.

TABLE 1. Demographic Data

	Control	*Intervention*	*Combined*
Members	128	89	217
Male	44 (34.4%)	22 (24.8%)	66 (30.4%)
Female	84 (65.6%)	67 (75.2%)	151 (69.6%)
Age in years, mean +/- standard deviation	54.7 +/- 11.4	57.1 +/- 9.0	56.6 +/- 10.5

FIGURE 1. Number of Members with a Discontinuation of an Opioid and/or Benzodiazepine from 2019 to 2020 (n=217).



**Not significant, Chi-square = 2.75, p=0.09*

The purpose of this study was to determine the effect of prescriber mailings on the discontinuation of opioids and/or benzodiazepines among members who are prescribed these medications concurrently.

Methods

Study Design

A retrospective analysis of the Double Threat DUR safety program was conducted. Prior to accessing data, the study received an IRB exemption. Two similar commercial health plans were selected, with one health plan as the control group and the other as the intervention group. Inclusion criteria consisted of active members within either commercial health plan during the pre- (March-June 2019) and post- (March-June 2020) intervention period. Members had to have pharmacy claims for both an opioid and benzodiazepine for at least two of four months during the timeframe of March 1, 2019, through June 30, 2019. Exclusion criteria were members who were in hospice or long-term care, had claims for an oncology medication, or were included in another DUR safety program. There were no age or medication quantity exclusion criteria.

The intervention consisted of letters mailed to all prescribers who concurrently prescribed an opioid or benzodiazepine to members in the intervention group. The mailings occurred on November 25, 2019, and March 30, 2020. These letters included the member's medication profile and a message referring to CDC guidelines, encouraging prescribers to use their clinical judgment to discontinue opioids or benzodiazepines when they were prescribed concurrently.

Post-intervention outcomes were collected from March 1, 2020, through June 30, 2020. The primary endpoint was the number of members with discontinuation of opioids and/or benzodiazepines after

prescriber mailings. Secondary endpoints were the change from 2019 to 2020 in average daily morphine milligram equivalent (MME), the number of unique prescriptions, day supply, and quantity in each class.

Statistical Analysis

The statistical analysis involved identifying eligible subjects in a database over the duration of the study. These individuals were identified by pharmacy claims using the Double Threat DUR program. After eligible subjects were identified, their opioid and benzodiazepine prescription claims data filled during 2019 and during 2020 were downloaded to an Excel spreadsheet. The data compiled included the average daily MME, quantity, day supply, and prescriptions per member for each opioid and benzodiazepine prescription filled. The second step of the analysis involved transferring the data into an SPSS.v27 data set and then calculating repeated measures analysis of variance (R-ANOVA) statistics for each of the outcome variables, using time (2019 vs. 2020), group (intervention vs. control), and the interaction of time by group as the independent factors. Significant main or interaction effects for any of these R-ANOVA statistics were then addressed through Tukey post hoc comparisons to determine which means were significantly different (alpha value of 0.05).[15]

Results

A total of 217 members were identified as eligible for the Double Threat DUR safety program. There were 128 members in the control group and 89 members in the intervention group. More than half of the population was female (69.6%) and the overall mean age was 56 years (Table 1). After the prescriber mailings, the primary endpoint showed 47 (52.8%) members in the intervention group discontinued an opioid and/or benzodiazepine compared to only 53 (41.4%) members in the control group (p=0.09) (Figure 1).

There was a significant difference in the change in average daily MME between the intervention group and control group [-10.4 mg (- 44.5%) versus - 4.1 mg (- 15.3%) (p<0.05)] (Table 2). The intervention group also experienced a significant decline compared to the control group in total opioid quantity (-43.6% versus -14.5%), day supply (-39.5% versus -13.3%), and prescriptions (-55.4% versus -34.8%) (p<0.05) (Table 2).

For benzodiazepines, a similar significant decrease in total quantity (-50% versus -13.9%), day supply (-52.7% versus -13%), and prescriptions (-56.4 versus -25%) were also observed for the intervention group compared to the control group (p<0.05) (Table 3).

TABLE 2. Comparing Opioid Prescriptions Between Intervention and Control Groups Over Time

Variable	2019		2020	
	Intervention Mean ± SE	Control Mean ± SE	Intervention Mean ± SE	Control Mean ± SE
Average Daily MME	23.3 ± 2.3	27.2 ± 1.9	12.9 ± 2.5*#	23.1 ± 2.1
Average quantity/member	336.0 ± 36.4	331.3 ± 30.1	189.6 ± 34.2*	283.2 ± 28.5
Average day supply/ member	85.0 ± 7.3	82.5 ± 6.1	51.4 ± 7.5*	71.5 ± 6.2
Average prescriptions/ member	1.4 ± 0.1	1.4 ± 0.1	0.6 ± 0.1*	0.9 ± 0.1

*p<0.05, *Indicates study group changed over time, #indicates study groups were different at a specific time, MME= Morphine Milligram Equivalents*

TABLE 3. Comparing Benzodiazepine Prescriptions Between Intervention and Control Groups Over Time

Variable	2019		2020	
	Intervention Mean ± SE	Control Mean ± SE	Intervention Mean ± SE	Control Mean ± SE
Average quantity/member	142.2 ± 13.8	175.5 ± 11.5	70.6 ± 13.3*#	151.1 ± 11.1
Average day supply/ member	71.8 ± 4.9	79.7 ± 4.1	33.9 ± 5.1*#	69.2 ± 4.2
Average prescriptions/ member	1.1 ± 0.0	1.1 ± 0.0	0.5 ± 0.1*#	0.8 ± 0.0

*p<0.05, *Indicates study group changed over time, #indicates study groups were different at a specific time*

Discussion

The results indicate that prescriptions for opioids and benzodiazepines were lower among patients whose prescribers received a mailing advising them of the risks of concurrent use and recommending they use their clinical judgment to discontinue opioids or benzodiazepines. Although not statistically significant, there appears to be clinical relevance to an almost 12% higher absolute rate of discontinuation of an opioid and/or benzodiazepine in the intervention group. These results may be impacted by the challenges that come with discontinuing an opioid or benzodiazepine over a short period of time, including withdrawal or an exacerbation of the symptoms being treated. Both classes of medications require a slow tapering regimen to safely discontinue.[11] There may be a significant finding if outcome measurements were longer than a year or if the study size were increased. All other metrics of opioid and benzodiazepine prescriptions were significantly lower in the intervention group following the intervention phase of the study. This finding indicates the potential efficacy of the intervention to result in significant reductions in opioids and benzodiazepine claims among these individuals who were concurrently prescribed these medications.

Similar outcomes were seen in other studies involving a notification to prescribers either through mailings or facsimile. One study mailed letters to prescribers of members using high-dose opioids with another opioid, benzodiazepine, or antidepressant.[16] The outcome was a 28.1% reduction in high-risk opioid use. A different study used a low-touch prescriber fax intervention to notify the prescriber of the recent benzodiazepine claim and

provide information about the CDC Opioid Prescribing Guideline's precautions regarding concurrent use of opioids and benzodiazepines.[17] This intervention resulted in a significantly improved percentage of patients without concurrent use of opioids and benzodiazepines with a number needed to treat of 26.[17] Additional studies using electronic databases of medication claims data to inform prescribers of patients concurrently prescribed opioids and benzodiazepines are needed to confirm the efficacy of prescriber mailings in reducing the rate of concurrently prescribed opioids and benzodiazepines.

Although the secondary findings indicate the potential efficacy of the intervention, these findings should be interpreted cautiously due to several limitations. First, the sample was small and drawn from a limited client database that may have limited the external validity. A larger, more heterogenous sample may reveal a different finding in the primary endpoint. A second limitation was that claims were not captured if members paid out-of-pocket for either class of medications. While the intervention letter provided information to the provider about the risks of concurrent use of opioids and benzodiazepines, the actions in response to this information were not examined in this study. Future investigators may wish to examine the prescriber responses to these types of intervention letters to provide further insight regarding the impact of the intervention letter on clinical practice. Finally, the intervention letter did not provide clinical guidelines for discontinuing concurrent use of opioids and benzodiazepines, and thus the provider was not provided with suggested approaches to address the issue revealed. Tools to educate providers on opioid and benzodiazepine tapering may improve the prescriber confidence to implement change.

Conclusions

Prescriber mailings appear to be a potentially effective intervention to reduce concurrent use of opioids and benzodiazepines.

NgocThanh Nguyen former Clinical Pharmacy Resident at Navitus Health Solutions in Madison, WI. Marleen Wickizer is the Director, Clinical Services and Residency Program Director at Navitus Health Solutions in Madison, WI. Agata Siwak is a Population Health Pharmacist at Navitus Health Solutions in Madison, WI. Maria Hurst is a Senior Product Manager, Population Health at Navitus Health Solutions in Madison, WI. Nicole Dahlk is a Team Lead, Analytics at Navitus Health Solutions in Madison, WI. Robert Topp is a Professor at the University of Toledo College of Nursing in Toledo, OH.

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Corresponding Author: *NgocThanh Nguyen - NgocThanh.Nguyen@navitus.com*

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