NEUROSCIENCE

Opioid prescribing decreases after learning of a patient's fatal overdose

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Most opioid prescription deaths occur among people with common conditions for which prescribing risks outweigh benefits. General psychological insights offer an explanation: People may judge risk to be low without available personal experiences, may be less careful than expected when not observed, and may falter without an injunction from authority. To test these hypotheses, we conducted a randomized trial of 861 clinicians prescribing to 170 persons who subsequently suffered fatal overdoses. Clinicians in the intervention group received notification of their patients' deaths and a safe prescribing injunction from their county's medical examiner, whereas physicians in the control group did not. Milligram morphine equivalents in prescriptions filled by patients of letter recipients versus controls decreased by 9.7% (95% confidence interval: 6.2 to 13.2%; $P < 0.001$) over 3 months after intervention. We also observed both fewer opioid initiates and fewer high-dose opioid prescriptions by letter recipients.

The United States is in the grips of its worst drug crisis in history, driven by twin epidemics of illicit and prescription opioid use. Opioid overdoses resulted in 351,630 deaths from 1999 to 2016, with deaths increasing from 2015 to 2016 for both illicit and prescription opioid users (*1*). In addition, more than 1.9 million Americans suffer from opioid addiction (*2*). Before the introduction of extended-release and long-acting opioids in the 1990s, long-term, high-dose opioid therapy was rare. The use of these drugs for cancer pain led to calls to address chronic noncancer pain with the same agents. Opioid proponents discounted historical evidence for opioid harms by frequently citing studies on small convenience samples (*3*, *4*). For example, there were more than 600 citations of a five-sentence letter to the editor published in the *New England Journal of Medicine* in 1980 titled "Addiction rare in patients treated with narcotics" (*3*), most in support of opioid safety (*5*). These and other factors may have encouraged unwarranted opioid prescribing.

In this randomized experiment, we aimed to counter factors that may promote high levels of opioid prescribing. We evaluated the effect of a personal letter from the medical examiner notifying clinicians of a controlled substance overdose drug death in their practice and reiterating guidelines for safe prescribing. We intervened on clinicians and allied health professionals with scheduled drug prescribing privileges in California. These individuals had prescribed a schedule II, III, or IV drug to a person who died as a result of a schedule II, III, or IV accidental overdose between the period of 1 July 2015 and 30 June 2016 in San Diego County. Prescriptions had to have been filled less than 12 months before the decedent's day of death.

Our study was a decedent-cluster randomized trial, in which clusters of individuals, rather than single persons, are randomly allocated to intervention groups. A decedent cluster is a distinct set of clinicians who wrote scheduled drug prescriptions to a person who suffered a fatal scheduled drug overdose. Decedent clusters were randomly assigned to either a control condition or a group receiving a letter signed by the Chief Deputy Medical Examiner of San Diego County (see supplementary text S1) that notified them of a death in their practice. The letter identified the decedent by name, address, and age; outlined the annual number and types of prescription drug deaths seen by the medical examiner; discussed the value of and way to access the state's prescription drug monitoring program; and discussed five U.S. Centers for Disease Control and Prevention (CDC) guideline–recommended safe prescribing strategies.

We abstracted data from the Controlled Substance Utilization Review and Evaluation System (CURES). This database provided a comprehensive record of opioids dispensed at California pharmacies to civilian, non–U.S. Department of Veterans Affairs, and non-institutionalized patients treated by clinicians in our sample. Descriptive and inferential statistics were carried out with the Stata software (*6*). The *cmp* command in Stata was used to compute a difference-in-differences estimator within a mixed-model two-part linear regression analysis (*7*). The difference-in-differences estimator compared the average change over time in milligram morphine equivalents (MMEs) dispensed for prescribers in the intervention group with the average change over time for prescribers in the control group. The natural log transformation of MMEs ensured a normal distribution of data. A two-part regression model has a discrete component and a continuous component: A binary event identifying whether there are opioid fill(s) in a prescriber's name each day represents the discrete part of the model, and the natural log of MMEs dispensed on days when opioids are filled in the name of a prescriber represents the continuous part. We also evaluated high-dosage prescriptions (≥50 or >90 MMEs per day) and the probability that a prescription fill was a "new start" (a new person entering the database).

Sample size calculations, described in the supplementary materials, indicate that we would need 65 decedents per study arm to have an 80% chance to detect an effect. This analysis assumes a 5% difference in daily MME prescribing between groups. Figure S1 illustrates the study timeline. Figure 1 describes the flow of decedent and prescriber identification, intervention allocation, follow-up, and data analysis. The medical examiner investigated 220 deaths in San Diego County between 1 July 2015 and 30 June 2016 for which a schedule II, III, or IV prescription drug was the primary or contributing cause of death. Of this group, 170 decedents (77.3%) had one or more prescriptions found in CURES 12 months before their death. Table S1 presents observed frequencies within randomization strata variables (cause of death and whether decedents received prescriptions from a clinician with multiple deaths), and Table 1 displays decedent characteristics. There were 861 prescribers to the 170 decedents whose deaths were caused by overdoses of schedule II, III, or IV drugs. Of these, 725 had prescribed to only one decedent, and 136 had prescribed to multiple decedents. There were, on average, 5.5 (±5.4) prescribers per decedent and 1.2 (±0.6) decedents per prescriber (numbers in parentheses indicate standard deviations). Sample characteristics of clinicians are presented in Table 2.

We observed 1,279,691 prescriptions filled during the study period. Using the dates of prescriptions dispensed, we computed daily MMEs for prescribers. Table 3 shows the average daily MMEs dispensed per prescriber in each of intervention and control groups 3 months before and 1 to 4 months after letters were sent. In the control group, opioid prescribing increased from 71.6 MMEs daily before intervention to 71.7 MMEs daily after intervention [i.e., +0.1 MME; 95% confidence interval (CI): −2.8 to 3.2 MMEs], whereas intervention group prescribing decreased from 72.5 to 65.7 MMEs (−6.8 MMEs; 95% CI: −9.9 to −3.8 MMEs) per prescriber per day. MMEs prescribed by clinicians in the intervention group decreased by 9.7% (95% CI: 6.2 to 13.2%) compared with control-prescribed MMEs over a period beginning 1 month and ending 4 months after the day the letters were mailed ($P < 0.001$). Letter recipients were 7% (95% CI: 2 to 11%) less likely than control prescribers to start a new patient on opioids ($P < 0.01$). We also

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observed a significant reduction in high-dose prescribing in the intervention group compared with the control group: a 3% decrease for 50 MME daily doses ($P < 0.05$) and a 4.5% decrease for 90 MME daily doses ($P < 0.05$) dispensed. There was no difference in the proportion of prescribers in the intervention or control group who made substantial (>20%) reductions in opioid prescribing in the postintervention period ($z = 1.279$, $P > 0.05$). Sensitivity analysis that transformed MMEs ensured normality, and a lag-correlation analysis to ensure independence of errors had no effect on results (fig. S2).

A simple letter, supportive in tone, to inform clinicians of a scheduled drug harm to their patient resulted in fewer subsequent opioids dispensed by those clinicians. Thus far, traditional state regulatory approaches to limiting opioid prescribing have not achieved great success. For example, Meara and colleagues found that adoption of controlled substance laws at the state level was not associated with reductions in potentially hazardous use of opioids or overdose among disabled Medicare beneficiaries (*8*). Another effort to send letters to potential high prescribers of controlled substances (individual health care clinicians who were at the 99.7th percentile of prescribing volume among prescribers of schedule II drugs in Medicare Part D) found no effect (*9*). In comparison, the success of the approach used in our study—notifying clinicians of a single fatal overdose—may have a number of explanations. First, people rely upon knowledge that is impactful, recent, and easy to retrieve from memory when judging probabilities and making decisions (*10*, *11*). Decisions to avoid harms could occur more frequently after receipt of the letter, because the effects of opioid harms are available to memory. Second, clinicians are also disproportionately exposed to patients who return to their clinics uneventfully for an opioid refill. The letter may alert clinicians to those patients who do not return, owing to death via an overdose. Third, individual behavior improves when outside persons attend to it (*12*). Clinicians may prescribe with greater care when they perceive that they are being watched, particularly by figures of authority (*13*). A message communicating a patient's overdose death from the medical examiner may have particular weight. Such information appears to encourage more cautious prescribing without restricting clinician freedom to prescribe opioids through mandated prescribing limits. Mandated limits do not account for individual patient circumstances that may arise in the course of care. We observed modest prescribing reductions, which suggest that clinicians exercised greater caution with opioids rather than abandoning use.

Brief exposure to opioids in opioid-naive persons makes long-term opioid use more likely (*14*, *15*), and excess prescription opioids (in medicine cabinets or diverted) are a source of misuse and are linked to transition to heroin (*16*, *17*). Correcting course in prescribing after learning of a patient's death from a prescription overdose may lessen the effect of the aforementioned harms.

Although the generalizability of these findings may be limited, San Diego County is a diverse county with a broad representation of providers and which constitutes ~1% of the U.S. population. The control condition involved no increased awareness of opioids or education; however, our study occurred 5 months after the U.S. Surgeon General issued CDC guideline pocket cards to

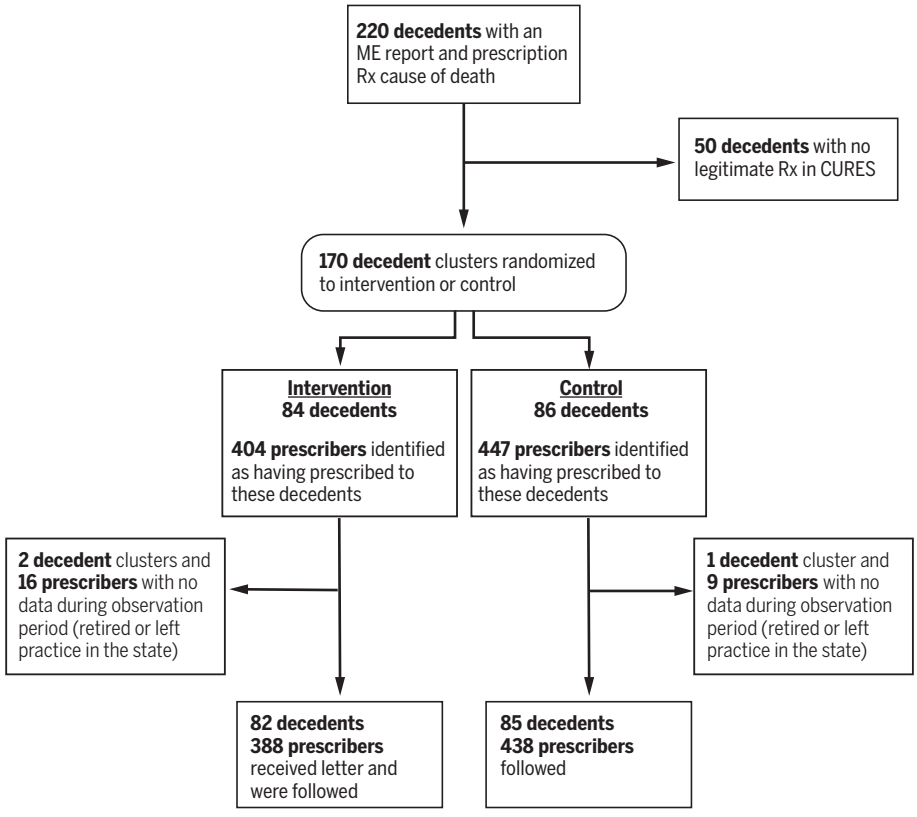

Fig. 1. Consort diagram. ME, medical examiner.

Table 1. Decedent characteristics. OTC, over the counter; *n*, number of clinicians.

Characteristic	Randomization group		Statistic	*P* value
	Letter (*n* = 82)	Control (*n* = 85)		
Age (±SD)	49.75 (11.15)	48.21 (14.85)	$t = 0.059$	0.954
Male	53 (65%)	44 (52%)	$\chi^2(1) = 0.591$	0.442
Race				
Black	6 (7%)	8 (9%)		
Hispanic	8 (10%)	4 (5%)		
Native American	0	1 (1%)	$\chi^2(5) = 4.752$*	0.447*
Asian/Pacific Islander	0	1 (1%)		
Non-Hispanic White	65 (79%)	70 (82%)		
Other	3 (4%)	1 (1%)		
Cause of death				
Prescription	41 (50%)	53 (62%)		
Prescription and illicit	27 (33%)	15 (18%)		
Prescription and alcohol	10 (12%)	13 (15%)	$\chi^2(5) = 5.300$†	0.380†
Prescription, illicit, and alcohol	2 (2%)	2 (2%)		
Prescription and OTC	1 (<1%)	1 (<1%)		
Prescription, alcohol, and OTC	1 (<1%)	1 (<1%)		

*For all races. †For all causes of death.

Table 2. Prescriber characteristics.

Professional practice	Randomization group		Statistic	*P* value
	Letter	Control		
Medical doctor (MD)	277	315		
Doctor of osteopathy (DO)	30	29		
Nurse practitioner (NP)	24	26		
Physician assistant (PA)	44	48	$\chi^2(4) = 1.173$*	0.883*
Dentistry (DDS/DND)	13	20		
Total	388	438		

*For all professional practices.

Table 3. Adjusted daily average milligram morphine equivalents (MMEs) dispensed per prescriber among persons randomized to the intervention or control groups. Values in parentheses are 95% CIs with 5% trimmed means.

Parameter	Randomization group	
	Letter	Control
Prescribers followed	388	438
Preintervention	72.5 (71.3 to 73.7)	71.6 (70.3 to 72.8)
Postintervention	65.7 (63.8 to 67.5)	71.7 (70.0 to 73.5)
Increment (pre- to post-)	−6.8 (−9.9 to −3.8)	0.1 (−2.8 to 3.2)
Difference in increment	−6.9 (−13.1 to −1.0)	
P value	0.001	

all U.S. clinicians, including those in our control arm. We do not address appropriate or inappropriate prescribing at the patient level.

Judicious prescribing represents only one of the components necessary to correct the missteps caused by overly enthusiastic use of opioids to alleviate pain. Access to medication-assisted therapy, counseling, and naloxone for resuscitation after overdose and efforts to address social determinants responsible for increased opioid use all play equally important roles in ending the crisis.

The intervention described here is scalable. Each county in the United States reports prescription opioid deaths to the National Center for Health Statistics, and each state maintains a vital records death file. Each state contains a prescription drug monitoring program that tracks prescriptions to decedents. It is thus feasible to "close the loop" on deaths by encouraging safe prescribing habits through the use of behavioral insights.

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/361/6402/588/suppl/DC1
Materials and Methods
Supplementary Text S1
Figs. S1 and S2
Tables S1 to S3
References (*18*–*22*)

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Science

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Feedback reduces opioid prescriptions

Most people addicted to opioids began taking them because they were legally prescribed. Little attention has been paid to changing physicians' prescribing behavior. Using a randomized controlled trial format, Doctor *et al.* monitored the effect of notifying physicians who had a patient die of opioid overdose within 12 months of a prescription. The physicians received an injunction to prescribe safely from their county's medical examiner. This intervention led to reductions in high-intensity prescribing, reductions in the likelihood that an opioid-naïve patient received a prescription, and a reduction in overall cumulative opioid intake.

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