Preventive Medicine Reports 36 (2023) 102493

Contents lists available at ScienceDirect

Preventive Medicine Reports

journal homepage: www.elsevier.com/locate/pmedr

Short communication

Effects of pharmacist-driven protocol on naloxone prescribing rates in two primary care clinics

Ashley Daffron [a,*], Kelly Koon [b], Nathan P Gruenke [c], Sara Wettergreen [a]

[a] Department of Clinical Pharmacy, University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, 12850 E. Montview Blvd, C238 Aurora, CO 80045, United States
[b] PGY-2 Ambulatory Care Pharmacy Resident, University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, 12850 E. Montview Blvd, C238 Aurora, CO 80045, United States
[c] Pharmacy Student, University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, 12850 E. Montview Blvd, C238 Aurora, CO 80045, United States

ARTICLE INFO

Keywords:
Naloxone
Pharmacist
Chronic pain
Opioid
Co-prescribing
Primary care

ABSTRACT

The Centers for Disease Control and Prevention (CDC) Guidelines for Prescribing Opioids for Chronic Pain recommend co-prescribing naloxone as a harm reduction strategy when there is an increased risk of opioid overdose. Although naloxone co-prescribing is an important harm reduction strategy, many at risk patients are not prescribed naloxone. The objective was to assess the effectiveness of a pharmacist-driven protocol at increasing the number of patients co-prescribed naloxone according to CDC recommendations. The study design was a multi-center retrospective cohort to evaluate the outcomes of a quality improvement intervention at two primary care clinics which aimed to increase naloxone co-prescribing. The intervention used a two-pronged approach consisting of telephonic outreach to eligible patients by pharmacists and pharmacy interns related to naloxone education and recommendations for naloxone co-prescribing. Additionally, recommendations were sent to the primary care provider in the electronic medical record (EMR) for consideration and implementation. After the 3 month intervention, 57 of the 86 patients contacted were co-prescribed naloxone (66.3%). Most naloxone initiation occurred at the time of telephonic outreach as a new medication order (n = 36), however an additional 12 patients were co-prescribed naloxone at a subsequent primary care provider visit. The proportion of patients at each clinic with MME ≥ 50 co-prescribed naloxone significantly increased after implementation of the intervention (pre 25/64 vs. post 43/76, p = 0.043). Overall, telephonic outreach to patients with recommendations to primary care providers in the EMR were effective methods to increase the rate of naloxone co-prescribing in primary care based on this study.

1. Background

In both the United States and Colorado, opioid overdose rates make up a large portion of the overall increase in total drug overdose deaths. (CHED, 2022) From 1999 to 2010, opioid prescribing in the United States increased fourfold, translating to increase in opioid related overdose deaths and incidence of opioid use disorders. (Dowell et al., 2022) While recent increases in fully-synthetic opioids such as fentanyl further propel the overdose epidemic, prescription opioid overdose rates remain a constant contributor to overdose deaths. (CHED, 2022) Opioids were the most commonly misused prescription drug in the United States in 2020, further emphasizing the need for harm reduction strategies related to opioids. (Dowell et al., 2022).

Centers for Disease Control and Prevention (CDC) Guidelines for Prescribing Opioids for Chronic Pain evaluates multiple aspects of opioid therapy, including addressing potential harms. (Dowell et al., 2022) A primary component of harm reduction is risk assessment and availability of naloxone when risks for opioid overdose exist. (Naloxone, 2022) The risk of overdose increases with opioid dosages greater than 50 morphine milligram equivalents (MME) per day. (Dowell et al., 2022) The CDC Guideline recommends incorporating naloxone for patients using chronic opioids with an MME of 50 or greater, concurrent use of a benzodiazepine, or those with a history of substance use disorder.

Many states, including Colorado, have issued standing orders for naloxone dispensing. (SAFE, 2022) At the time of this intervention, Colorado Senate Bill 15–053 enabled pharmacies to dispense naloxone

* Corresponding author.
E-mail address: Ashley.Daffron@CUAnschutz.edu (A. Daffron).

https://doi.org/10.1016/j.pmedr.2023.102493
Received 4 August 2023; Received in revised form 31 October 2023; Accepted 1 November 2023
Available online 2 November 2023

to specific populations. (Naloxone Standing Orders, 2022) Those whom may receive naloxone pursuant to the standing order include individuals at risk of overdose, first responders, employees or volunteers of harm reduction organizations, and anyone in a position to assist a person at risk of overdose. However, a majority of opioid abuse involves the misuse of prescription pain relievers for which patients may or may not be familiar with naloxone therapy. (Key Substance, 2020) While great nationwide efforts are underway to help address the prescription opioid crisis, co-prescribing of naloxone is one harm reduction strategy recommended by the CDC.

Many high-risk patients are not prescribed naloxone. (Guy et al., 2019; Torres et al., 2022) Different methods have been studied evaluating the effectiveness of efforts to increase naloxone co-prescribing. (Wilson et al., 2003; Cariveau et al., 2003; Hoefling et al., 2020; Watson et al., 2020; Kirk et al., 2021; Rothbauer et al., 2022; Griffin et al., 2019; Rawal et al., 2023) Current literature supports naloxone co-prescribing in primary care as acceptable to both patients and providers, and is feasible to implement. (Behar et al., 2018) Prescribers' willingness to prescribe naloxone has continued to increase, but several barriers remain, including time constraints, lack of prescriber familiarity with naloxone, and lack of patient interest.Watson et al., 2020.

Pharmacists are often engaged in opioid-related harm reduction efforts. In one example, pharmacists in primary care clinics developed provider education, electronic medical record alerts, and a report to easily identify candidates for naloxone, however targeted telephonic outreach was not part of the intervention. (Cariveau et al., 2003) Telephonic outreach by pharmacists in primary care settings has demonstrated success in increasing the rate of naloxone co-prescribing for people who use opioids long-term (Wilson et al., 2003; Rothbauer et al., 2022) This study aims to evaluate if similar approaches combined yield positive results.

2. Objective

The purpose of this study was to evaluate if a pharmacist-driven protocol would increase the proportion of eligible patients co-prescribed naloxone in alignment with CDC recommendations.

3. Methods

The study design was a multi-center retrospective cohort to evaluate the outcomes of a quality improvement intervention. The primary outcome was to assess the effectiveness of a clinical pharmacy intervention at increasing the number of patients prescribed naloxone. This includes assessing the proportion of patients at each clinic with MME of 50 or greater co-prescribed naloxone. The secondary outcome was to assess if relationships existed between patient-specific variables and acceptance of the intervention.

A pharmacist-driven patient outreach protocol was utilized for a quality improvement project at two academic medical center outpatient clinics (one primary care, one internal medicine) with the aim to increase naloxone co-prescribing. The project occurred between 4/1/21–6/30/21. The project was completed in collaboration with primary care providers (PCPs), clinical pharmacists, and pharmacy interns. The intervention used a two-pronged approach consisting of both telephonic outreach to eligible patients and providing recommendations to PCPs in the electronic medical record (EMR) for consideration and implementation. Patients were identified through the development of an EMR report. Eligible patients were those who were taking opioids for at least 3 months with either MME of 50 or greater used per day, use of a concurrent benzodiazepine, or a history of substance use disorder. For telephonic outreach, pharmacists and pharmacy interns contacted eligible patients to discuss risks associated with opioid use, provide naloxone education, and recommend naloxone co-prescribing. If the patient agreed, a medication order for naloxone was pended for PCP verification and signature. As a second element to the intervention, clinical documentation was provided in the EMR for all patients identified as eligible for naloxone. The clinical documentation consisted of summarizing current opioid use, including MME and indication, assessment of the patient's risks for opioid-related adverse drug events (ORADEs), date of last controlled substance agreement signature, and results of telephonic outreach. The purpose of the two-pronged approach was to provide additional information to PCPs about patients' specific risks and additional measures to support safe use of opioids.

This research was submitted to the Colorado Multiple Institutional Review Board (IRB) and deemed exempt from IRB review. SPSS was used for statistical analysis, with significance defined as $p < 0.05$. To assess for significant unadjusted univariate relationships between patient characteristics and acceptance of naloxone co-prescribing for the secondary outcome, Kruskal-Wallis was used for MME, and Fisher's exact test was used for gender and clinic setting comparisons.

4. Results

A total of 86 patients were identified as eligible for naloxone co-prescribing between the two clinics. The mean patient age was 53 years and a majority were female (59.3%). The mean MME at the time of outreach was 103, 18.6% were using multiple opioids, 47.7% were co-prescribed a benzodiazepine, and 11.6% had a history of substance use disorder.

Telephonic outreach was attempted for all 86 patients, and 61 patients were successfully reached. Within 3 months of the intervention, 57 patients were co-prescribed naloxone (66.3%). The majority of naloxone initiation occurred at the time of telephonic outreach as a new prescription ($n = 36$, 59%). However, 9 patients stated they had already received naloxone from their community pharmacy, thus naloxone was added to the patient's medication list in the EMR. An additional 12 patients were co-prescribed naloxone by the PCP based on recommendations provided in the EMR. (Fig. 1).

The proportion of patients at each clinic with MME ≥ 50 per day co-prescribed naloxone was compared pre and post intervention, as seen in Table 1. This comparison focused on patients with MME ≥ 50 per day based on our standard clinic reporting related to this measure. In the total included population between both clinics, the proportion of patients co-prescribed naloxone significantly increased, as measured within one month (7/30/21) of completion of the intervention (25/64 vs. 43/76, $p = 0.043$).

For the secondary outcome, there was no significant relationship identified between acceptance of naloxone co-prescribing and age, gender, or clinic setting. Patients taking a higher dose of opioids based on MME were more likely to accept naloxone co-prescribing (121.1 ± 110.6 versus 68.44 ± 81.1; $p = 0.0005$).

5. Discussion

This pharmacist-led initiative increased the rate of naloxone co-prescribing across two primary care clinics. The utilization of embedded clinical pharmacists and pharmacy interns for targeted naloxone outreach circumvent PCP time constraints and potential lack of familiarity of naloxone prescribing. To supplement statewide community pharmacy efforts, clinical pharmacists within primary care clinics can utilize outreach methods targeting patients at high risk of prescription opioid overdose based on information in the EMR. (Dowell et al., 2022) Pharmacists are well-trained to educate patients and providers on signs and symptoms of opioid overdose, when to use naloxone therapy, and naloxone administration. We found this intervention was within the skill set of pharmacy interns involved in the project who provided meaningful contributions. The provision of patient education during telephonic outreach by clinical pharmacists and pharmacy interns allowed for the expanded prescribing of naloxone to high-risk patients in the primary care setting.

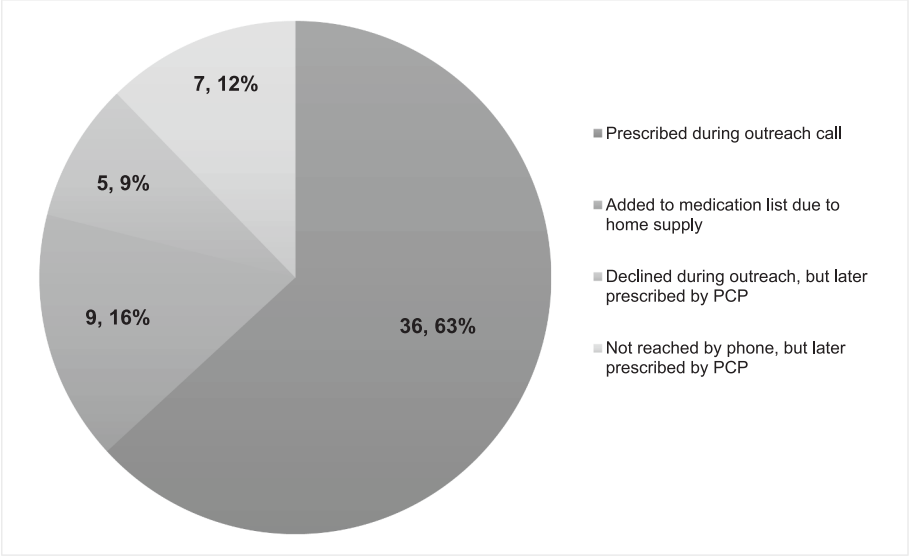

Fig. 1. Occurrence of Naloxone Co-Prescribing Among Adult Patients Within Two Academic Medical Center Outpatient Clinics from 4/1/21 to 6/30/21 (N = 57).

Table 1
Eligible Adult Patients Co-prescribed Naloxone Within Two Academic Medical Center Outpatient Clinics from 4/1/21 to 6/30/21.

Eligible Adult Patients Co-Prescribed Naloxone	Pre (n)	Post (n)	Fisher's Exact Comparisons
Both Clinics/Total Population			p = 0.043*
Prescribed Naloxone	25	43	
Patients with MME > 50	64	76	
Family Medicine Clinic			p = 0.016*
Prescribed Naloxone	9	25	
Patients with MME > 50	40	52	
Internal Medicine Clinic			p = 0.75
Prescribed Naloxone	16	18	
Patients with MME > 50	24	24	

MME = morphine milligram equivalents; *p < 0.05 = statistically significant.

A similar initiative by Cariveau and colleagues evaluated naloxone prescribing rates after a clinical pharmacy intervention. (Cariveau et al., 2003) In this study, pharmacists from a single primary care clinic identified patients indicated for naloxone, provided education to patients, providers, and staff, and created EMR quick links for ease of ordering. Rates of naloxone co-prescribing increased to 37.2% from just 3.4% at baseline. In comparison, our study included direct patient outreach in addition to providing recommendations in the EMR, which contributed to an increased rate of naloxone co-prescribing.

In another example, pharmacists in a primary care practice focused on provider education and addressing logistical barriers (i.e., provision of EMR alerts notifying providers of patients indicated for naloxone therapy). (Wilson et al., 2003) While their effort focused on improving provider prescribing by reducing barriers, our study involved initial naloxone outreach by pharmacists and pharmacy interns.. Although the approach varied, both initiatives increased patient access to naloxone therapy. Choice of approach may be guided by provider preference and time constraints. (Martino et al., 2020).

High-risk patients indicated for naloxone can be identified in different ways. In a study by Watson and colleagues, pharmacists used the Risk Index for Overdose or Serious Opioid-induced Respiratory Depression (RIOSORD) score to identified high-risk patients. (Watson et al., 2020) The RIOSORD score takes into account patient-specific factors such as history of substance use disorder, use of benzodiazepines, as well as the total MME. While our study did not utilize this score, we performed manual chart review to identify high-risk patients based on CDC guidance. Both methods of risk stratification led to an increase in naloxone co-prescribing, with slightly higher recommendation acceptance in our study (66.3% versus 44%). Additionally, our study evaluated for relationships between patient characteristics and acceptance of naloxone co-prescribing. We found patients using a higher MME were more likely to accept naloxone prescribing. This supports that higher-risk patients are more likely to be interested in naloxone co-prescribing.

In a recent systematic review of naloxone services provided by pharmacists beyond the community pharmacy practice setting, 76 studies were identified that addressed naloxone services provided by pharmacists predominately conducted in Veterans Affairs and academic medical institutions (30 and 21% respectively). (Rawal et al., 2023) The study identified several pharmacy services that were utilized including staff education, education to patients regarding naloxone and overdose risk, naloxone dispensing, and identification of high-risk patients via screening tools While most of the studies utilized one or two of the listed pharmacy services, our study utilized multiple avenues in order to identify high risk-patients, provide telephonic outreach to eligible patients, and send recommendations to PCPs in the EMR.

There are several limitations to our study. First, the sample size was small; including only patients from two primary care clinics. We also did not analyze actual naloxone prescription fill data. As our patients choose to have their prescriptions filled at a variety of pharmacies, fill data are not readily available through the EMR. Therefore, social desirability bias could have occurred if patients said they would get naloxone filled to please the pharmacist/intern even if they weren't actually planning on filling the prescription. Lastly, our data are limited to two primary care clinics at an academic medical center with embedded clinical pharmacists. Replication of the intervention may prove more challenging in settings without an embedded clinical pharmacist.

6. Conclusion

Despite many public health efforts, naloxone co-prescribing rates remain a concern, including in our health-system. Future directions should focus on expansion of naloxone co-prescribing initiatives by clinical pharmacists in the primary care setting to system-wide efforts, with the inclusion of prescription fill data. In Colorado, pharmacists can prescribe opiate antagonists directly without the need for standing orders pursuant to Senate Bill 21–094. (Board, 2022) This is a big step in the expansion of pharmacist services in Colorado and negates the need for provider signature on naloxone orders. A multi-faceted approach utilizing clinical pharmacists and pharmacy interns within primary care clinics should be the focus of future initiatives to increase access to

naloxone.

Our study demonstrates telephonic patient outreach in combination with provider recommendations placed in the EMR is an effective method to increase naloxone co-prescribing in the primary care setting. Results of this study utilizing a multi-faceted approach to increase naloxone co-prescribing rates add to the growing literature emphasizing the positive impact telephonic outreach by clinical pharmacists can have on patient care.

Previous presentations of the work: We have presented our findings as a virtual poster presentation at the 2021 American College of Clinical Pharmacy Annual Meeting.

CRediT authorship contribution statement

Ashley Daffron: Conceptualization, Methodology, Validation, Investigation, Data curation, Writing – original draft, Writing – review & editing, Project administration. **Kelly Koon:** Conceptualization, Methodology, Investigation, Data curation, Visualization, Writing - original draft. **Nathan P Gruenke:** Writing - original draft, Writing - review & editing. **Sara Wettergreen:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgements

The authors would like to acknowledge Nicole Kovac, PharmD and Briana Barganier, PharmD for their contributions to the quality improvement initiative during their time as student pharmacists at the University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences. The authors would also like to acknowledge Eric Gutierrez, MPH for statistical support of this project.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

Behar, E., Bagnulo, R., Coffin, P.O., 2018. Acceptability and feasibility of naloxone prescribing in primary care settings: A systematic review. Prev. Med. 114, 79–87. https://doi.org/10.1016/j.ypmed.2018.06.005.

Sunset Continue State Board of Pharmacy, SB 21-094, s 3, 12, 21. Colorado General Assembly. Accessed June 29, 2022.https://leg.colorado.gov/sites/default/files/2021a.

Cariveau, D., Fay, A.E., Baker, D., Fagan, E.B., Wilson, C.G., 2003. Evaluation of a pharmacist-led naloxone coprescribing program in primary care. J. Am. Pharm. Assoc. 59 (6), 867–871. https://doi.org/10.1016/j.japh.2019.07.012.

Center for Health and Environmental Data (CHED), Demont C, Yocum K, Bol K. HealthWatch No. 118; 2022. Accessed June 29, 2022. https://drive.google.com/file/d/1VGOSUU15rxV-Zj37T5c9GW13w2D76uzm/view.

Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. MMWR Recomm Rep 2022;71 (No. RR-3):1–95.

Griffin, S., Wishart, B., Bricker, K., Luebchow, A., 2019. Impact of a pharmacist-driven intervention on the outpatient dispensing of naloxone. J. Am. Pharm. Assoc. 59 (4S), S161–S166. https://doi.org/10.1016/j.japh.2019.06.011.

Guy GP Jr., Haegerich TM, Evans ME, Losby JL, Young R, Jones CM. Vital Signs: Pharmacy-Based Naloxone Dispensing — United States, 2012–2018. MMWR Morb Mortal Wkly Rep 2019;68:679–686. DOI: https://doi.org/10.15585/mmwr.mm6831e1external icon.

Hoefling AD, Ash LR, Linneman TW. Impact of pharmacist contact via telephone vs letter on rate of acquisition of naloxone rescue kits by patients with opioid use disorder [published online ahead of print, 2020 Sep 3]. Subst Abus. 2020;1-5. doi:10.1080/08897077.2020.1809606.

Key Substance Use and Mental Health Indicators in the United States: Results from the 2020 National Survey on Drug Use and Health (HHS Publication No. PEP21-07-01-003, NSDUH Series H-56). Substance Abuse and Mental Health Services Administration. https://www.samhsa.gov/data/sites/default/files/reports/rpt35325/NSDUHFFRPDFWHTMLFiles2020/2020NSDUHFFR1PDFW102121.pdf.

Kirk, J.K., Tran, M.Q., Pelc, S., Moore, K.G., 2021. Improving harm reduction with a naloxone intervention in primary care to prescribe and educate a support person. J. Opioid Manag. 17 (2), 109–113. https://doi.org/10.5055/jom.2021.0621.

Martino, J.G., Smith, S.R., Rafie, S., Rafie, S., Marienfeld, C., 2020. Physician and Pharmacist: Attitudes, Facilitators, and Barriers to Prescribing Naloxone for Home Rescue. Am. J. Addict. 29 (1), 65–72. https://doi.org/10.1111/ajad.12982.

Naloxone Standing Orders. Colorado Department of Public Health & Environment. Accessed June 29, 2022.https://cdphe.colorado.gov/prevention-and-wellness/injury-prevention/overdose-prevention/naloxone-standing-orders.

Life-Saving Naloxone from Pharmacies. Centers for Disease Control and Prevention. Accessed June 29, 2022. https://www.cdc.gov/vitalsigns/naloxone/index.html.

Rawal, S., Osae, S.P., Cobran, E.K., Albert, A., Young, H.N., 2023. Pharmacists' naloxone services beyond community pharmacy settings: A systematic review. Res. Soc. Adm. Pharm. 19 (2), 243–265. https://doi.org/10.1016/j.sapharm.2022.09.002. Epub 2022 Sep 15 PMID: 36156267.

Rothbauer, K., Genisot, A., Frey, T., JohnsonPharmacy William, S., Middleton,, 2022. Memorial Veterans Hospital D. Integration of Pharmacy Student Interns into a Naloxone Telephone Outreach Service. J. Pain Palliat. Care Pharmacother. 36 (4), 208–215. https://doi.org/10.1080/15360288.2022.2113595.

State Naloxone Access Rules and Resources. Stop the Addiction Fatality Epidemic (SAFE) Project. Accessed June 29, 2022. https://www.safeproject.us/naloxone-awareness-project/state-rules/.

Torres, E.L., Evoy, K.E., Thomas, L.O., 2022. Outpatient Opioid and Naloxone Prescribing Practices at an Academic Medical Center during the COVID-19 Pandemic. J. Pain Palliat. Care Pharmacother. 36 (3), 178–186. https://doi.org/10.1080/15360288.2022.2105471.

Watson, A., Guay, K., Ribis, D., 2020. Assessing the impact of clinical pharmacists on naloxone coprescribing in the primary care setting. Am. J. Health Syst. Pharm. 77 (7), 568–573. https://doi.org/10.1093/ajhp/zxaa007.

Wilson CG, Rodriguez F, Carrington AC, Fagan EB. Development of a targeted naloxone coprescribing program in a primary care practice. J. Am. Pharm. Assoc. *(2003)*. 2017;57(2S):S130-S134. doi:10.1016/j.japh.2016.12.076.