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Effectiveness of direct patient outreach with a narrative naloxone and overdose prevention video to patients prescribed long-term opioid therapy in the USA: the Naloxone Navigator randomised clinical trial

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ABSTRACT

Introduction Public health efforts to reduce opioid overdose fatalities include educating people at risk and expanding access to naloxone, a medication that reverses opioid-induced respiratory depression. People receiving long-term opioid therapy (LTOT) are at increased risk for overdose, yet naloxone uptake in this population remains low. The objective of this study was to determine if a targeted, digital health intervention changed patient risk behaviour, increased naloxone uptake and increased knowledge about opioid overdose prevention and naloxone.

Methods We conducted a pragmatic randomised clinical trial among patients prescribed LTOT in a healthcare delivery system in Colorado. Participants were randomly assigned to receive an animated overdose prevention and naloxone educational video (intervention arm) or usual care (control arm). The 6 min video was designed to educate patients about opioid overdose and naloxone, increase overdose risk perception and prompt them to purchase naloxone from the pharmacy. Over an 8-month follow-up, opioid risk behaviour was assessed with the Opioid-Related Behaviours in Treatment survey instrument, and overdose and naloxone knowledge was measured with the Prescription Opioid Overdose Knowledge Scale after viewing the video at baseline. Naloxone dispensations were evaluated using pharmacy data over a 12-month period. Data were analysed with generalised linear mixed effects and log-binomial regression models.

Results There were 519 participants in the intervention arm and 485 participants in the usual care arm. Opioid risk behaviour did not differ between the study arms over time (study arm by time interaction p=0.93). There was no difference in naloxone uptake between the arms (risk ratio 1.13, 95% CI 0.77 to 1.66). Knowledge was significantly greater in the intervention arm compared with usual care (p<0.001).

Conclusions A targeted, digital health intervention video effectively increased knowledge about opioid overdose and naloxone, without increasing opioid risk behaviour. Naloxone uptake did not differ between the intervention and usual care arms.

Trial registration number NCT03337009.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Uptake of take-home naloxone is low among patients prescribed long-term opioid therapy despite high rates of overdose.

⇒ While naloxone standing orders can help ensure access to naloxone, effective interventions to encourage patients to obtain naloxone and provide education on overdose risk and naloxone are needed.

WHAT THIS STUDY ADDS

⇒ In this randomised clinical trial, patients prescribed long-term opioid therapy who watched a web-based, animated 6 min video about overdose prevention and naloxone had increased knowledge about opioid overdose and naloxone and were not more likely to engage in risk behaviours than a similar group of patients who did not watch the video.

⇒ There was no difference in naloxone uptake across the groups.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Additional interventions to encourage naloxone uptake among patients prescribed long-term opioid therapy are needed. Overdose and naloxone knowledge content may need reinforcement over time.

INTRODUCTION

From 2017 to 2021, more than 78 000 people in the USA died from a drug overdose involving prescription opioids.[1 2] Approximately 5% of adults in the USA are prescribed long-term opioid therapy (LTOT),[3] and patients receiving opioid doses of greater than 20 mg per day are at increased risk for overdose compared with patients receiving lower doses.[4–6]

Efforts to reduce overdose fatalities include educating people at risk and expanding access to naloxone, a medication that reverses opioid-induced respiratory depression. Naloxone has been widely used by emergency medical personnel for decades; since the 1990s, community-based programmes have provided overdose prevention education, overdose management training and take-home naloxone to laypersons, including people who use drugs and potential bystanders.[7 8] Although such programmes are effective at preventing opioid overdose deaths,[9] rapidly increasing overdose fatality rates attributed to prescription and high-potency synthetic opioids have prompted practices, policies and laws to increase access to naloxone, such as standing orders, protocol orders, collaborative practice agreements,[10 11] coprescribing naloxone with opioids and over-the-counter status for certain naloxone products.[12–14] Despite these efforts, however, naloxone uptake remains low in the USA and other countries.[15–18]

Patients prescribed LTOT experience numerous barriers to naloxone access. Clinicians tend to recognise the benefits of prescribing naloxone for take-home use, but they may be reluctant to prescribe it because of competing clinical demands and fears that prescribing naloxone may stigmatise patients.[19] Clinicians have also expressed concerns about risk compensation (also referred to as 'moral hazard'),[19–21] a theory that suggests individuals may be more likely to engage in risky opioid use behaviours because they are aware of and have access to naloxone. Patients may not request naloxone directly from clinicians because of knowledge gaps about overdose and naloxone, beliefs that they are not at risk of overdose because they take their opioid medications as prescribed, or concerns that requesting naloxone will imply they are misusing prescribed opioids.[22] Standing order laws, which allow individuals at risk of overdose to obtain naloxone from a community[23] or pharmacy setting[24] without an individual prescription,[25] could overcome some of these barriers; however, naloxone dispensing remains suboptimal despite standing order laws, possibly because of stigma, low overdose risk perception, naloxone's cost and limited awareness that naloxone is available under a standing order.[26] Studies have also cited pharmacist confusion about how laws pertain to naloxone dispensing and lack of clarity on how to bill for naloxone as factors contributing to poor naloxone uptake.[27–30] Under a standing order, codispensing naloxone with opioid medications is an effective approach to increase access,[31 32] but implementing codispensing requires significant resources to educate staff, establish consistent workflows and stock the medication.[17 33] The Food and Drug Administration approved naloxone for over-the-counter status in March 2023 to facilitate access and potentially mitigate stigma; but cost, low-risk perception and limited knowledge about naloxone among people prescribed LTOT will likely remain barriers to uptake.[34 35]

To address barriers to expanding access to naloxone, we developed and tested an intervention by directly outreaching to patients prescribed LTOT and providing them with an animated overdose and naloxone educational video in narrative form called the Naloxone Navigator. The video was designed to educate patients about opioid overdose and naloxone, increase their overdose risk perception and prompt them to purchase naloxone under a system-wide naloxone standing order. We conducted a pragmatic randomised clinical trial (RCT) to determine whether this intervention changed patient risk behaviour, naloxone uptake and patient knowledge about opioid overdose prevention and naloxone.

METHODS

Study design

We conducted a pragmatic RCT to evaluate the effectiveness of the Naloxone Navigator intervention among patients receiving LTOT. Participants were randomised to receive either the intervention or usual care. Participants in both arms could access naloxone by prescription from their physicians or directly from pharmacies without an individual prescription under a standing order. Participants were administered surveys at time 0 (T0), 4 months and 8 months to assess overdose risk behaviour and knowledge; electronic pharmacy records were used to measure naloxone uptake over a 12-month period from T0. We hypothesised that the intervention would not increase opioid risk behaviour, but that it would increase overdose prevention and naloxone knowledge, and increase naloxone uptake.

We used the Consolidated Standards of Reporting Trials guideline.

Study setting, participants and randomisation

All participants were members of Kaiser Permanente Colorado (KPCO), an integrated insurance and healthcare delivery system that serves more than 550 000 members across Colorado, with 29 outpatient pharmacies located within KPCO ambulatory medical offices. The KPCO patient population is demographically representative of Colorado.[36] Under statewide standing order legislation,[37] the study team collaborated with KPCO pharmacy operations to implement a naloxone standing order in January 2017, allowing pharmacists to dispense naloxone for take-home use without patients having to obtain individual prescriptions from their physicians.

Patients were recruited in 2-month waves starting on 21 December 2017. At the beginning of each wave, electronic pharmacy records were used to identify patients receiving

LTOT, defined as three or more opioid dispensations in the previous 90 days with no more than a 5-day gap in opioid coverage. This included short-acting and long-acting opioid medications except for tramadol or medications used for opioid use disorder treatment. Patients also had to be 18 years or older, English-speaking and have internet access. Patients were ineligible if they were enrolled in hospice or had a do-not-resuscitate order, since the focus of this trial was the safety of chronic pain opioid management rather than end-of-life care. In each wave, a random sample of 500–1000 eligible patients were invited to participate first by mail, followed by email and telephone. Patients were directed to a study enrolment website where they could provide informed consent. After consent (T0), participants were randomised to the intervention or usual care arm at a 1:1 allocation ratio using the SAS/STAT (SAS Institute) procedure Proc Plan. The statistician and investigators were blinded to study arm assignment. Participants received a US$20 gift card for completing surveys at each time point, and all survey data were stored in a Research Electronic Data Capture database.[38 39]

Patient and public involvement

Patients and the public were not directly involved in the design of the study.

Usual care

Under usual care, patients could be prescribed naloxone by their physicians or request it from a pharmacist under a naloxone standing order, which made naloxone available without an individual prescription in all pharmacies in KPCO. Pharmacists were trained on standing order naloxone dispensing process, counselling points and cost quotes. Opioid prescribers were encouraged to prescribe naloxone to patients in continuing medical education sessions and made aware of the naloxone standing order in system-wide pharmacy communications. Member-facing system-wide communications informed members when naloxone was made available in system pharmacies under a standing order. The costs of naloxone ranged from US$0 to US$140, depending on the patient's insurance plan. Patients in the usual care arm were not required to view a sham video intervention.

Intervention

Intervention participants received usual care and a web-based, 6 min animated educational video. The video presented standardised messages on how to prevent, recognise and respond to an opioid overdose through a first-person narrative of a patient prescribed opioids. It aimed to heighten patients' overdose risk perceptions and increase their self-efficacy to acquire and use naloxone in an overdose emergency. Specifically, the video informed viewers about the overdose risk associated with opioid treatment for pain and encouraged them to purchase naloxone from the pharmacy under the standing order.

The intervention was iteratively developed using the integrate, design, assess and share (IDEAS) framework.[40] Guided by the theory of planned behaviour[41] and the health belief model,[42] qualitative data were collected from semistructured interviews with patients prescribed high-dose opioid therapy and from focus groups with primary care staff[19 22] to delineate key intervention targets. The intervention's content was designed to address patients' limited knowledge about naloxone, low overdose risk perception and reluctance to have difficult conversations about overdose with clinicians. The intervention was delivered as a video directly to patients—without requiring an appointment—to minimise clinician effort, reduce bias in patient identification and assuage clinician concerns that initiating conversations about overdose would stigmatise patients. The messages were conveyed as a fictional first-person narrative to elicit emotion and enhance recollection of the content, with foreshadowing and humour to help generate interest and sustain attention throughout the video.[43 44]

Study investigators wrote the draft content for the video, which was assessed for comprehension and acceptability in 11 cognitive interviews of patients and their caregivers, and further refined by the research team. Interviewees provided input on how the messages should be framed, whether they resonated and whether they were stigmatising. The research team then developed the animated video using Vyond Studio® software.[45] The narrator is a female patient prescribed LTOT for chronic pain. After foreshadowing the overdose emergency, she visits her primary care physician, who provides clinical information on the signs of an overdose, risk factors and how to acquire and use naloxone. The narrator shares this information with her partner. She subsequently attends a party, uses both alcohol and prescribed opioid analgesics and accidentally experiences an overdose. Her partner revives her using naloxone he has with him, and she is transported to the emergency department. The couple later picks up a refill at the pharmacy under the standing order and engages in other preventive behaviours, including having a lock box for safer home opioid storage. Professional actors provided voiceovers for the main characters, and final editing was conducted using Adobe® Audition® software in a recording studio.[46] The video was embedded within a password protected, single page website using WordPress® software and underwent usability testing with three patients.

Participants receiving LTOT who were randomised to the intervention arm received a link to the video and were required to play the video in its entirety at T0 to obtain renumeration for their research participation. One month after T0, participants in the intervention arm were emailed a weblink to view the video again with three additional weblinks that could be shared with family, friends or caregivers.

Baseline data

Demographic survey questions (race, ethnicity, education and income) were derived from the Behavioural Risk Factor Surveillance System and assessed at T0.[47] Baseline (past year before T0) clinical characteristics were identified using the electronic health and pharmacy records.

Outcomes

We examined two primary outcomes: opioid risk behaviour and naloxone uptake. Opioid risk behaviour was assessed at T0, 4 months and 8 months with the Opioid-Related Behaviours In Treatment (ORBIT) instrument, a validated, self-administered 10-item scale.[48] The ORBIT measures risk behaviours, such as using opioids for purposes other than pain or requesting early refills.[19] ORBIT items are presented on a 5-point Likert scale and can be used to assess behaviour changes over time.[48 49] We modified the ORBIT to measure behaviours over the previous 4 months. The ORBIT was administered to participants in the intervention prior to viewing the video at T0. Risk behaviour was analysed as a binary outcome, with a positive response defined as endorsing one or more risk behaviours on the ORBIT scale.[50]

Naloxone dispensings were ascertained over a 12-month follow-up period using National Drug Codes from electronic pharmacy data indicating that the products were sold by KPCO pharmacies and from claims demonstrating that a patient purchased naloxone from an external pharmacy. Participants were also asked on the survey if they or a family member had obtained naloxone. We conducted a post hoc analysis in which the survey naloxone uptake data were combined with the pharmacy and claims data, and participants who had received naloxone prior to T0 were excluded. For another post hoc analysis, naloxone uptake 12 months prior to T0 was compared with uptake 12 months after T0.

In addition to the primary outcomes, we assessed overdose and naloxone knowledge at T0, 4 months and 8 months with the Prescription Opioid Overdose Knowledge Scale (Rx-OOKS). Rx-OOKS is a validated 25-item scale measuring knowledge of overdose risks, overdose warning signs, steps to address overdose and appropriate use of naloxone. Rx-OOKS scores range from 0 to 25, with a higher Rx-OOKS score representing greater knowledge.[51] Missing Rx-OOKS item responses received a score of zero. Rx-OOKS was administered to participants after they viewed the video at T0. It was analysed as a continuous variable.

We also used the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) to examine the following secondary risk behaviour outcomes: cannabis use, other drug use (heroin, cocaine, methamphetamine, hallucinogens, inhalants, other drugs) and non-medical sedative use.[52 53] The ASSIST was assessed as a binary outcome, in which endorsement of one or more behaviour was considered a positive response. We assessed hazardous drinking with the Alcohol Use Disorders Identification Test–Concise (AUDIT-C).[54] The AUDIT-C is scored on a scale of 0–12, where a score of 0 indicates no alcohol use. We assessed the AUDIT-C as a binary outcome, in which scores of ≥4 for men and ≥3 for women represented positive responses.

At 12 months, we compared the incidence of opioid overdose and all-cause mortality between the study arms. Opioid overdoses were identified using International Classification of Diseases-10 CM codes (online supplemental eTable 1) from emergency department and hospital records, and from Denver County paramedic records. To identify deaths and causes of deaths, identifiers for all patients were linked to the Colorado Department of Public Health and the Environment vital records. When available, participants' medical records were reviewed to confirm opioid overdoses and the cause of death.

Statistical methods

A priori statistical power and sample size calculations were based on a continuous ORBIT score. There were approximately 8300 patients receiving LTOT who were eligible for the study, and prior work suggested that between 10% and 30% of these patients would participate in the trial. Based on a 10% participation rate and a two-sided α=0.05, we could detect a 0.31 difference in ORBIT scores between the intervention and usual care arms with 80% power. However, the ORBIT scores were skewed with little variability: mean at T0=1.6 (SD=2.3) on a scale of 0 to 40. For the analysis, we elected to dichotomise the ORBIT score as endorsing ≥1 opioid risk behaviour vs endorsing 0 behaviours.

Generalised linear mixed-effects models for repeated measures were used to assess the change in risk behaviour and knowledge scores between the study arms over time. The use of mixed models accounted for the correlation between observations made by the same participant across time. Primary and secondary risk behaviours were analysed as binary outcomes, using a binary distribution and log link function. The Rx-OOKS knowledge score was modelled as a continuous outcome, using a normal distribution and identity link function. Each model included the following variables: study arm (intervention or usual care), survey time point (T0, 4 months, 8 months), and interaction between the study arm and survey time point. Risk ratios or risk differences and 95% CIs comparing outcomes between study arms at each time point and the interaction p-values assessing change over time are reported. To account for missing survey data, we imputed 20 complete datasets by the method of fully conditional specification using all variables that could be potentially associated with the missing data. Each of the 20 complete datasets was analysed using a generalised linear mixed model with repeated measures, and the parameter estimates obtained from each analysed dataset were combined. We imputed missing data using PROC MI and combined parameter estimates using PROC MIANALZE in SAS. We also conducted sensitivity analyses for the ORBIT and Rx-OOKS that excluded missing survey data

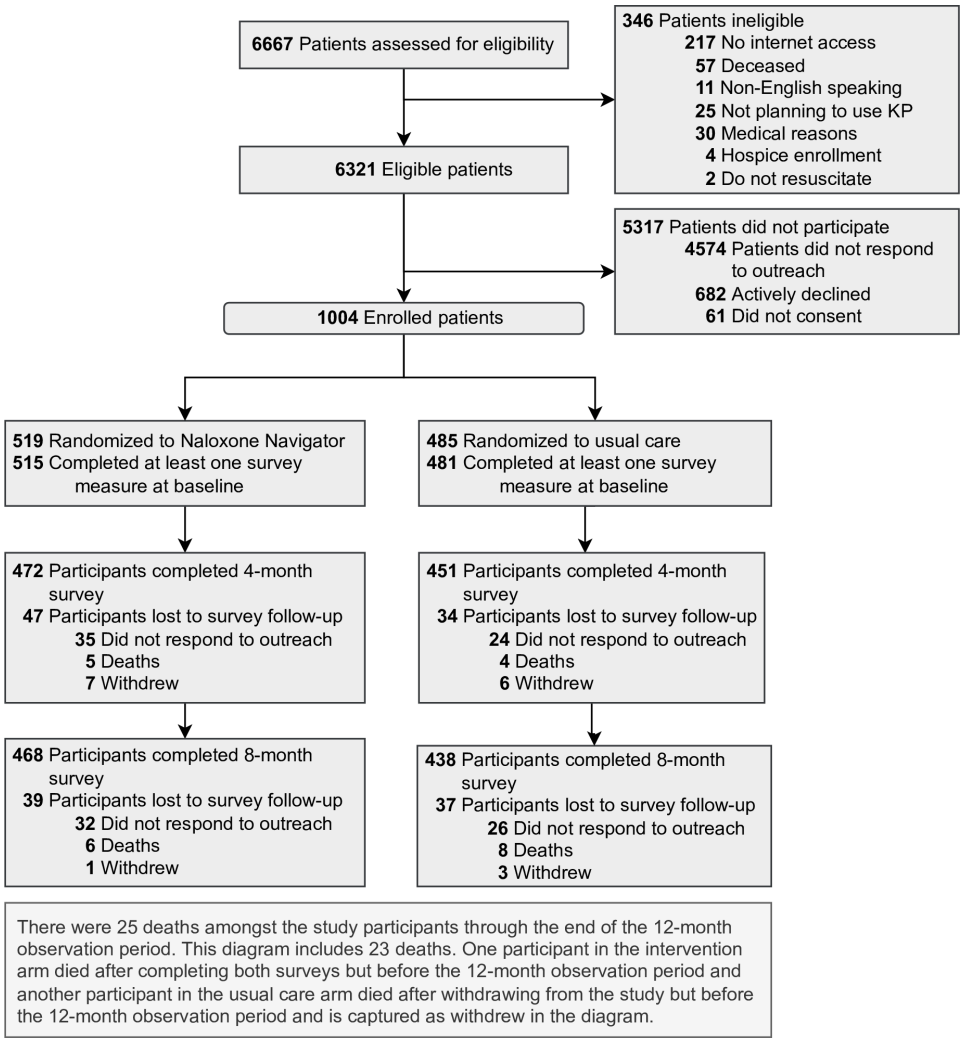

Figure 1 Consolidated Standards of Reporting Trials diagram of screening, enrolment and follow-up of patients.

and only included individuals who completed the respective survey measures at each time point.

Receipt of at least one naloxone dispensation (in primary and post hoc analysis), opioid overdose and death were analysed as dichotomous outcomes using a log-binomial model with the study arm as the exposure variable. Risk ratios and 95% CIs were calculated. For the post hoc analysis comparing naloxone uptake 12 months prior to T0 to uptake 12 months after T0, we used generalised linear mixed-effects model. We analysed naloxone uptake as a binary variable and included the following variables in the model: study arm (intervention or usual care), study time point (preintervention, postintervention) and interaction between the study arm and study time point.

All outcomes were analysed by the intention-to-treat principle. A 5% significance level using two-sided tests was applied in all analyses, and data were analysed using SAS Studio Software V.3.8 (SAS Institute).

RESULTS

Participants (N=1004; figure 1) had a mean age of 60.2 years, 63.8% were female and 41.6% completed college or more. Intervention (n=519) and usual care (n=485) participants were similar in terms of baseline demographic characteristics, substance use disorder diagnoses, medical comorbidities and mean opioid dose (table 1). All participants in the intervention arm watched the video at baseline; 35 participants or caregivers logged into the website to watch the video after baseline.

The proportion of participants who reported one or more opioid risk behaviours (ORBIT) decreased over time in both arms (figure 2). The most common reported risk behaviour was 'I have saved up my opioid medication, just in case I needed it later' (online supplemental eTable 2). From T0 to 8 months, reported risk behaviour decreased from 59.9% to 43.4% in the intervention arm and from 52.0% to 38.8% in the usual care arm. However, risk behaviour did not differ between the study arms over time (study arm by time interaction p=0.93; table 2). Across the three surveys, missingness ranged from 1.0% to 10.0% in the intervention arm and from 1.0% to 10.1% in the usual care arm. The sensitivity analysis that excluded missing survey data produced similar results (study arm by time interaction p=0.93; online supplemental eTable 3).

Table 1 Baseline demographic and clinical characteristics of study participants, overall and by trial arm

Characteristic	Overall study participants (N=1004)	Intervention arm (N=519)	Usual care arm (N=485)
Age, mean (SD), year	60.2 (12.5)	60.2 (12.8)	60.2 (12.2)
Female, n (%)	641 (63.8)	335 (64.6)	306 (63.1)
Race/ethnicity, n (%)*			
Hispanic	102 (10.2)	48 (9.3)	54 (11.1)
White	779 (77.6)	401 (77.3)	378 (77.9)
Black	40 (4.0)	21 (4.1)	19 (3.9)
All other racial and ethnic groups	60 (6.0)	33 (6.4)	27 (5.6)
Missing	23 (2.3)	16 (3.1)	7 (1.4)
Education, n (%)*			
Less than high school	23 (2.3)	11 (2.1)	12 (2.5)
Completed high school	158 (15.7)	82 (15.8)	76 (15.7)
Attended some college	375 (37.4)	179 (34.5)	196 (40.4)
Completed college or a higher degree	418 (41.6)	227 (43.7)	191 (39.4)
Missing	30 (3.0)	20 (3.9)	10 (2.1)
Annual household income, US dollars, n (%)*			
Less than 20 000	159 (15.8)	74 (14.3)	85 (17.5)
20 000 to <40 000	167 (16.6)	85 (16.4)	82 (16.9)
40 000 to <75 000	282 (28.1)	150 (28.9)	132 (27.2)
75 000 or more	251 (25.0)	135 (26.0)	116 (23.9)
Missing	145 (14.4)	75 (14.5)	70 (14.4)
Insurance, n (%)†			
Commercial	283 (28.2)	143 (27.6)	140 (28.9)
Medicaid	139 (13.8)	74 (14.3)	65 (13.4)
Medicare	529 (52.7)	271 (52.2)	258 (53.2)
Other	53 (5.3)	31 (6.0)	22 (4.5)
Modified Charlson Comorbidity Index, median (IQR) ‡	1.0 (0–2.0)	1.0 (0–2.0)	1.0 (0–2.0)
Opioid use disorder, n (%)‡	46 (4.6)	22 (4.2)	24 (5.0)
Alcohol use disorder, n (%)‡	25 (2.5)	14 (2.7)	11 (2.3)
Tobacco use or nicotine use disorder, n (%)‡	217 (21.6)	107 (20.6)	110 (22.7)
Prior naloxone receipt, n (%)§	87 (8.7)	41 (7.9)	46 (9.5)
Average daily opioid dose, median morphine milligram equivalents, median (IQR)¶	30.2 (15.7–60.0)	30.2 (16.4–60.0)	30.2 (15.1–60.9)

*Assessed using survey measures.
†Assessed at the time of study enrolment.
‡Assessed in the year prior to study enrolment.
§Assessed using naloxone dispensations in the year prior to study enrolment and self-report at time 0 survey.
¶Assessed in the 6 months prior to study enrolment.

By the end of follow-up, 52 (10.0%) and 43 (8.9%) of the participants had been dispensed naloxone in the intervention and usual care arms, respectively. In the intervention arm, 3 (5.8%) of the 52 of the participants received naloxone outside of a KPCO pharmacy, and 6 (14.0%) of the 43 participants in the usual care arm received naloxone externally, as indicated by a claim. The difference in naloxone dispensations between the study arms was not statistically significant (risk ratio=1.13, 95% CI 0.77 to 1.66). In both study arms, 87 participants had received naloxone prior to T0 and 35 participants reported that they or caregiver had acquired naloxone during the study period on the survey. In the post hoc analysis that excluded the former and included the latter, 13.6% of the intervention and 11.4% of the usual care participants received naloxone during the follow-up period, and the difference was not statistically significant (risk ratio 1.19, 95% CI 0.85 to 1.69). In the post hoc

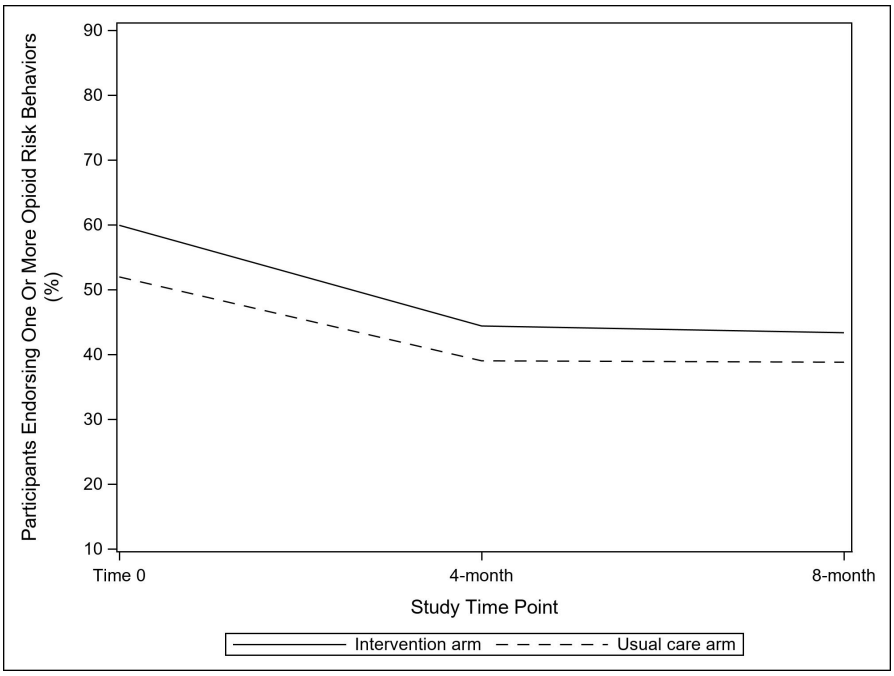

Figure 2 Proportion of study participants endorsing one or more opioid risk behaviours on the Opioid-Related Behaviours in Treatment Scale, by trial arm.

analysis comparing 12 months prior to and 12 months after T0, naloxone uptake increased from 3.9% to 10.0% in the intervention arm (p<0.001) and from 5.4% to 8.9% in the usual care arm (p=0.03); however, the difference between the study arms over time was not statistically significant (p=0.17) (online supplemental eFigure 1).

After viewing the intervention video at T0, the mean knowledge (Rx-OOKS) score was 19.3 and decreased to 15.5 at 8 months. In the usual care arm, the mean knowledge score at T0 was 11.4 and increased to 14.0 at 8 months (table 3, online supplemental eFigure 2). Knowledge was significantly greater in the intervention arm compared with usual care, but the difference between the arms attenuated over time (study arm by time interaction p<0.001). Across the three surveys, missingness ranged from 2.7% to 9.8% in the intervention arm and from 1.4% to 9.9% in the usual care arm. The sensitivity analysis that excluded missing survey data produced similar results (study arm by time interaction p<0.001; online supplemental eTable 4).

The secondary risk behaviour outcomes—cannabis use, other drug use, non-medical sedative use and hazardous drinking—did not differ over time between the study arms (online supplemental eTable 5).

Across the follow-up, there was 1 (0.2%) opioid overdose in the intervention arm and 3 (0.6%) opioid overdoses in the usual care arm; one of the overdoses in the usual care arm was fatal. The difference between the arms was not statistically significant (risk ratio 0.31, 95% CI 0.03 to 2.98). There were 12 (2.3%) and 13 (2.7%) all-cause deaths in intervention and usual care arms, respectively; the difference was not statistically significant (risk ratio 0.86, 95% CI 0.40 to 1.87).

DISCUSSION

This pragmatic RCT demonstrated that exposure to a video-based overdose prevention and naloxone narrative increased opioid overdose and naloxone knowledge, without increasing opioid risk behaviours among patients

Table 2 Opioid risk behaviour* among study participants over time, by trial arm

Risk behaviour	Proportion endorsing risk behaviour (95% CI)		Risk ratio (95% CI)	Time×intervention P value
	Intervention arm (n=519)	Usual care arm (n=485)		
Opioid risk behaviour				
Time 0	59.9 (55.7 to 64.1)	52.0 (47.5 to 56.4)	1.15 (1.03 to 1.29)	
4 months	44.4 (40.0 to 48.8)	39.0 (34.6 to 43.5)	1.14 (0.98 to 1.32)	
8 months	43.4 (38.9 to 47.8)	38.8 (34.3 to 43.3)	1.12 (0.96 to 1.30)	0.93

*Opioid risk behaviour was analysed as a binary outcome, with a positive response defined as endorsing one or more risk behaviours on the Opioid-Related Behaviours in Treatment Scale.

Table 3 Opioid overdose prevention and naloxone knowledge among study participants over time, by trial arm

Rx-OOKS	Rx-OOKS score* mean (95% CI)		Difference (95% CI)	Time×intervention P value
	Intervention arm (n=519)	Usual care arm (n=485)		
Time 0	19.3 (18.9 to 19.8)	11.4 (11.0 to 11.8)	7.97 (7.41 to 8.54)	
4 months	14.8 (14.4 to 15.1)	13.2 (12.8 to 13.6)	1.57 (1.04 to 2.10)	
8 months	15.5 (15.1 to 15.8)	14.0 (13.6 to 14.3)	1.50 (0.95 to 2.05)	<0.001

*Range of the Rx-OOKS scale is 0–25. Higher Rx-OOKS score represents greater knowledge.
Rx-OOKS, Prescription Opioid Overdose Knowledge Scale.

prescribed LTOT. However, while naloxone uptake increased in both arms over time, the difference between the arms was not statistically significant.

Qualitative and survey data show that some providers have concerns about risk compensation. While data on naloxone-related risk compensation do not support this concern, the data have largely been derived from observational cohort and ecological studies involving people who use illicit opioids.[55 56] In this patient-level RCT, we did not find evidence that providing overdose education and facilitating access to naloxone increases the likelihood of risk behaviour among patients receiving LTOT.

While the intervention effectively increased knowledge, it was insufficient to increase naloxone uptake relative to the control group. It is possible that cost considerations and stigma associated with requesting naloxone at the pharmacy counter remained barriers to obtaining naloxone for some intervention participants. It is also possible that exposure to the intervention—a single required viewing of a 6 min video—was not intense enough to prompt participants to purchase naloxone. The intervention may, therefore, have to be repeated and augmented with a more resource-intensive approach such as naloxone codispensing, which has been shown to effectively increase naloxone uptake compared with usual care.[28]

In the primary analysis, approximately 10% of participants who acquired naloxone obtained it outside of a KPCO pharmacy. It is possible that more participants would have acquired naloxone externally if we had conducted the trial after the Food and Drug Administration approved naloxone nasal spray for over-the-counter, non-prescription use in March 2023. However, it is also possible that cost, stigma and low-risk perception among patients receiving LTOT remain barriers to uptake. Additional research is needed to assess the impact of over-the-counter status on access to naloxone.

The incidence rate of overdose was 0.4% (n=4) in both study arms, aligning with other published estimates among patients prescribed LTOT.[57] This suggests that, while patients receiving LTOT are at increased risk of overdose, the absolute risk of overdose in this population is low. However, since overdose is a very serious event and the population receiving LTOT in the US is large (approximately 5% of adults), expanding access to naloxone is a public health priority because it could potentially prevent thousands of overdoses in this population.[14 58]

The Centers for Disease Control and Prevention Clinical Practice Guideline for Prescribing Opioids for Pain encourages clinicians and practices to offer naloxone to patients prescribed opioids, as well as to provide education on overdose prevention and naloxone use to patients and their household members.[59] The guideline further emphasises that such efforts should focus on patients at high risk for overdose, including patients with a history of overdose, patients with a prior substance use disorder diagnosis and patients being tapered to a lower opioid dose. Similarly, the WHO recommends training on overdose management and making naloxone available to people who regularly use opioids and their families.[60] Given that the Naloxone Navigator intervention positively impacted overdose knowledge, clinicians and healthcare systems could use the video intervention to effectively counsel patients as part of a comprehensive effort to reduce the risks associated with opioid therapy.

This study had limitations. Participants were not blinded to their study arm assignment or the research topic (overdose and naloxone) and were repeatedly tested about naloxone knowledge with the Rx-OOKS instrument, factors which may have attenuated differences in both knowledge and naloxone uptake between the arms. Knowledge in the intervention arm decreased over time, and differences in knowledge between the study arms attenuated over time, suggesting that exposure to the intervention would need to be reinforced or repeated if implemented into practice. Although a priori statistical power was based on continuous ORBIT scores, we analysed risk behaviour as a dichotomous variable, which may have reduced the statistical power. Deaths that might have occurred outside of Colorado were not captured in the vital records. Lastly, the video was only tested in English; thus, the trial's findings may not be generalisable to other languages and populations.

The Naloxone Navigator is a scalable intervention that effectively increased overdose prevention and naloxone knowledge among patients prescribed LTOT. While the intervention did not increase naloxone uptake relative to usual care, we did not find evidence that it increases opioid risk behaviours among patients receiving LTOT. We believe the intervention could be implemented across large health systems, complement other approaches to

increase naloxone uptake and be adapted to account for regulatory changes in naloxone, such as over-the-counter status and new formulations designed for higher potency synthetic opioids.

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Contributors JMG accepts full responsibility for the conduct of the study, had access to the data, and controlled the decision to publish. JMG and IAB conceived the idea and designed the study. JMG, IAB, SM, NW, SB and CK developed the Naloxone Navigator. SM and NW coordinated and supervised the research assistants. KW led electronic data collection. KJN and SX conducted the analyses. JMG, IAB, SM, NW, SB, KJN and SX interpreted the results. JMG wrote the first draft of the manuscript and is the guarantor of this manuscript. All authors critically revised the manuscript. Each author contributed important intellectual content during drafting or revision of the manuscript and accepted accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity.

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Data availability statement Data are available on reasonable request. Investigators interested in using the data from this study must submit a written request. Requests must address regulatory and compliance requirements for data usage. Investigators must outline the necessary resources required to support their data request, including personnel and infrastructure. The original study team will evaluate each request based on scientific merit, ethical considerations and alignment with the original study's objectives. Deidentified survey and electronic health record (EHR) data will be shared with investigators on approval of written request. Investigators are responsible for obtaining necessary approvals and adhering to relevant laws and regulations and will be required to sign a data use agreement (DUA) outlining the terms and conditions of data usage. The data sharing period is limited to 3 years following the publication of the primary study. The Naloxone Navigator video is available on request; please send an email to: jason.m.glanz@kp.org. This data availability statement is reflected in the individual participant data (IPD) sharing statement of the ClinicalTrials.gov registration (ClinicalTrials.gov number NCT03337009).

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REFERENCES

1 Centers for Disease Control and Prevention. Trends & statistics: drug overdose death rates. 2023. Available: https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates [Accessed 25 May 2023].
2 Breen P, Butt A. *Deaths related to drug poisoning in England and Wales: 2021 registrations*. Office for National Statistics, 2022.
3 Mojtabai R. National trends in long-term use of prescription opioids. *Pharmacoepidemiol Drug Saf* 2018;27:526–34.
4 Dunn KM, Saunders KW, Rutter CM, *et al*. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med* 2010;152:85–92.
5 Agnoli A, Xing G, Tancredi DJ, *et al*. Association of dose tapering with overdose or mental health crisis among patients prescribed long-term opioids. *JAMA* 2021;326:411–9.
6 Glanz JM, Xu S, Narwaney KJ, *et al*. Association between opioid dose reduction rates and overdose among patients prescribed long-term opioid therapy. *Subst Abuse* 2023;44:209–19.
7 Centers for Disease Control and Prevention (CDC). Community-based opioid overdose prevention programs providing naloxone - United States, 2010. *MMWR Morb Mortal Wkly Rep* 2012;61:101–5.
8 Maxwell S, Bigg D, Stanczykiewicz K, *et al*. Prescribing naloxone to actively injecting heroin users: a program to reduce heroin overdose deaths. *J Addict Dis* 2006;25:89–96.
9 Clark AK, Wilder CM, Winstanley EL. A systematic review of community opioid overdose prevention and naloxone distribution programs. *J Addict Med* 2014;8:153–63.
10 Policy Surveillance Program Staff. Naloxone overdose prevention laws. 2022. Available: https://pdaps.org/datasets/laws-regulating-administration-of-naloxone-1501695139 [Accessed 12 Mar 2024].
11 Davis C, Carr D. State legal innovations to encourage naloxone dispensing. *J Am Pharm Assoc (2003)* 2017;57:S180–4.
12 Weiner J, Murphy S, Behrends C. *Expanding access to naloxone: a review of distribution strategies*. Philadelphia, PA: Leonard Davis Institute of Health Economics, 2019.
13 Bohler RM, Freeman PR, Villani J, *et al*. The policy landscape for naloxone distribution in four states highly impacted by fatal opioid overdoses. *Drug Alcohol Depend Rep* 2023;6:100126.
14 Office of the Surgeon General. U.S. surgeon general's advisory on naloxone and opioid overdose. 2022. Available: https://www.hhs.gov/surgeongeneral/reports-and-publications/addiction-and-substance-misuse/advisory-on-naloxone/index.html [Accessed 12 Mar 2024].
15 Jones CM, Compton W, Vythilingam M, *et al*. Naloxone co-prescribing to patients receiving prescription opioids in the medicare part D program, United States, 2016-2017. *JAMA* 2019;322:462–4.
16 Roberts AW. Naloxone prescribing among frequent opioid prescribers in medicare part D from 2013 to 2017: a retrospective study. *J Gen Intern Med* 2021;36:543–5.
17 Slocum S, Ozga JE, Joyce R, *et al*. If we build it, will they come? Perspectives on pharmacy-based naloxone among family and

friends of people who use opioids: a mixed methods study. *BMC Public Health* 2022;22:735.
18 Carre Z. Zoe Carre: take home naloxone is not reaching those who most need it. *BMJ Opin* 2019.
19 Binswanger IA, Koester S, Mueller SR, *et al*. Overdose education and naloxone for patients prescribed opioids in primary care: a qualitative study of primary care staff. *J Gen Intern Med* 2015;30:1837–44.
20 Winograd RP, Werner KB, Green L, *et al*. Concerns that an opioid antidote could "make things worse": profiles of risk compensation beliefs using the naloxone-related risk compensation beliefs (NaRRC-B) scale. *Subst Abuse* 2020;41:245–51.
21 Winograd RP, Davis CS, Niculete M, *et al*. Medical providers' knowledge and concerns about opioid overdose education and take-home naloxone rescue kits within veterans affairs health care medical treatment settings. *Subst Abuse* 2017;38:135–40.
22 Mueller SR, Koester S, Glanz JM, *et al*. Attitudes toward naloxone prescribing in clinical settings: a qualitative study of patients prescribed high dose opioids for chronic non-cancer pain. *J Gen Intern Med* 2017;32:277–83.
23 Wheeler E, Jones TS, Gilbert MK, *et al*. Opioid overdose prevention programs providing naloxone to laypersons - United States, 2014. *MMWR Morb Mortal Wkly Rep* 2015;64:631–5.
24 Davis CS, Walley AY, Bridger CM. Lessons learned from the expansion of naloxone access in Massachusetts and North Carolina. *J Law Med Ethics* 2015;43:19–22.
25 The Network for Public Health Law. Opioid misuse and overdose prevention: 50-state survey. 2021. Available: https://www.networkforphl.org/wp-content/uploads/2021/02/50-State-Survey-Legal-Interventions-to-Reduce-Overdose-Mortality-Naloxone-Access-Laws.pdf [Accessed 4 Apr 2022].
26 Mercer F, Parkes T, Foster R, *et al*. Patient, family members and community pharmacists' views of a proposed overdose prevention intervention delivered in community pharmacies for patients prescribed high-strength opioids for chronic non-cancer pain: an explorative intervention development study. *Drug Alcohol Rev* 2023;42:517–26.
27 Evoy KE, Hill LG, Groff L, *et al*. Naloxone accessibility without a prescriber encounter under standing orders at community pharmacy chains in Texas. *JAMA* 2018;320:1934–7.
28 Thompson EL, Rao PSS, Hayes C, *et al*. Dispensing naloxone without a prescription: survey evaluation of Ohio pharmacists. *J Pharm Pract* 2019;32:412–21.
29 Bessen S, Metcalf SA, Saunders EC, *et al*. Barriers to naloxone use and acceptance among opioid users, first responders, and emergency department providers in New Hampshire, USA. *Int J Drug Policy* 2019;74:144–51.
30 Green TC, Case P, Fiske H, *et al*. Perpetuating stigma or reducing risk? Perspectives from naloxone consumers and pharmacists on pharmacy-based naloxone in 2 States. *J Am Pharm Assoc (2003)* 2017;57:S19–27.
31 Binswanger IA, Rinehart D, Mueller SR, *et al*. Naloxone co-dispensing with opioids: a cluster randomized pragmatic trial. *J Gen Intern Med* 2022;37:2624–33.
32 Evoy KE, Groff L, Hill LG, *et al*. Impact of student pharmacist-led naloxone academic detailing at community pharmacies in Texas. *J Am Pharm Assoc (2003)* 2020;60:81–6.
33 Evoy KE, Hill LG, Davis CS. Considering the potential benefits of over-the-counter naloxone. *Integr Pharm Res Pract* 2021;10:13–21.
34 Peet ED, Powell D, Pacula RL. Trends in out-of-pocket costs for naloxone by drug brand and payer in the US, 2010-2018. *JAMA Health Forum* 2022;3:e222663.
35 Zhu DT, Tamang S, Humphreys K. Promises and perils of the FDA's over-the-counter naloxone reclassification. *Lancet Reg Health - Am* 2023;23:100518.
36 Davis AC, Voelkel JL, Remmers CL, *et al*. Comparing Kaiser Permanente members to the general population: implications for generalizability of research. *Perm J* 2023;27:87–98.
37 DISPENSE SUPPLY OF EMERGENCY DRUGS FOR OVERDOSE VICTIMS, SB15-053 (Colo 2015). 2016. Available: https://statebillinfo.Com/bills/fiscal/15/sb053_f1.Pdf [Accessed 26 Aug 2023].
38 Harris PA, Taylor R, Thielke R, *et al*. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.
39 Harris PA, Taylor R, Minor BL, *et al*. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform* 2019;95:103208.
40 Mummah SA, Robinson TN, King AC, *et al*. Ideas (integrate, design, assess, and share): a framework and toolkit of strategies for the development of more effective digital interventions to change health behavior. *J Med Internet Res* 2016;18:e317.
41 Montaño DE, Kasprzyk D. Theory of reasoned action, theory of planned behavior, and the integrated behavioral model, Chapter 4. In: Glanz K, Rimer BK, Lewis FM, eds. *Health behavior and health education: theory, research, and practice*. 4th edn. San Francisco: Jossey-Bass, 2008.
42 Champion VL, CS S. The health belief model, Chapter 3. In: Glanz K, Rimer BK, Lewis FM, eds. *Health behavior and health education: theory, research, and practice*. 4th edn. San Francisco: Jossey-Bass, 2008.
43 Bagri G, Jones GV. The role of first person perspective and vivid imagery in memory for written narratives. *Educ Psychol Pract* 2018;34:229–44.
44 Hoeken H, van Vliet M. Suspense, curiosity, and surprise: how discourse structure influences the affective and cognitive processing of a story. *Poetics (Amst)* 2000;27:277–86.
45 Vyond Studio. Goanimate, Inc [computer software]. San Mateo, California, USA Available: https://vyond.com
46 Adobe. Adobe audition CC 2017 (version 10) [computer software]. San Jose, California, USA Available: https://adobe.com/products/audition.html
47 Centers for Disease Control and Prevention (CDC). *Behavioral risk factor surveillance system survey questionnaire*. Atlanta, georgia: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2014.
48 Larance B, Bruno R, Lintzeris N, *et al*. Development of a brief tool for monitoring aberrant behaviours among patients receiving long-term opioid therapy: the Opioid-Related Behaviours in Treatment (ORBIT) scale. *Drug Alcohol Depend* 2016;159:42–52.
49 Smith SM, Paillard F, McKeown A, *et al*. Instruments to identify prescription medication misuse, abuse, and related events in clinical trials: an ACTTION systematic review. *J Pain* 2015;16:389–411.
50 Campbell G, Noghrehchi F, Nielsen S, *et al*. Risk factors for indicators of opioid-related harms amongst people living with chronic non-cancer pain: findings from a 5-year prospective cohort study. *E Clin Med* 2020;28:100592.
51 Shoup JA, Mueller SR, Binswanger IA, *et al*. Modifying and evaluating the opioid overdose knowledge scale for prescription opioids: a pilot study of the Rx-OOKS. *Pain Med* 2020;21:2244–52.
52 McNeely J, Strauss SM, Wright S, *et al*. Test-retest reliability of a self-administered alcohol, smoking and substance involvement screening test (ASSIST) in primary care patients. *J Subst Abuse Treat* 2014;47:93–101.
53 Humeniuk R, Ali R, Babor TF, *et al*. Validation of the alcohol, smoking and substance involvement screening test (ASSIST). *Addiction* 2008;103:1039–47.
54 Harris AHS, Bradley KA, Bowe T, *et al*. Associations between AUDIT-C and mortality vary by age and sex. *Popul Health Manag* 2010;13:263–8.
55 Bruzelius E, Cerdá M, Davis CS, *et al*. Naloxone expansion is not associated with increases in adolescent heroin use and injection drug use: evidence from 44 US States. *Int J Drug Policy* 2023;114:103980.
56 Tse WC, Djordjevic F, Borja V, *et al*. Does naloxone provision lead to increased substance use? A systematic review to assess if there is evidence of a 'moral hazard' associated with naloxone supply. *Int J Drug Policy* 2022;100:103513.
57 Bohnert ASB, Valenstein M, Bair MJ, *et al*. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA* 2011;305:1315–21.
58 Nielsen S, Scott N, Tidhar T, *et al*. The cost and impact of distributing naloxone to people who are prescribed opioids to prevent opioid-related deaths: findings from a modelling study. *Addiction* 2022;117:1009–19.
59 Dowell D, Ragan KR, Jones CM, *et al*. CDC clinical practice guideline for prescribing opioids for pain - United States, 2022. *MMWR Recomm Rep* 2022;71:1–95.
60 World Health Organization. Opioid overdose. 2023. Available: https://www.who.int/news-room/fact-sheets/detail/opioid-overdose [Accessed 21 Sep 2023].