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Abstract

Purpose

The purpose of the MOON study was to apply a systems-level approach to improving delivery of and access to pharmacy-based naloxone (PBN).

Scope

This was a two-state demonstration project, conducted in close collaboration with chain (CVS Pharmacy), independent, and outpatient hospital pharmacies in Rhode Island (RI) and Massachusetts (MA).

Methods

Primary data collection included focus groups, interviews, surveys, and secret shopping. PBN materials were iteratively developed and subsequently tested before being broadly implemented. All study pharmacies in communities heavily burdened by fatal overdose were selected for implementation of initial and complete demonstration study materials. ANOVAs and interrupted time series analyses of administrative pharmacy naloxone dispensing examined effects of the demonstration; linear mixed modeling was used to identify factors associated with naloxone dispensing and explore impacts on distal outcomes.

Results

PBN access flourished during the study period. Focus groups helped finalize PBN materials and design approaches to reducing stigma in the pharmacy. Using academic detailing, pharmacies increased naloxone dispensing, and multiple detailing visits expanded access for places less ready to implement PBN. Store- and community-level factors independently associated with dispensing underscore how PBN complements community naloxone programs and extends naloxone availability to ex-urban areas. The demonstration project's effects were bolstered by strong pharmacy leadership and corporate culture change as well as shifts in the environment: new naloxone product availability, the Surgeon General's public advisory, and the prominence of illicitly manufactured fentanyl. To facilitate dissemination, the website prevent-protect.org houses all study materials.

Key Words

Opioids; medication safety; naloxone; pharmacy; syringes

Scope

Background

Use and nonmedical use of opioid medications in the United States (US) are at unprecedented levels, and preventable adverse events—especially unintentional poisoning ("overdose")—involving opioids are among the most common.[1] Nationally, drug poisoning is the leading cause of adult accidental death,[2] associated with 43 potential life years lost and annual estimated costs of $20.4 billion.[3] Nationally and in New England, trends in overdose mortality indicate that rates now exceed mortality rate due to motor vehicle crashes. Opioids are the most common drugs involved in overdose death,[2] with the majority being prescription opioid (i.e., opioid analgesic) medications. In Rhode Island (RI), from 2009 to 2012, there was a 32.8% increase in overdose deaths; within 2 years, this rate doubled (65% increase), rendering an overall 119% increase in overdose deaths from 2009 to 2014. Nonfatal opioid overdose is also a significant public health problem contributing to excessive and long-term morbidity[4] and to an increasing number of hospitalizations in the state[5] and nation.[6] Data indicate that access to healthcare - and to pharmacists in particular - is associated with greater community-level availability of prescription opioids, which, in turn, is associated with higher rates of both nonmedical prescription opioid use[7] and overdose mortality. In response, public health and medical institutions have deployed several approaches, including altering the supply of opioid medications in a community by instituting and encouraging use of prescription drug monitoring programs (PDMPs), enforcing "pill mill" laws that regulate healthcare facilities that prescribe and dispense controlled substances outside of standard medical practices, and distributing naloxone, an opioid antagonist that reverses the effects of the opioid-induced respiratory depression that causes death, to high-risk individuals.

The goal of this proposal is to apply a systems-level approach to reducing harm of opioid-related adverse events by acknowledging the inherent need to manage opioid medication use more safely and prepare patients for the possibility of opioid-induced adverse events.

Pharmacies, an underutilized component of the healthcare system, are staffed by highly trained professionals who are skilled at medication error management, safe dispensing, and patient counseling. Interventions, including HIV testing and counseling, vaccinations, and tobacco cessation counseling, have been implemented effectively in community pharmacies and are cost-effective complements and alternatives to traditional, office- and clinic-based healthcare. Prior research suggests that pharmacists view overdose prevention interventions favorably, especially those that provide an opportunity to promote safe opioid use, that reduce the risk of illicit drug use for patients, that respect the time constraints and limited space and privacy in most pharmacies, and that capitalize on pharmacist's professional and patient-oriented skills.[8]

Two states, RI and Massachusetts (MA), provide a unique opportunity to develop a pharmacy-based demonstration and research project for secure and safe opioid medication use (Secure Opioid Safety Project, the SOS Project). In RI, a first-in-the-nation statewide program provides access to naloxone and overdose prevention counseling directly from pharmacists, through a collaborative practice agreement (CPAN). CPAN has been implemented statewide, including at all Walgreens and CVS pharmacies. Neighboring MA, with similar trends in opioid prescribing and overdose mortality, has a pharmacy "standing order" model for naloxone, which authorizes pharmacists to dispense naloxone rescue kits to a person either at risk of experiencing an opioid-related overdose themselves or in a position to assist a person at risk of experiencing an opioid-related overdose. The two states differ in their legal and regulatory approach to pharmacy-based naloxone (PBN), health insurance climate, and endemic community-based naloxone access, permitting contrast and an efficient means of detecting facilitators and barriers of PBN in a demonstration project.

Purpose

Our specific aims were:

AIM 1: Implement PBN in all RI (n=63) and MA (n=355) CVS pharmacies, providing initial and ongoing training to pharmacists and dispensing naloxone to patients when indicated.

AIM 2: Determine organizational factors associated with successful implementation of PBN by examining (a) structural characteristics of pharmacies (e.g., size, types/hours, location, opioid medications dispensed) and communities (e.g., age, gender, income distribution) associated with greater program uptake, (b) the impact on uptake of techniques aimed at raising awareness about opioid medication safety and PBN (e.g., store signage, public health department messaging), and (c) fidelity to the PBN guidance.

AIM 3: Evaluate the impact of implementing PBN by measuring change in proximal - a) naloxone dispensed; b) pharmacist PDMP use - and distal - c) use of naloxone in an overdose by laypersons prior to EMS arrival; d) increased substance use disorder treatment uptake; and e) reach: proportion of patients at risk who receive PBN] over time - outcomes, comparing within and between the two states.

AIM 4: Assess project sustainability and disseminate results, in collaboration with AHRQ, to policymakers and those responsible for quality improvement and patient safety in pharmacy and community settings.

Methods

Aim 1: Implementing PBN

To begin implementing PBN during year 1, the research team developed and implemented public education and awareness-raising campaigns targeted to general public about PBN (focus groups); conducted online surveys of CVS pharmacists in MA and RI who have been trained in the Collaborative Practice Agreement (CPA) and pharmacy standing order; conducted patient interviews who participants who had retrieved PBN and non-PBN; performed fidelity checks; and provided technical assistance and outreach to pharmacists and pharmacies.

Dr. Walley coordinated an advisory group composed of experts in overdose epidemiology and intervention, pharmacy, and patients. In his role as medical director of the MA naloxone program, Dr. Walley held quarterly meetings with community organizations and task forces implementing naloxone trainings in their locales to support validity and safety of the program implementation. Advisory Group members for this project included individuals in both states from behavioral health agencies, health department pharmacy board and injury prevention programs, CVS, and patient/opioid consumers. In addition to providing guidance to our project, advisory group members served as key informants regarding prevention, policy, and pharmacy-specific activities in their respective states relevant to project implementation. The advisory group met multiple times per year, for each year of the grant, and provided feedback on study activities.

Ongoing public health educational efforts communicated to patients throughout RI and MA know about the PBN opportunity. These included promotion of PBN at drug treatment and other social service providers throughout both states, publicity at the annual Recovery Awareness Day, discussion of PBN in state-affiliated continuing medical/pharmacy education content on safe opioid prescribing, and inclusion on the list of possible actions for providers who are sent unsolicited reports from the state PDMPs. In year 1, we explicitly pursued the promotion of PBN on the state PDMP website, the RI and MA state departments of public health websites, and state pharmacist association meetings and websites.

Several of our pharmacy partner sites, including all Lifespan hospital outpatient pharmacies, had not adopted a pharmacy naloxone standing order. The RI team's efforts over the first year were to support the adoption of the standing order at the hospital pharmacies and several other independent pharmacies in the community. By the end of year 1, all Lifespan pharmacies and an additional four independent pharmacies in RI were able to provide PBN and became study pharmacies for subsequent study years. An additional two outpatient pharmacies that are part of the BMC pharmacy campus adopted standing orders in year 2 and were then also made part of the study sites.

To raise awareness and generate evidence-based communications appropriate for the pharmacy setting, the RIH Injury Prevention Center held overdose awareness and naloxone availability poster contests. Based on focus group year 1 findings, we derived contest guidance and a judging matrix. The RIH team led the poster contest organizing, judging, and dissemination activities. The winning posters were included in the subsequent year's focus group, to review for inclusion in public awareness and patient education materials at CVS, PBN materials, and health department campaigns.

We also undertook efforts to crowdsource experiences getting naloxone in the pharmacy. We worked with several university projects and student activist groups (Harvard School of Public Health, Boston University School of Medicine) to support their involvement as secret shoppers; however, limited data were obtained from these activities. Unlike the poster contests, which spread far beyond the study state areas, the crowdsourced efforts were time limited, not fruitful, and thus not continued past the first study year.

Four processes provided critical insight into implementation for this demonstration project: 1) anonymous online surveys of pharmacists; 2) focus groups and interviews with PBN receivers and nonreceivers; 3) secret shopping; and 4) iterative quasi-experimental (i.e., "off-on-off") studies testing materials that optimize PBN uptake. Eligibility criteria for participants in the first two groups included a) age 18 or older; b) English speaking; c) willing and able to consent (if applicable); and d) membership in the specified participant group. Exclusion criteria were not fulfilling all inclusion criteria. The second two processes involved research staff who followed specific protocols to ensure consistency of the data collection. Each process is described below:

We conducted annual, anonymous online surveys of pharmacists in RI and MA to measure retention of knowledge from trainings, assess implementation challenges, and learn about barriers and facilitators of PBN during years 1 and 2. Two manuscripts based on survey findings are currently under peer review, and a third is in preparation.

In the first year, eight focus groups were conducted with four groups of individuals in each state: pharmacists and pharmacy staff, consumers of illicit opioids and patients in early recovery, caregivers of patients who use opioids, and consumers of prescription opioids. Semi-structured interview guides used open-ended questions and probes to explore the following topics: (1) attitudes toward general opioid safety; (2) awareness of overdose prevention with the use of naloxone; (3) general pharmacy experiences and interactions with pharmacists; and (4) perceptions regarding pharmacy naloxone and feedback on specific logistics (based on hypothetical scenarios).

In the second year, an additional eight focus groups were conducted with the same four groups (pharmacists and pharmacy staff, consumers of illicit opioids and patients in early recovery, caregivers of patients who use opioids, and consumers of prescription opioids) as the previous year. A semi-structured interview guide was used, and the purpose of these focus groups was to a) obtain feedback on materials for awareness campaigns, specifically focused on themes of medication safety; b) obtain feedback on patient education materials accompanying the PBN (including treatment referral resources); and c) generate ideas for social marketing and awareness campaign placement, both in store and in public. The appendix contains the materials that were created, including:

- A dispensing guide for pharmacists
- Various public awareness posters, contests for which were held in each year of the grant
- A tear-off pad that was placed at the pickup counter of the pharmacy
- Stickers for packs of syringes sold at pharmacies

To recruit for these focus groups in years 1 and 2, CVS and other study partner pharmacists with a range of exposure to PBN were recruited through the URI College of Pharmacy PBN CEU participant list and our partner employee intranets. Patients and caregivers were recruited by self-referral and through posters distributed online and on social media and posted in a random sample of 10 stores throughout the state. Focus groups for patients and caregivers were hosted in community locations (i.e., public library, hospital conference room). Pharmacist focus groups occurred and were held at a conference that all were attending. Patients and caregivers were paid $50 for their involvement, and transportation assistance was provided. CVS and other pharmacy partners supported involvement of their staff in evaluation efforts. Focus groups were led by Dr. Donovan, Dr. Baird, or Dr. Burstein, and they were accompanied by Dr. Green or Dr. Bratberg. The focus group sessions were audio recorded, transcribed, and then analyzed for prominent themes and summary findings. Two manuscripts based on the first-year focus groups have been published; a manuscript based on the second-year focus groups is currently under review.

A major premise of the demonstration study was to provide technical assistance to pharmacies in implementing PBN. Early on, we developed and adapted (from our Prescribetoprevent.org content) educational materials and academic detailing scripts to support PBN. The first year's academic detailing of pharmacies included that initial content. Based on our own critical evaluation and the vastly changing environmental risks posed by illicitly manufactured fentanyl, we sought improvements in our approach. We conducted additional focus groups, sought input from our advisors, and created, then iteratively tested, components of the academic detailing script that were incomplete (e.g., language for how to offer naloxone to a patient). These improvements were made to the subsequent year's academic detailing and implemented once again, providing a repeat detailing visit to 180 pharmacies. The impact of one, two, and any academic detailing visits was then analyzed, and two manuscripts cataloguing effects are currently in preparation.

In addition to the focus groups, patient interviews were conducted with PBN purchasers. In the first year, we recruited, from community postings, targeted recruitment, and snowball sampling, 42 people who reported having obtained naloxone at the pharmacy. We interviewed participants using a semi-structured interview guide, we audio recorded and transcribed the interviews, and we then analyzed them for key themes associated with naloxone purchasing. Though this design yielded many important insights, we refined the second-year interview design to hear from patients who had more recently obtained naloxone at the pharmacy.

In this case, we recruited 42 people (two states, up to seven from each of patients with chronic pain, caregivers of people who use opioids, and people who use illicit opioids or who are in early recovery from OUD) willing to obtain naloxone at the pharmacy. We then met the participant at the pharmacy, waited for them to obtain the naloxone, and then interviewed them thereafter. This design addressed concerns about recall bias and allowed for more detailed data collection. Similar processes of analysis were applied to the audio recorded and transcribed data resulting from this qualitative interview design.

To ensure that the PBN program was being implemented as planned, and thus informing the interpretation of outcomes, we employed "secret shoppers" to assess interaction with PBN-trained pharmacy staff in our study pharmacies. Each year, several members of the research teams from both MA and RI were trained in the validation protocol. This protocol require that the team members dress as usual and approach pharmacy staff to request a consultation away from other customers. In the first year, the secret shoppers approached the pharmacy counter and inquired about naloxone but did not purchase it. Immediately after the encounter, the research team member scored the staff pharmacy staff on several factors, including the interaction itself, the pharmacy environment, overall feedback on the encounter, and a nonverbal bias scale (created for the purposes of the study). In the second year, this protocol was revised to first ask for and purchase nonprescription syringes at the pharmacy and then to ask for naloxone, as had been done in the first year. The purpose of doing so was to gauge the pharmacy's level of comfort and confidence in interacting with patients who may be using drugs. Reports of the interactions were input into a survey database via a tablet immediately following the visit.

Quasi-experimental studies conducted during this phase built from the focus group, interview, and academic detailing results. Specifically, we conducted a series of "off-on-off" studies for 1 month at a time, testing the materials and procedures we developed, including handouts/flyers given to every patient at prescription fill; public service announcement/media messaging (i.e., poster winners posted in communities as public communications during a limited time) in select communities; recovery month public service announcements; and stickers on 10-packs of syringes, display pads at the pharmacy counter, or both. In this design, we examined naloxone dispensing in the 3 months before the intervention and during the intervention; then, we removed the intervention and followed the intervention sites for an additional 3 months. The change pre-post intervention allowed for an analysis of effect and maintenance of effect.

Aim 2: Determine organizational factors associated with successful implementation of PBN
We undertook multivariable regression analyses, conducted at the CVS store level, and used data from project years 1 and 2 so that maximum exposure to PBN was measured.

We conducted a longitudinal analysis of pharmacy-level quarterly naloxone dispensed from one large US community pharmacy chain from the 1st quarter of 2013 to the 2nd quarter of 2017, examining associations between naloxone provision and pharmacy-level characteristics and community factors in two US states, Rhode Island and Massachusetts. Rurality was defined using the rural urban commuting area (RUCA) scale scores, calculated based on US 2010 Census variables. Pharmacy-level characteristics (e.g., 24-hour store, average daily volumes of total prescriptions, drive-through status) were derived from the pharmacy chain; community factors (e.g., RUCA score, ZIP-code level, age, race distribution, and median household income) were obtained from the decennial census files. The linear mixed-effects methods modeled dispensing history and the number of naloxone doses dispensed through binomial and negative binomial distributions, respectively, accounting for trend and covariates.
In addition, for comparison purposes, aggregate counts of naloxone prescriptions dispensed from CVS pharmacies in New Hampshire and Maine were tracked during the study period.

Aim 3: Impact of PBN: proximal and distal outcomes
Accomplishment of Aim 3 entailed conducting growth mixture models of CVS pharmacy store-level dispensing data (from 2011 [pre-implementation] to 2018 [3 years post-implementation]). Impact assessment for the distal outcomes of naloxone use by laypersons prior to EMS arrival was not conducted due to data quality concerns.

Treatment and harm reduction uptake, defined as buprenorphine prescriptions dispensed and nonprescription syringe sales, were assessed for correlation with naloxone dispensing.

Aim 4: Assess project sustainability and disseminate results
Through interviews with CVS and other study pharmacy leadership and review of pharmacy data, we assessed how well the process of adopting the PBN program has been accomplished. In-depth interviews were conducted with 12 pharmacy leaders in Massachusetts and Rhode Island study pharmacies. Participants were recruited from three types of community pharmacies: (1) chain; (2) independent; and (3) hospital outpatient. A model of healthcare quality was used to inform deductive coding of the interview data, with predetermined categories of staff, organization, and process.

To facilitate dissemination of lessons learned from the dissemination project, all study materials were made readily available on prevent-protect.org. Our study pharmacy partners also created their own websites and dissemination tools, including edits to the internal and public-facing CVS websites. In addition, we continue to present the project findings at national conferences and to publish findings in peer-reviewed publications.

Results

Principal Findings

Aim 1:

Focus group year 1: Sixty-one participants included patients with chronic pain (n=15), people with opioid use disorders (n=19), caregivers (n=16), and pharmacists (n=11). Most pharmacists had dispensed naloxone to patients; a minority of all consumer participants had obtained pharmacy naloxone. Four themes emerged: consumer fear of future consequences if requesting naloxone; pharmacists' concerns about practice logistics related to naloxone; differing perceptions of how opioid safety is addressed in the pharmacy; and solutions to addressing these barriers. Though consumer groups differed in awareness of naloxone and availability at pharmacies, all groups concluded support for the pharmacist's role and preferences for a universal offer of naloxone based on clear criteria.

Focus group year 2: Fifty-six participants included patients with chronic pain (n=13), people with opioid use disorders (n=15), caregivers (n=13), and pharmacists (n=16). Though a prominent theme persisted from the prior year, fear of future consequences and stigma in the pharmacy, four new themes emerged: experience providing pharmacy naloxone, team-based approach, naloxone co-prescription, and fentanyl as motivator for pharmacy naloxone. Prototypes for prompting consumers about naloxone availability, materials facilitating naloxone conversations, and posters designed to address stigma were well received by all groups.

Our first poster contest was very successful, and we had 96 entries from across the US in the first year. The final judging of the posters was completed in April 2016, and the four winners and four honorable mentions were contacted. The winning posters were distributed to community partners, and our study pharmacies selected their preferred poster for printing and inclusion in their pharmacy setting. We then printed and installed all posters at the study sites. Our second poster contest was launched in January 2017. We had a total of 114 English language entries and 13 Spanish language entries. Final judging was completed in May 2017, and four winners and four honorable mentions were selected. We held a third and final contest in 2018, when we received a total of 145 English entries and 11 entries in Spanish. That year, five winners and three honorable mention posters were selected. The posters were used by the Rhode Island Department of Health and our partners in pharmacies and other public places to increase naloxone awareness. All the poster winners are at www.prevent-protect.org.

Interviews year 1: Of the 52 people interviewed, 24 participants had obtained naloxone from the pharmacy in the past year, of which 4% (n=1) self-disclosed during the interview current illicit drug use and 29% (n=7) mentioned using prescribed opioid pain medication. Of the 28 people who had not obtained naloxone from the pharmacy, 46% (n=13) had obtained an over-the-counter syringe from a pharmacy in the past month and had used an opioid in the past month, and 54% (n=15) had used a prescribed opioid pain medication in the past month but did not report a syringe purchase. Several main themes emerged from the interview data. Individual-level themes were as follows: helplessness and fear, naloxone as empowerment to help, and past experiences at the pharmacy. Interpersonal-level themes were as follows: concern for family and friends, and sources of harm reduction information.

Themes associated with pharmacy-level influence were as follows: perceived stigma from pharmacists, confusion at the pharmacy counter, and receptivity to pharmacists' offer of naloxone. Community-level themes were as follows: community caretaking, and need for education and training. Finally, themes at the societal level of influence were as follows: generational crisis, and frustration at lack of response to opioid crisis.

Interviews year 2: Of the 45 participants (MA n=24, RI n=21), 41 successfully received naloxone during their first attempt (91%). Three of the four participants (75%) who were initially denied naloxone returned to the pharmacy and successfully attained naloxone the second time (the fourth did not return due to cost concerns). Those that initially had difficulty attaining naloxone shared two primary reasons the pharmacy staff would not provide the naloxone: (1) the insurance would not cover the naloxone, and/or (2) pharmacy staff claimed participants needed a prescription. Specific usability factors explored in this analysis indicated that there was poor visibility of naloxone in the pharmacy (noted by four of 45); there was poor workflow around PBN, causing confusion on both sides of the pharmacy counter; there were missed opportunities to use the private consultation spaces in the pharmacy environment; and patients, especially pain patients, sought more information and counseling than was offered and received. Overall experience at the pharmacy was rated high, at 7 on a 10-point scale, with a 7 for all MA patients (n=22) and an 8 for all RI patients (n=22). Participants of Black race rated the experience lower than participants of other races.

Surveys in year 1 revealed important findings about the state policies and pharmacist attitudes. Of the ~2900 pharmacists who received the survey, 402 responded (13%), and 245 (137 from MA and 108 from RI) were included in the analyses. The majority (79%) identified as White/Caucasian, and 127 (51.8%) stated they had ever dispensed naloxone. Of those, 85 (67%) had done so in the past 30 days. Attitudes toward opioid overdose prevention (12 questions) were used to develop the Opioid Overdose Prevention Attitude (OOPA) scale, which consisted of three subsets: Opioid Overdose Prevention Attitude, Public Health Attitude, and Naloxone Dispensing Attitude. We examined differences in the OOPA subscales by pharmacist characteristics and pharmacy practice settings. Working in a pharmacy that had a standing order or collaborative practice agreement allowing pharmacists to dispense naloxone without a physician prescription, and working in a pharmacy that stocked naloxone resulted in more positive attitudes toward opioid overdose prevention and public health prevention.

The subsequent year's survey uncovered several additional findings influential to our understanding of the pharmacy itself as a place of opioid safety and overdose response. In the survey year 2, of approximately 3100 invitations, there were 357 pharmacist survey respondents (11.5% response rate). An analysis exploring experiences of pharmacists who had varied histories of providing naloxone analyzed data from the survey sample (n=179 licensed pharmacists from Massachusetts and Rhode Island). More than half (n=119, 66.5%) had ever dispensed naloxone. Naloxone dispensing was associated with practicing in a chain store setting ($p=0.02$), at a pharmacy that stocks naloxone ($p<0.0001$), and have standing order to dispense naloxone without a physician prescription ($p<0.0001$). Dispensing naloxone was also associated with feeling prepared to offer education to the patient on using naloxone for an opioid overdose ($p=0.0001$) and offer information on community opioid use resources ($p=0.04$). Frequent dispensers of naloxone indicated that naloxone dispensing and counseling took the same or less time than other medications that require counseling. The qualitative data from those who had dispensed naloxone report this as a positive experience for most pharmacists. Interestingly, 17.5% reported having at least one suspected overdose onsite at their practice location, and 42.9% reported that they were knowledgeable about and could locate at their practice location an onsite overdose protocol detailing how to respond to an overdose. Pharmacists who were knowledgeable about protocols were also more likely to offer naloxone to patients ($p=0.02$) and did not practice at a chain pharmacy ($p=0.01$).

Quasi-experimental trials: Of the trials conducted, the only one that resulted in significant findings involved both stickers on the 10-packs of syringes and display pads at the counter about naloxone. In a sample of 40 study pharmacies, over a 1-month period, pharmacies that included one or both initiatives exhibited an increase in naloxone dispensing compared with the previous months and, when the intervention was removed, the effect was sustained over time. Unlike other trials, in which removal of the intervention resulted in removal of effect (e.g., the "recovery month naloxone distribution campaign"), this two-pronged intervention provided insight into a more effective pathway for supporting PBN. These materials subsequently became the core of the academic detailing for year 2.

Fidelity checks in year 1 indicated that naloxone availability in the study states was high, and problems with obtaining naloxone were linked more to stocking at the pharmacy.

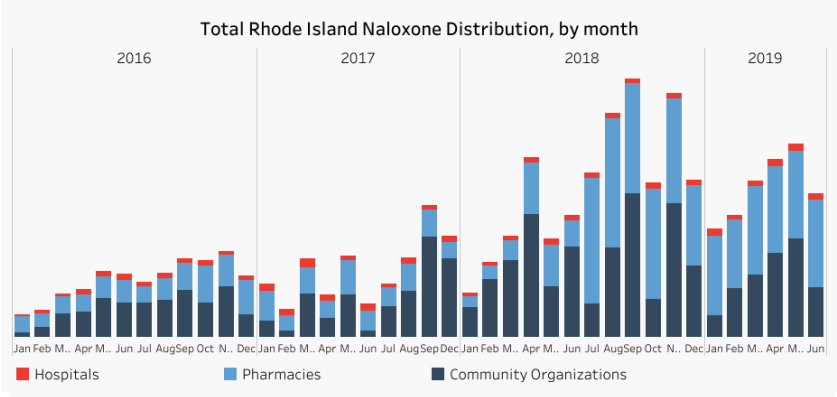
Observed nonverbal bias in the PBN interaction was rare. When it occurred, the nonverbal bias was associated with the pharmacy technician, not with the pharmacist. In the subsequent year's fidelity checks, however, our design shifted to allow us to first purchase syringes and then ask for naloxone. In this case, though PBN availability remained high, the observed nonverbal bias was more slightly common and was detected among pharmacists and pharmacy technicians.

Aim 2:

Adjusted analyses of dispensing data from 449 RI and MA pharmacies indicated that more rural pharmacies (i.e., stores in areas with higher rural urban commuting area (RUCA) scores), pharmacies with higher volumes of prescriptions, those that have drive-throughs and longer weekend hours, and those that are located in communities with younger age distributions were associated with increased likelihood of ever dispensing naloxone and a greater number of naloxone doses dispensed (all $p<0.05$). Results are reported in a manuscript currently under review.

Aim 3:

Adjusted analyses of dispensing data from 449 pharmacies in the two study states indicated that pharmacies with increased likelihood of ever dispensing naloxone and a greater number of naloxone doses dispensed (both $p<0.05$) had higher volumes of buprenorphine and sell more nonprescription syringes.



Data on total pharmacy distribution in the state of RI illustrated here shows the contribution made to naloxone access in the state. At study's end, we found that our study pharmacies (chain, outpatient, hospital, and independent) distributed the most naloxone of all pharmacies dispensing naloxone in the state. The figure to the left indicates the trends over time in naloxone administration prior to arriving to the hospital for a suspected overdose when 911 was called, as reported to the RI 48-hour mandatory overdose registry maintained by the department of health. Increased layperson-administered naloxone in a suspected overdose correlated with the increase in community organization and pharmacy distribution of naloxone. In our models, across both states, communities with greater distribution of pharmacy naloxone exhibited higher counts of nonfatal overdose (0.025, p=<.001), controlling for community kit distribution (0.0004, p=0.24). Similarly, for MA and RI, communities with higher dispensed doses were associated with higher fatal overdose counts (beta=0.032 p<.001) after controlling for state and year as linear trend.

Aim 4:

Pharmacy leadership interviews identified five main themes: (1) importance of staff training to increase comfort; (2) strength through coordination of efforts; (3) pharmacy as a community leader in the opioid crisis; (4) persisting stigma; and (5) ongoing workflow challenges. Pharmacy leaders described taking an active role in efforts to institutionalize the implementation and dissemination of PBN, such as requiring staff training and coordinating efforts to efficiently provide naloxone to their communities. Pharmacy leaders also described challenges that continue to undermine PBN and disrupt workflow including ongoing stigma; insurance coverage; and the need to continue to find ways to proactively offer naloxone to patients and caregivers.

The key dissemination process for the materials created and tested in our study for improving implementation and dissemination of the pharmacy naloxone model is through the website established by the study: www.prevent-protect.org.

We found that certain groups of people obtaining naloxone at the pharmacy sought detailed information about naloxone. Some information was fundamental (i.e., what it is, how does it work, how to use it), and many sought additional information about treatment or other harm reduction services after obtaining naloxone.

Thus, the website contains these simple resources, in nonjudgmental and plain language.

The other website consumer represents health departments or community organizations who are supporting or navigating pharmacy naloxone access. The website includes pathways for these institutions, who, as we learned from our research, seek effective public awareness campaigns about naloxone's availability at the pharmacy, onsite overdose policies, processes for notifying patients at the pharmacy counter about naloxone, tools for improving pharmacy interactions and standardizing naloxone access, and tools for checking the quality of interactions at the community pharmacy through fidelity checks ("secret shopping"). Based on our experiences training community members in academic detailing and fidelity checking, we created these resources for implementation and dissemination. In February 2018, the AHRQ Director's blog featured our website, and in April 2018, the Surgeon General's advisory cited the website. Traffic to the website has remained strong, alongside our companion website www.prescribetoprevent.org, which focuses on prescribers and pharmacists.

Outcomes

By study end, all 10,000 CVS pharmacies display pharmacy naloxone posters and play audio recorded messages encouraging naloxone uptake. All CVS pharmacies have onsite overdose policies and stock naloxone. During the study, the multi-site independent pharmacy chain Eaton Apothecary was purchased by CVS Pharmacies, as was AllCare Pharmacy, a large independent pharmacy in Worcester, MA. There were in total nine independent pharmacies in our sample that were purchased by CVS over the study period, and they all adopted CVS pharmacy policies, including the signage, stocking, and onsite overdose policy orientation. All BMC and Lifespan hospital outpatient pharmacies have standing orders in place and readily provide both standing order and prescribed naloxone. All study pharmacies have tried out and/or have incorporated an algorithm for identifying and offering naloxone to patients at high risk of overdose. Naloxone dispensing in the pharmacy represents between one third and one half of all community-distributed naloxone in Massachusetts and Rhode Island. Although trends in both states appear to indicate a slowing of the opioid epidemic curve, the fatal overdose mortality rates remain high in the study states. It is unclear just how much naloxone is needed to be provided in the community for overdose mortality to slow, let alone decline. However, a range of individuals obtain naloxone at the pharmacy, and a growing need for naloxone has led to the medication being sold at pharmacies across a range of geographies and demographics. Following the Surgeon General's warning about overdoses and encouraging people to obtain naloxone, as well as the Department of Health and Human Service's guidance to co-prescribe naloxone and individual state laws mandating co-prescription of naloxone, the prescribetoprevent.org and prevent-protect.org websites have greatly expanded in viewing and navigating. On a monthly basis, we receive requests to use, adapt, or cite the materials included on the website. Requests include local municipalities as well as universities, such as the City of Philadelphia, City of Chicago, State of California, County of Alta Dena in California, and University of Arkansas.

Discussion

We found considerable growth in PBN over the demonstration study period in both states. Pharmacies were amenable to change and responded to several interventions, both at the pharmacy and pharmacist levels. We ultimately saw that a combination of targeted pharmacy education with the pharmacists (i.e., academic detailing visits) and focused efforts in the pharmacy, coupled with supportive state and store-level policies, are key factors in the uptake and dissemination of pharmacy naloxone in our study states. Finally, strong leadership from the pharmacy chain, hospital administration, or independent owner facilitated implementation. In many regards, our findings are not unlike those of other pharmacy interventions, like adult immunizations. However, the distinguishing characteristics cutting across both study states and over time was the specter of stigma and discrimination. Perceptions of discomfort and experiences of ill treatment distinguish this health intervention and patient experience. In this way, the pharmacy naloxone experience is more consistent with pharmacy-based studies of nonprescription syringe access and buprenorphine provision, more generally.

It is telling that our analysis indicated greater naloxone provision in pharmacies with higher rates of buprenorphine provision and nonprescription syringe sales. For this reason, future studies (of which our team is now leading) should couple the three topics and aim to reduce stigma in the pharmacy.

Over the course of the study, major shifts in the opioid epidemic occurred, including a massive rise in illicit opioids containing fentanyl and fentanyl analogs but also the entrance of additional naloxone products, namely the single-step branded nasal spray, Narcan. Our study captured these shifts in detail, but they pale in comparison to the rise in nonfatal and fatal overdoses. More naloxone, in more places, and in more people's hands, is a critical step in overdose prevention. A perennial question about naloxone is its effectiveness in layperson rescues and which distribution pathway is the most efficient in equipping those at risk of experiencing or witnessing an overdose. Unfortunately, it is not possible to disentangle whether the layperson naloxone used to reverse an overdose derived from the pharmacy, the hospitals (i.e., the emergency department), a community organization, or somewhere else (e.g., neighboring state). Future research may derive ways to track such pathways, but our study indicates that, even with two neighboring states, there is enormous variability in naloxone availability and redistribution. For instance, a patient treated in a detoxification unit and provided naloxone dispensed to them through a coordinated effort at a nearby pharmacy may not know that their naloxone came from a pharmacy source.
The discharged patient who has his naloxone used on him by his sober house roommate may also not know the source of the naloxone. Naloxone obtained through these routes that are given away to others in need further lose their identity. Once multiple pathways to naloxone have been established in a community, the most salient point is that naloxone is on hand when needed, not where it was obtained.

Conclusions
Pharmacies complement community naloxone provision to patients and caregivers. To overcome stigma of naloxone receipt, increased public awareness of naloxone and pharmacist training about naloxone and addiction are required. Pharmacists should offer naloxone via universal opt-out strategies, in which all patients meeting evidence-based criteria are offered naloxone, rather than targeted or opt-in strategies, in which only patients perceived as high-risk or patients who request it are offered naloxone.

Factors at multiple levels play a role in likelihood of obtaining naloxone at the pharmacy. These factors can be used to inform interventions seeking to increase provision of pharmacy-based naloxone. Experiences dispensing naloxone are quickly evolving, and a greater diversity of patients are obtaining pharmacy naloxone. Persistent stigma-related concerns about getting naloxone underscore the need for tools to help pharmacists offer naloxone, facilitate patient requests, and provide reassurance to patients getting naloxone.

Pharmacies are a key evolving element in the overdose risk environment, striving to develop reputations as sources of wellness, prevention, and harm reduction supplies, like naloxone. Pharmacy naloxone access may be an especially effective strategy to alter the overdose risk environment in rural communities. Pharmacy leaders can implement effective strategies like PBN as public health initiatives during the opioid crisis. Establishing standing orders, stocking naloxone, orienting pharmacy staff to its availability, and developing onsite overdose response protocols all cultivate a norm of naloxone provision to patients as patient safety and workplace security.

Significance
Because pharmacies are extant healthcare institutions in nearly every US community, there is enormous potential to directly apply our findings and scale up naloxone provision. Because naloxone access is an evidence-based approach to reducing overdose mortality, as many urban and ex-urban access points as possible for as many people at risk of overdose as possible should be leveraged as a prevention strategy. Our project suggests that pharmacies reach people who inject drugs and communities with emerging drug problems, not just people prescribed medications and filled through traditional prescribing pathways. The key to the pharmacy, as our project indicates, is that it is malleable for prevention and treatment and is responsive to changes through community-based public health need (i.e., demand). By systematically focusing on two states to refine, adjust, and understand the barriers, facilitators, and optimal mechanisms to improve naloxone uptake in the community, our findings have created a generalizable and disseminable set of tools (www.prevent-protect.org) that is available for other states and communities that adopt pharmacy naloxone.

Implications

With focused training and deliberate attention to stigma reduction, in policy and practice, pharmacies can be optimized for broader naloxone distribution. Doing so can complement community naloxone provision and has the potential to vastly improve the amount of naloxone available in a community for overdose response.

List of Publications

1. TC Green, P Case, H Fiske, J Baird, S Cabral, D Burstein, V Schwartz, N Potter, AY Walley, J Bratberg. Perpetuating stigma or reducing risk? Perspectives from naloxone consumers and pharmacists on pharmacy-based naloxone in two states. Journal of the American Pharmacists Association. 2017 Mar - Apr;57(2S):S19-S27.e4. PMID: 28214219 DOI: 10.1016/j.japh.2017.01.013.
2. TC Green, N Potter, J Bratberg. Detecting naloxone prejudices in the pharmacy setting. Journal of the American Pharmacists Association. 2017 Mar - Apr;57(2S):S10-S1. PMID: 28159504 DOI: 10.1016/j.japh.2016.12.068.
3. E Donovan, J Baird, P Case, S Cabral, D Burstein, AY Walley, J Bratberg, TC Green. Beliefs associated with pharmacy-based naloxone: A qualitative study of pharmacy-based naloxone purchasers and people at risk for opioid overdose. Journal of Urban Health. 2019 Feb 11. PMID: 30747371 PMCID: PMC6565759 [Available on 2020-06-01] DOI: 10.1007/s11524-019-00349-1.
4. S Kurian, B Balloy, J Baird, D Burstein, Z Xuan, J Batberg, A Tapper, AY Walley, TC Green. Attitudes and perceptions of naloxone dispensing among a sample of Massachusetts community pharmacy technicians. Journal of the American Pharmacists Associatio*n.* 2019 Sep 30. pii: S1544-3191(19)30406-6. PMID: 31582224 DOI: 10.1016/j.japh.2019.08.009.
5. TC Green, J Bratberg, J Baird, D Burstein, K Lenz, P Case, AY Walley, Z Xuan. Rurality and differences in pharmacy characteristics and community factors associated with provision of naloxone in the pharmacy. International Journal of Drug Policy 2019 (under review)
6. D Burstein, J Baird, A Soipe, A Tapper, J Bratberg, AY Walley, Z Xuan, TC Green. Pharmacist attitudes toward pharmacy-based naloxone, a cross-sectional survey study. Journal of the American Pharmacists Association (under review)
7. TC Green, A Soipe, B Baloy, D Burstein, Z Xuan, A Tapper, AY Walley, P Case, J Bratberg, J Baird. Pharmacy on-site overdose protocols and prevention of overdose. Substance Abuse (under review).
8. TC Green, Z Xuan, C Davis, J Bratberg, AY Walley. Mandating co-prescription of naloxone and access to life-saving medication in five US states, 2013-2018. American Journal of Public Health (under review).
9. E Donovan, J Bratberg, J Baird, D Burstein, P Case, AY Walley, TC Green. Pharmacy leaders' beliefs about how pharmacies can support implementation and dissemination of naloxone. Research in Social and Administrative Pharmacy (under review)
10. TC Green, E Donovan, B Klug, P Case, J Baird, D Burstein, A Tapper, AY Walley, J Bratberg. Revisiting pharmacy-based naloxone with naloxone consumers and pharmacists in two states: 2017 perspectives and refining approaches. Journal of the American Pharmacists Association (under review)

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